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

Title	:	A double blind, placebo-controlled first time in human study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK3036656 in healthy adult volunteers
Compound Number	:	GSK3036656
Effective Date	:	28-MAR-2017

Description :

The purpose of this reporting and analysis plan (RAP) is to describe:

- The planned analyses and output to be included in Clinical Pharmacology Study Report for Protocol 201040. This RAP is intended to describe exploratory analysis requirements during the study to support dose escalation decisions as well as the safety, tolerability and pharmacokinetic analyses required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC).

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the Reporting and Analysis Plan
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe: • The planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol 201040. This RAP is intended to describe the safety, tolerability and pharmacokinetic analyses required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC).
Protocol	• Reporting and Analysis Plan is based on amended protocol (Dated: [27-FEB-2017]) for study 201040 [GlaxoSmithKline Document Number: 2014N202803_01 and eCRF version1].
Primary Objective	1. To investigate the safety and tolerability of GSK3036656 after single ascending and repeat oral doses in healthy adult subjects. 2. To determine the pharmacokinetics of single and repeat doses of GSK3036656 in healthy subjects.
Primary Endpoint	1. Safety and tolerability of GSK3036656: o Adverse Events o Clinically relevant changes in safety parameters: 12-lead ECG, telemetry, vital signs (systolic and diastolic blood pressure, heart rate, temperature), clinical laboratory data (haematology, clinical chemistry, urinalysis) 2. Derived pharmacokinetic parameters for GSK3036656 including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-∞), AUC(0-τ)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life (t1/2) as appropriate

Overview	Key Elements of the Reporting and Analysis Plan
Study Design	A double blind (sponsor unblind), randomised, placebo-controlled first time in human, dose escalation study enrolling healthy adult subjects. **Part A**: Subjects will receive single doses of GSK3036656 or matching placebo. It will include up to two cohorts. Each cohort will participate in up to 4 treatment periods (including a food effect treatment period). Up to 18 subjects (9 in each cohort, 6A:3P) (excluding possible replacements) will be recruited into the single ascending dose part of the study. **Part B**: Subjects will receive repeat doses of GSK3036656 or matching placebo. It will include up to four cohorts. Each cohort will participate in only one treatment period. Up to 40 subjects (10 in each cohort, 8A:2P) (excluding possible replacements) will be recruited for the repeat dose. The total duration of the study will be approximately 12 weeks for subjects recruited into Part A and approximately 8 weeks for subjects recruited into part B.
Planned Analyses	• Interim Analysis No formal interim analysis is planned for this study, however, safety, tolerability, and pharmacokinetic data will be reviewed before each dose escalation in Part A (single dose) and Part B (repeat dose), and prior to the investigation of the food effect. • The final planned analyses will be performed, as defined in this RAP document, after database freeze has been declared.
Analysis Population	• Enrolled Population: Defined as all subjects who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exists on the study database. • Safety Population: Defined as all randomised subjects who receive at least one dose of study medication. If subjects receive a treatment different to their randomised treatment, they will be analysed according to the treatment actually received.

Overview	Key Elements of the Reporting and Analysis Plan
	• Pharmacokinetic (PK) Population: Subjects in the Safety population who administered at least one dose of active treatment and have at least one evaluable PK sample.
Hypothesis	No formal hypotheses will be tested.
Interim Analyses	No formal interim analyses are planned for this study. However, safety, tolerability, and pharmacokinetic data will be reviewed before each dose escalation in Part A (single dose) and Part B (repeat dose), and prior to the investigation of the food effect.
PK Analyses	PK concentration data and derived PK parameters will be summarised appropriately using the PK population.
Safety Analyses	Safety data will be summarized descriptively, using the safety population, according to GSKs Integrated Data Standard Library (IDSL) standards.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol are outlined in below table.

Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Bayesian dose escalation model: $y = \exp(\theta_1+\varepsilon)\cdot \text{dose}^{\theta 2}$	• Bayesian dose escalation model: $y = \exp(\theta_1+ r_i+\varepsilon)\cdot \text{dose}^{\theta 2}$	• An additional random effect (r_i) has been included in the power model for the Bayesian dose escalation analyses in Study Part A to account for the within subject correlation, see Section 7.1.2

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

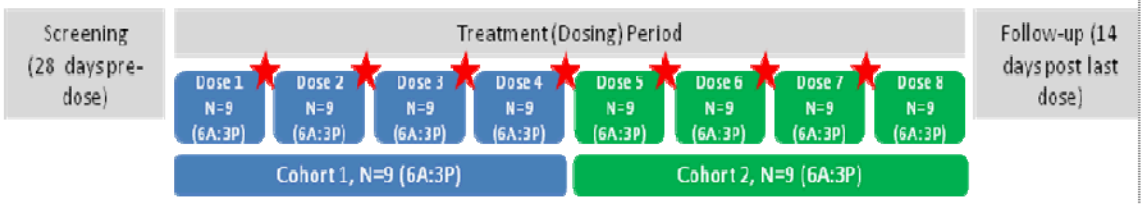
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To investigate the safety and tolerability of GSK3036656 after single ascending and repeat oral doses in healthy adult subjects	• Safety and tolerability of GSK3036656: o Adverse Events o Clinically relevant changes in safety parameters: 12-lead ECG, telemetry, vital signs (systolic and diastolic blood pressure, heart rate, temperature), clinical laboratory data (haematology, clinical chemistry, urinalysis)
• To determine the pharmacokinetics of single and repeat doses of GSK3036656 in healthy subjects	• Derived pharmacokinetic parameters for GSK3036656 including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-∞), AUC(0-τ)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life (t1/2) as appropriate
Secondary Objectives	**Secondary Endpoints**
• To assess the effect of food on the pharmacokinetics of GSK3036656 following an oral dose in healthy subjects	• Derived pharmacokinetic parameters for GSK3036656 including AUC(0-t), AUC(0-∞), Cmax, tmax, and apparent terminal half-life (t1/2)
• To assess preliminary dose proportionality of GSK3036656 following single and repeat oral doses, as data permit	• AUC(0-t), AUC(0-∞), and Cmax following single dose and AUC(0-τ) and Cmax following repeat dose for the assessment of dose proportionality
• To examine the extent of accumulation and achievement of steady-state following repeat oral doses of GSK3036656, as data permit	• Observed accumulation ratio based on AUC(Ro) and Cmax (RCmax) and steady-state ratio (Rss) following repeat dosing • Trough plasma concentrations at the end of the dosing interval (Cτ) to assess the achievement of steady-state of GSK3036656 following repeat oral doses
• To define the metabolic profile of GSK3036656 by identifying and quantifying, where possible and	• Structure and concentration of GSK3036656-related material in

Objectives	Endpoints
appropriate, GSK3036656-related material in plasma and urine following a single and repeated oral administration of GSK3036656	plasma and urine

2.3. Study Design

Overview of Study Design and Key Features

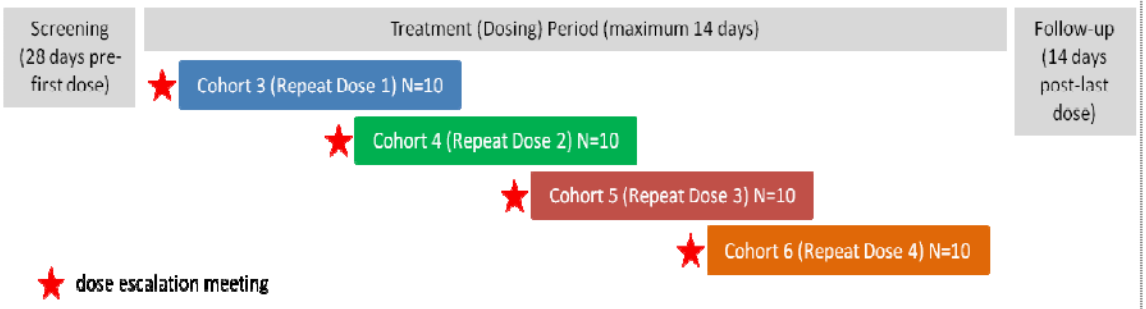
2.3.1. Part A (Single Dose)



★ Dose escalation meeting

- One of the dosing periods will be a food effect group – the dose will be determined based on data from previous cohorts
- There will be a 2 week washout between doses initially but the washout period may be modified depending on emerging data from previous cohorts.
- Cohorts 1 and 2 will be dosed sequentially. If it is considered desirable to dose Cohorts 1 and 2 in an overlapping/interlocking fashion, approval will be sought from the Regulatory Agency first.

2.3.2. Part B (Repeat Dose)



- Overlapping cohorts are shown for repeat dosing however sequential dosing may be done (i.e., dosing in Cohort 4 starts after dosing in Cohort 3 is completed). The sequence will be determined together with the site investigator based on emerging PK information

Design Features	A double blind, placebo-controlled first time in human study enrolling healthy adult subjects. **Part A**: Subjects will receive single doses of GSK3036656 or matching placebo. It will include up to two cohorts. Each

Overview of Study Design and Key Features	
	cohort will participate up to 4 treatment periods (including a food effect treatment period). **Part B**: Subjects will receive repeat doses of GSK3036656 or matching placebo. It will include up to four cohorts. Each cohort will participate in only one treatment period.
Dosing	**Part A (single ascending dose)** • Subjects randomized on Day 1 followed by a single dose of study drug administration. • 2 subjects in each cohort will be initially randomized to receive GSK3036656 or placebo in 1:1 ratio. Dosing in the remaining 7 subjects in each cohort will occur at least 24 hours later after review of safety results from the initial 2 subjects in a 5:2 ratio (GSK3036656: placebo). **Part B (repeat dose)** • Subjects randomized on Day 1 followed by first study drug administration. • Subsequent daily drug administrations are planned for up to 2 weeks.
Treatment Assignment	• Part A consists of up to 18 subjects in up to 2 cohorts (excluding possible replacements) (6 active: 3 placebo in each cohort) • Part B consists of up to 40 subjects in up to 4 cohorts (excluding possible replacements) (8 active: 2 placebo in each cohort)

Overview of Study Design and Key Features	
	• GSK RANDALL NG will be used to generate randomisation schedules.
Interim Analyses	• No planned formal interim analysis • Blinded review of safety data, unblinded review of PK data at aggregate level and calculation of Bayesian predictive probabilities (after the third dose) of area under the concentration-time curve AUC[0-24] and maximum observed plasma drug concentration (Cmax) will be used to help drive decision making for dose escalation in Part A (single dose) and Part B (repeat dose).

2.4. Statistical Hypotheses

No formal hypotheses will be tested for this study given that this is a first time in human study.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses are planned for this study. However, safety, tolerability, and pharmacokinetic data will be reviewed before each dose escalation in Part A (single dose) and Part B (repeat dose), and prior to the investigation of the food effect.

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.

[3] All criteria for unblinding the randomisation codes have been met.

[4] Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Endpoint(s) Evaluated
Enrolled Population	• Defined as all subjects who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exists on the study database.	• Screen Failure
Safety Population	• Defined as all randomised subjects who receive at least one dose of study medication. If subjects receive a treatment different to their randomised treatment, they will be analysed according to the treatment actually received.	• Study Population • Safety
Pharmacokinetic (PK) Population	• Subjects in the Safety population who administered at least one dose of active treatment and have at least one evaluable PK sample.	• PK

NOTES :

- Please refer to Appendix 10 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.
- 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 unblinding and 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
10.1	Appendix 1: Protocol Deviation Management
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Treatment States and Phases
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 55: Derived and Transformed Data
10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
10.7	Appendix 7: Values of Potential Clinical Importance
10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
10.9	Appendix 9 : Abbreviations & Trade Marks
10.10	Appendix 10: List of Data Displays
10.11	Appendix 11: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population displays will be based on the "Safety" population, unless otherwise specified. Outputs will be presented separately for study part A and study part B.

Table 2 provides an overview of the planned study population displays, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated	
	Table	Listing
Randomisation		
Planned and Actual Treatment		Y
Subject Disposition		
Subject Disposition	Y	
Reasons for Screening Failures[1]	Y	Y
Reasons for Study Treatment Discontinuation	Y	Y
Reasons for Withdrawals	Y	Y
Important Protocol Deviations	Y	Y
Inclusion and Exclusion Criteria Deviations	Y	Y
Demography		
Demographic Characteristics	Y	Y
Race & Racial Combinations	Y	Y
Study Populations	Y	Y
Medical/Surgical History & Concomitant Medications		
Medical/Surgical History		Y
Concomitant Medication	Y	Y
Exposure and Treatment Compliance		
Exposure to Study Treatment	Y	Y
Treatment compliance	Y	Y

NOTES:

- Y = Yes display generated.

1.Conditional displays, if data is available table and listing will be generated.

Categorical variables will be summarized by the number and percentage of subjects, and the continuous parameters will be summarized by n, mean, median, sample standard deviation, minimum and maximum unless otherwise specified.

7. PRIMARY STATISTICAL ANALYSES

7.1. Interim Analyses

No formal interim analyses are planned for this study. However, safety, tolerability, and pharmacokinetic data will be reviewed before each dose escalation in Part A (single dose) and Part B (repeat dose), and prior to the investigation of the food effect.

7.1.1. Overview of Planned Bayesian Dose Escalation Analyses

The Bayesian Dose Escalation analyses will be utilised to guide dose selection after 3 doses in each part of the study. The analyses will be based on the PK population, unless otherwise specified.

During dose escalation, a Bayesian predictive probability of geometric mean AUC[0-24] >4.9µg.h/ml and Cmax >0.443µg/ml will be calculated for potential future dose levels and used together with safety and tolerability data to aid next dose selections. The Bayesian predictive probability will be based on Whitehead's method (Whitehead 2001).

7.1.2. Planned Bayesian Statistical Analyses

Bayesian Statistical Analyses

Endpoint(s)

- AUC[0-24]
- Cmax

Model Specification

To guide dose selection after 3 doses in each part of the study have been observed, Bayesian posterior inferences about population probability distributions of model parameters of PK parameters will be assessed by using the following power model:

$$y = \exp(\theta_1 + r_i + \varepsilon) \cdot \text{dose}^{\theta 2}$$

where y denotes the PK parameter being analyzed and r the random subject effect. The θ_s, s=1,2, in the power model will be estimated by linear regression of the $\log_e$-transformed PK parameters on $\log_e$ dose levels.

$$\log(y_{ij}) = \theta_1 + \theta_2 \cdot \log(d_{ij}) + r_i + \varepsilon_{ij} \qquad (1)$$

where

- y_{ij} is the observed or predicted PK variable of the j-th dose d_{ij} administered to the i-th subject. In particular, it is an AUC[0-24] or a Cmax, as applicable.
- θ_1, θ_2 are population intercept and slope, respectively.
- r_i is the random effect associated with subjects, it has mean zero and variance s^2
- ε_{ij} is a random error term, with mean zero and variance σ^2.

Note, for part B, subjects will not receive more than one dose, therefore the random subject effect (r_i) will not be included in that model.

In general, Bayesian inference seeks to quantify the probability distributions of model parameters such as the $(\theta_1, \theta_2, \sigma, s)$ defined in Equation (1). The present inference will

Bayesian Statistical Analyses

incorporate a normal prior distribution, to express the prior information about the parameters (θ_1, θ_2) and a gamma prior distribution for (s^2, σ^2). Due to limited information available about the GSK3036656 compound, a non-informative prior with large variance will be used. For ease of parameterization for the normal distribution in computer programming, use $\nu = \sigma^{-2}$ and $w = s^{-2}$ as the precision. Model parameters are assumed *a* priori to be independent.

Table 3 Prior Distributions

Model Parameter	Prior
θ_1 (intercept)	~ Normal (0, precision=0.001)*
θ_2 (slope of log-dose)	~ Normal (0, precision=0.001)*
ν (random error precision)	~ Gamma (0.01, iscale=0.001)*
w (random effect precision)	~ Gamma (0.01, iscale=0.001)*

All model parameters are *a* prioiri independent.

*SAS Version 9. 3 or later or R version 3.1.1 or later will be used for the Bayesian analysis, specifying the normal distribution using mean and precision. At least two chains will be run for the estimation of each parameter.

Model Checking & Diagnostics

The posterior distributions of the model parameters will be estimated using the Markov Chain Monte Carlo (MCMC) method.

MCMC chains will be run for as many iterations as needed until convergence is achieved. Convergence will primarily be assessed using trace plots: All chains' trace plots will be inspected visually, to assess the mixing of each chain. Convergence is indicated when all chains appear to be mixing well and overlapping each other randomly (no chain's convergence is indicated until the chains of all model parameters appear well-mixed).

Additional convergence diagnostics, such as Monte Carlo Standard Error divided by the standard deviation of the posterior distribution (MCSE/SD), Gelman-Rubin statistic, effective sample size (ESS) and autocorrelation plots may also be reviewed.

The modelling will be subject to independent quality control, the final results for the probability of exceeding the pre-defined thresholds for both Cmax and AUC[0-24] should have a percentage of difference of ≤5% to conclude agreement.

Model Results Presentation

Once the posterior distributions have been estimated, the following inferences and predictions will be estimated using the associated posteriors:

- Predictions of PK parameters AUC[0-24] and Cmax for potential future dose levels: mean, median, 5th and 95th percentiles.

- The Bayesian predictive probability that an individual subject will have AUC[0-24] or Cmax values greater than 4.9 µg.h/mL and 0.443 µg/mL (a 30-fold

Bayesian Statistical Analyses
margin from the dog no observed adverse effect level (NOAEL) exposure), respectively, will be calculated for each potential future dose level in Part 1 and Part 2. Note, prediction in Part 2 will be independent of Part 1. • Graphical representation of the predictive distribution for AUC[0-24] and Cmax via line plots and density plots.

7.1.3. Overview of Planned PK Dose Escalation Analyses

Dose escalation for the first 2 dose levels will be based on population PK modelling (if feasible) or on the assumption of dose–exposure proportionality (i.e., doubling the dose gives an approximate doubling of exposure). If prior PK results show less than proportional increase in exposure with increasing dose, the prediction will be based on the assumption that the fold exposure increase to fold dose increase ratio will be the same with the current dose escalation as it was with the previous one. If prior PK results show more than proportional increase in exposure with dose, subsequent dose escalations will not be higher than 3-fold.

The population PK model will be a fit for purpose model. Candidate model selection will be primarily based on a significant reduction in the objective function value (≥ 3.32, $\chi 2$ <0.05) and improvement in the fits of diagnostic scatter plots. Inter-individual variability will be modelled using an exponential error model and residual error will be described by a proportional, proportional plus additive, or additive error model, depending on the data. Model performance will be evaluated using a visual predictive check. Simulations for dose recommendations will be conducted to determine the probability of an individual subject exceeding the defined exposure margins for AUC and Cmax.

7.2. Final Analyses

7.2.1. Pharmacokinetic Analyses

The reconciliation of the PK Case Report Form (CRF) and will be performed by, or under the direct auspices of, Clinical Pharmacology Science and Study Operations (CPSSO), GlaxoSmithKline.

The merge of PK concentration data, randomisation and CRF data will be performed by, or under the direct auspices of QSI, GlaxoSmithKline.

Derivation of pharmacokinetic parameters will be performed by or under the direct auspices of CPMS, QSci, GlaxoSmithKline.

Statistical Analysis of pharmacokinetic parameters will be performed by or under the direct auspices of, QSI, GlaxoSmithKline.

7.2.1.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the "Pharmacokinetic" population, unless otherwise specified.

Table 4 provides an overview of the planned non-compartmental pharmacokinetic analyses, with full details being presented in Appendix 10: List of Data Displays.

Table 4 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
Descriptive statistics														
Plasma Drug Concentrations				Y	Y	Y	Y				Y			
PK Urine Concentrations				Y	Y	Y	Y							
Derived PK Parameters				Y	Y		Y				Y			
PK Urine Parameters							Y							
Statistical Analysis of Primary PK Parameters														
Dose Proportionality								Y		Y[1]				
Food Effect								Y		Y[1]				
Time Invariance of GSK3036656								Y		Y[1]				
Accumulation ratio								Y		Y[1]				
Achievement of Steady State								Y		Y[1]				

NOTES :

- T = Table, F = Figure, L = Listings, Y = 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. Supportive SAS Output from Statistical Analysis

7.2.1.2. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.4.3. Reporting Process & Standards).

7.2.1.3. Pharmacokinetic Parameters

7.2.1.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.4.3. Reporting Process & Standards).
- Plasma GSK3036656 concentration-time data will be analyzed by non-compartmental methods according to current working practices with WinNonlin 5.2 or higher.
- Non-compartmental analysis will be performed in accordance with GSK PK Guidance document GUI_51487.
- All calculations of non-compartmental parameters will be based on actual sampling times recorded during the study.
- Pharmacokinetic parameters described in Table 5 will be determined from plasma concentration-time data and urine concentration data, as data permits.

Table 5 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
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 log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
AUC(0-24h)	Area under the concentration-time curve from time zero to 24 hours post-dose
AUC(0-τ)	AUC from time zero during a dosing interval of duration "τ"
AUC(Ro)	Observed accumulation ratio (Ro) for AUC will be calculated as follows: Day 14 AUC(0-τ)/Day 1 AUC(0- τ)
Ae	Urinary excretion of unchanged drug
Cmax	Maximum observed blood concentration, determined directly from the concentration-time data.

Parameter	Parameter Description
Ctrough	Pre-dose observed concentration, will be obtained directly from the concentration-time data.
CLr	Renal clearance
Fe	Fraction of the dose excreted in the urine
Lambda_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
Rss	Steady state ratio (Rss) will be calculated as follows: Day 14 AUC(0-τ)/Day 1 AUC(0-∞)
RCmax	Observed accumulation ratio for Cmax (RCmax) will be calculated as follows: Day 14 Cmax/Day 1 Cmax
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal phase half-life will be calculated as: **t½ = ln2 / Lambda_z** (NOTE: Lambda_z is the terminal phase rate constant).

7.2.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

For each of the parameters AUC (AUC(0-∞), AUC (0-t), AUC(0- τ), AUC(Ro)), RCmax, Rss, Cτ, Ae, fe, CLr and Cmax the following summary statistics will be calculated and tabulated by dose group for study Part A and Part B separately:

- **Untransformed Data:** N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum.
- **Log_e-transformed Data:** Geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and %CVb.

For tmax, and t½ the summary statistics specified for untransformed data above will be generated.

The following pharmacokinetic 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 Modeling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameter data will be the responsibility of QSI Stats & Programming.

Pharmacokinetic Statistical Analyses (Dose Proportionality - Single and Repeat Dose Study Phases)
Endpoint(s)
• Single Dose: AUC(0-t), AUC(0-∞) and Cmax • Repeat Dose : AUC(0-τ) and Cmax
Model Specification
• Will be statistically analysed using the power model • $y = \alpha * dose^{\beta}$ Where y =PK parameter being analyzed and α= subject • Log_e transformed data will be analysed by fitting the following terms in the mixed effect model: • Fixed effect: log_e (dose) • Random effect: Subject
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
Estimates of the mean slopes of log_e (dose) will be reported along with corresponding 90% confidence intervals (slope≈1 implies dose proportionality).

Pharmacokinetic Statistical Analyses (Food Effect - Single Dose Study Phase)
Endpoint(s)
• AUC(0-t), AUC(0-∞), Cmax and t1/2
Model Specification
• Will be statistically analysed using a mixed model (MM). • Terms fitted in the mixed effect ANOVA model will include: • Fixed effect : fed/fasted • Random Effect : Subject • Only data from the same dose level as the fed dose group will be included in this analysis, all other dose level data will be excluded. • 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. • An unstructured covariance structure for the G matrix will be used. o In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS. o Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

Pharmacokinetic Statistical Analyses (Food Effect - Single Dose Study Phase)
Model Results Presentation
Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest of GSK3036656 fed – GSK3036656 fasted, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% confidence intervals for the geometric mean ratios fed:fasted.
Endpoint(s)
• Tmax
Model Specification
• Wilcoxon matched pair test • Only data from the same dose level as the fed dose group will be included in this analysis, all other dose level data will be excluded.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
Point estimate and 90% confidence interval for the median difference (fed – fasted)

Pharmacokinetic Statistical Analyses (Time Invariance of GSK3036656 - Repeat Dose Study Phase)
Endpoint(s)
• time invariance ratio
Model Specification
• Will be statistically analysed using a mixed model (MM) ANOVA. • Fixed, categorical effect : day • Random Effect : Subject AUC(0-inf) on Day 1 will be the reference phase in the analysis, while AUC(0- τ) on Day 14 will be the test phase, using log-transformed AUC. • 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. • An unstructured covariance structure for the G matrix will be used. o In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS. o Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The time invariance ratio of GSK3036656 will be estimated by calculating the ratio of the generalized least square means of AUC (0- τ) on Day 14 to AUC (0-inf) on

Pharmacokinetic Statistical Analyses (Time Invariance of GSK3036656 - Repeat Dose Study Phase)
Day 1, along with the corresponding 90% CI at each dose level.

Pharmacokinetic Statistical Analyses (Accumulation - Repeat Dose Study Phase)
Endpoint(s)
• AUC (Ro) and Cmax (RCmax)
Model Specification
• Will be statistically analysed using a mixed model (MM) using a $\log_e$-transformation. • Fixed effects : dose, day and dose*day • Random Effect : Subject • 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. • An unstructured covariance structure for the G matrix will be used. o In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS. o Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Point estimates and 90% confidence intervals for the differences "Day 14- Day 1" will be constructed using the appropriate error term. The point estimates and associated 90% confidence intervals will then be exponentially back-transformed to provide point and 90% confidence interval estimates for the ratios "Day 14: Day 1" for each active dose. If both the dose and day by dose interaction terms are not significant, a single point estimate and confidence interval pooled across all doses will also be constructed.

Pharmacokinetic Statistical Analyses (Achievement of Steady State - Repeat Dose Study Phase)
Endpoint(s)
• Trough plasma concentrations at the end of the dosing interval ($C\tau$)
Model Specification
• Will be statistically analysed using a mixed models (MM) using log-transformed dose data. • Fixed effects : dose, day and dose*day • Random Effect : Subject • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed

Pharmacokinetic Statistical Analyses (Achievement of Steady State - Repeat Dose Study Phase)

effects will be used.
• An unstructured covariance structure for the G matrix will be used.
  o In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS.
  o Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
The coefficients of the slopes for the day effect for each dose, along with corresponding 90% confidence intervals, will be used to determine whether steady state was achieved. If the day-by-dose interaction were not significant, then the point estimates and 95% CIs for the individual dose levels will also be pooled across all doses for a single D14/D1 ratio. Trough concentration levels collected pre-morning dose will be plotted by collection day and dose.

8. SAFETY ANALYSES

The safety analyses will be based on the "Safety" population, unless otherwise specified. Outputs will be presented separately for study part A and study part B.

8.1. Overview of Planned Adverse Events Analyses

Adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary and summarized by dose group.

Counting of AEs will be based on the number of subjects – not the number of AEs. For example if a subject experiences the same AE (i.e. same preferred term) more than once, they are counted only once under the count for the preferred term. If a subject experiences more than one AE in a particular SOC, they will only be included once in the count for the SOC, but will appear in the count for each appropriate preferred term within the SOC. Therefore, the sum of the numbers of subjects with each preferred term event within a SOC may exceed the total number of subjects with at least one event. For the summary of AEs by maximum intensity, subjects who experience the same event several times with different intensity will only be counted once with the maximum intensity.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 6 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AE's	Y		Y
Serious AE's	Y		Y
Drug Related AEs	Y		Y
AE's leading to withdrawal	Y		Y
Common (>=5% in any treatment group) Non-serious AEs by SOC and PT – number of subjects and occurrences	Y		
Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Y		
Relationship Between System Organ Class And Verbatim Text			Y
Subject Numbers for Individual Adverse Events			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Summary = Represents TF 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.

8.2. Overview of Planned Clinical Laboratory Analyses

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 7 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Clinical Chemistry	Y		Y	Y		Y
Haematology						
Haematology	Y		Y	Y		Y
Urinalysis						
Urinalysis	Y		Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- 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.

8.3. Overview of Planned Other Safety Analyses

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 8 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y		Y			
ECG Values	Y		Y	Y		Y
ECG Values Outside the PCI Range			Y			
Telemetry			Y			
Vital Signs						
Vitals Values	Y		Y	Y		Y
Vital Signs Measurements Outside the PCI Range			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- 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.

9. REFERENCES

- GlaxoSmithKline Document Number 2014N202803_00 (Original – 13-JAN-2017):A double blind, placebo-controlled first time in human study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK3036656 in healthy adult volunteers.

- GUI_137354, Information for Authors: Reporting and Analysis Plan (RAP), Global

- SOP_54838, Development, Review & Approval of Reporting & Analysis Plan (RAP), Global

- GUI_51487, Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global

10. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Treatment States & Phases
Section 10.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.5	Appendix 5: Derived and Transformed Data • General • Study Population • Safety • Pharmacokinetic

Section 10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
	• Premature Withdrawals
	• Handling of Missing Data
	  ○ Handling of Missing Dates
	  ○ Handling of Partial Dates

Section 10.7	Appendix 7: Values of Potential Clinical Importance • Laboratory Values • ECG • Vital Signs
Section 10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.9	Appendix 9 : Abbreviations & Trade Marks
Section 10.10	Appendix 10: List of Data Displays
Section 10.11	Appendix 11: Example Mock Shells for Data Displays

10.1 Appendix 1: Protocol Deviation Management

There are no pre-defined categories leading to exclusion from the PK population but all protocol deviations will be reviewed on a case-by-case basis.

No subjects will be excluded from the safety population.

10.2 Appendix 2: Time & Events

10.2.1 Protocol Defined Time & Events

Part A

Part A	Screening		Day					Follow-up
Days	**-28 to -2**		**–1**	**1**	**2**	**3**	**4**	**15**
Informed consent	X							
Inclusion/exclusion criteria[1]	X		X					
Medical/surgical history	X							X
Admission			X					
Inpatient stay			←	—	—	—	→	
Dose of GSK3036656[2]				X				
Echocardiogram[3]	X							X
Discharge							X	X
Outpatient visit[4]	X	X						X
Safety assessments								
Physical examination[5]	X		X		X		X	X
Height & weight[5]	X							
Vital signs[6]	X		X	X	X	X	X	X
12-lead ECG[7]	X			X	X	X	X	X
Holter monitoring[8]	←	—	—	—	→			
Telemetry[9]				←	—	→		
Clinical laboratory assessments								
Screening tests (incl blood FSH & estradiol for female subjects only)	X							
Haematology, biochemistry and urinalysis[10]	X		X		X		X	X
Pregnancy test (female only)[11]	X		X					
Urine drug screen, alcohol & smoking breath tests	X		X					
PK samples								
Blood for PK GSK3036656[12]				X	X	X	X	
Total urine collection[13]				X	X	X	X	
Concomitant therapy review[14]	←	—	—	—	—	—	—	→
Adverse events[14]	←	—	—	—	—	—	—	→

1 Inclusion/exclusion criteria will only be assessed at Day-1 of the first period.
2 In the event of a divided dose, alterations to event time points may be communicated in a file note. For the food effect assessment, the selected dose will be given with a high fat meal.
3 Echocardiograms may be done at a separate screening visit.
4 When there is Holter monitoring at screening, subjects will return after 24 h to have the Holter removed.
5 Brief physical examination will be done at admission (Day–1) and in the morning on Days 2 and 4 in each

treatment session. Full physical examination will be done at screening and follow-up (to include height and weight at screening only).

6 Blood pressure, heart rate, tympanic temperature and respiratory rate. Vital signs will be recorded: at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Day 1.

7 ECGs will be recorded at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Day 1. Triplicate measurements (about 2-5 mins apart) will be taken at pre-dose; single measurements will be taken at all other time points.

8 24 h Holter monitoring at screening only.

9 Telemetry will be recorded from -1 h pre-dose until 24 h post-dose

10 Haematology, clinical chemistry, and urinalysis will be done at Day-1 and at 24 and 72 h post-dose.

11 Pregnancy testing of female subjects only. At screening pregnancy test will be done using the blood sample; urine pregnancy test will be done on admission.

12 Blood samples for assay of GSK3036656 will be taken: at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after dosing on Day 1.

13 Total urine collections for GSK3036656 will be performed at the following time points: pre-dose and 0-6, 6-12, 12-24, 24-48 and 48-72 h after dosing on Day 1.

14 AEs and concomitant medications will be recorded collected from the start of informed consent until the follow-up contact.

Part B

Part B	Screening		Day																		Follow-up
Days	**-28 to -2**		**–1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**28**
Informed consent	X																				
Inclusion/exclusion criteria	X		X																		
Medical/surgical history	X																				X
Admission			X																		
Inpatient stay			←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Dose of GSK3036656[1]				X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Echocardiogram[2]	X																				X
Discharge																		X			X
Outpatient visit[3]	X	X																	X	X	X
Safety assessments																					
Physical examination[4]	X		X		X		X		X				X					X			X
Height & weight[4]	X																				
Vital signs[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X			X	X	X	X		X				X				X				X
Holter monitoring[7]	←	—	→																		
Telemetry[8]				←	—	→															
Clinical laboratory assessments																					
Screening tests (incl blood FSH & estradiol for female subjects only)	X																				
Haematology, biochemistry and urinalysis[9]	X		X				X		X				X					X			X
Serum pregnancy test (female only)[10]	X		X																		
Urine drug screen, alcohol & smoking breath tests	X		X																		
PK samples																					
Blood for PK GSK3036656[11]				X	X	X	X								X	X	X	X	X	X	
Total urine collection[12]				X	X												X	X			
Concomitant therapy review[13]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Adverse events[13]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→

1 Dosing of GSK3036656 should be at approximately the same time each day. In the event of a divided dose, alterations to event time points may be communicated in a file note.
2 Echocardiograms may be done at a separate screening visit.
3 When there is Holter monitoring at screening, subjects will return after 24 h to have the Holter removed.
4 Brief physical examination will be done on Days-1, 2, 4, 6, 10, and 15. Full physical examination will be done at screening and follow-up (to include height and weight at screening only).
5 Blood pressure, heart rate, tympanic temperature and respiratory rate. Vital signs will be recorded: at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Days 1 and 14; and at pre-dose on Days 5-13.
6 ECGs will be recorded at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Days 1 and 14; and at pre-dose on Days 6 and 10. Triplicate measurements (about 2-5 mins apart) will be taken at pre-dose; single measurements will be taken at all other time points.
7 24 h Holter monitoring at screening only.
8 Telemetry will be recorded from -1 h pre-dose until 24 h post-dose on Day 1.
9 Haematology, clinical chemistry and urinalysis will be done on Day-1 and in the morning (pre-dose if feasible) on Days, 4, 6, 10, and 15.
10 Pregnancy testing of female subjects only. At screening pregnancy test will be done using the blood sample; urine pregnancy test will be done on Day-1.
11 Blood samples for assay of GSK3036656 will be taken: at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after dosing on Day 1; and at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36 48 and 72 h after dosing on Day 14. PK samples will also be taken pre-dose on Days 12 and 13.
12 Total urine collections for GSK3036656 will be performed at the following time points: pre-dose and 0-6, 6-12 and 12-24 h after dosing on Days 1 and 14.
13 AEs and concomitant medications will be recorded collected from the start of informed consent until the follow-up contact.

10.3 Appendix 3: Treatment States

10.3.1 Treatment States

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

Treatment State	Definition
Pre-Treatment	Date and time < Study Treatment Start Date and time
On-Treatment	If onset date is on or after treatment start date and time & on or before the treatment stop date and time Study Treatment Start Date and time ≤ Date and time ≤ Study Treatment Stop Date and time
Post-Treatment	If onset date and time is after the treatment stop date and time Date and time> Study Treatment Stop Date and time
AE Onset Time Since First 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
AE Duration (Days)	AE Resolution Date – AE Onset Date + 1
AE Drug-related	If relationship is marked 'YES' on eCRF or value is missing.

NOTES:

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

10.4 Appendix 4: Data Display Standards & Handling Conventions

10.4.1 Study Treatment & Display Descriptors:

Treatment Group Descriptions			
RandAll NG			Data Displays for Reporting
Part	**Code**	**Description**	**Description[1]**
A	P	Placebo	Placebo
A	D1	GSK3036656 Dose 1	Dose X mg
A	D2	GSK3036656 Dose 2	Dose X mg
A	D3	GSK3036656 Dose 3	Dose X mg
A	D4	GSK3036656 Dose 4	Dose X mg
A	D5	GSK3036656 Dose 5	Dose X mg
A	D6	GSK3036656 Dose 6	Dose X mg
A	D7	GSK3036656 Dose 7	Dose X mg
A	D8	GSK3036656 Dose 8	Dose X mg
B	P	Placebo	Placebo
B	R1	GSK3036656 Repeat Dose 1	Repeat Dose X mg
B	R2	GSK3036656 Repeat Dose 2	Repeat Dose X mg
B	R3	GSK3036656 Repeat Dose 3	Repeat Dose X mg
B	R4	GSK3036656 Repeat Dose 4	Repeat Dose X mg

NOTES:

The decision to proceed to each subsequent dose level will be made by the Dose Escalation Committee (DEC)

Note, in tables, figures and listings, treatments should be presented with placebo first, then in order of increasing dose within each study part.

1. 'Dose X' to be replaced by actual dose.

10.4.2 Baseline Definition & Derivations

10.4.2.1 Baseline Definitions

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

Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

If the latest pre-dose assessment is missing then the previous assessment time point would be considered as baseline where possible (i.e. if Day 1 (Pre-dose) is missing the Day -1 will be used).

10.4.2.2 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]

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.4.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries. Unless otherwise stated, if baseline data is missing or post-dose data is missing no derivation will be performed and (%) change from baseline will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.4.3 Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: arenv/arprod/GSK3036656/201040/final
QC Spreadsheet	: arenv/arwork/GSK3036656/201040/final/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & AdaM IG Version 1.0). • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for SAC.	

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 : o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. o 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: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings. o Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in 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, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 and Standards for the Transfer and Reporting of PK Data using HARP.

Reporting Standards	
	For NQ values, refer to GUI_51487.
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics. (Log_e Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log transformed data and between subject geometric coefficient of variation (CVb (%)) will be reported. $CVb\ (\%) = \sqrt{(\exp(SD^2) - 1)} * 100$ [NOTE: SD = SD of log_e transformed data]
Parameters Not Being Log_e Transformed	Tmax, t1/2
Summary Tables	Cmax, tmax, AUC(0-τ), AUC(0-t), AUC (0-∞), AUC (Ro), RCmax, Cτ, t1/2, Rss, Ae, fe, CLr, as data permit
Listings	Include PK Parameters Cmax, tmax, AUC(0-τ), AUC(0-t), AUC (0-∞) , AUC (Ro), RCmax, Cτ, t1/2, Rss, Ae, fe, CLr, as data permit
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13 and Standards for the Transfer and Reporting of PK Data using HARP.	

10.5 Appendix 5: Derived and Transformed Data

10.5.1 General

Multiple Measurements at One 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 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

10.5.2 Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

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 randomized 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.

10.5.3 Safety

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 decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. • Example 1: 2 Decimal Places = '< x ' becomes x – 0.01 • Example 2: 1 Decimal Places = '> x' becomes x + 0.1 • Example 3: 0 Decimal Places = '< x' becomes x – 1

10.5.4 Pharmacokinetic

PK Parameters
• The PK Population will include all subjects who undergo PK sampling and have evaluable PK assay results. • See table 5 for derived Pharmacokinetic parameters

10.6 Appendix 6: Premature Withdrawals & Handling of Missing Data

10.6.1 Premature Withdrawals

Element	Reporting Detail
General	• A completed subject is one who has completed all phases of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study. • All subjects who withdraw prematurely from the study/study drug will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). • All available data collected up until the point of withdrawal, and the follow-up visits will be used in the analyses and will be listed and all available planned data will be included in the summaries according to the populations defined in Section 4 unless otherwise specified.

10.6.2 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.

10.6.2.1 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: First of the month will be used unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered

Element	Reporting Detail
	On-treatment as per Appendix 3: Treatment States and Phases). • 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. • AEs with entirely missing or unknown start dates will be assumed to be on-treatment for reporting. • AEs with missing end dates are not anticipated to affect reporting.

10.6.2.2 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.

Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made for calculating the time to onset and the duration of the event:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month, unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered on-treatment as per Appendix 3: Treatment States).
	  • 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, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• The recorded partial date will be displayed in listings.

10.6.2.3 Handling of PK Concentration Data

Element	Reporting Detail
General	• The PK Population will include all subjects who undergo PK sampling and have evaluable PK assay results. This population will be used for the concentration listing, summaries and plotting of the individual concentration-time profiles. • PK assay results from samples collected from a subject with vomiting occurring within 2 times the median Tmax will not be considered as evaluable for that period. • If the pre-dose concentration is ≤ 5% of Cmax value in a subject, the concentration data for that subject without any adjustments will be included in pharmacokinetic and statistical analysis. If the pre-dose concentration is > 5% of Cmax value in a subject, then the concentration data for that subject will not be included in pharmacokinetic and statistical analysis and only the concentration data of that subject(s) will be presented • For missing and NQ values, refer to GUI_51487.

10.6.2.4 Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Imputation	• No imputation will be performed for missing data

10.7 Appendix 7: Values of Potential Clinical Importance

10.7.1 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
While 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	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

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
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

10.7.2 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
Change from Baseline			
Increase from Baseline QTc	msec		> 60

10.7.3 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

10.8 Appendix 8: Model Checking and Diagnostics for Statistical Analyses

10.8.1 Statistical Analysis Assumptions

Endpoint(s)	• PK End points AUC and Cmax
Analysis	• Mixed Model

Assumptions:

- For the Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data.
- 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.
- Non-parametric analyses will be conducted if the normality assumption does not hold.

10.9 Appendix 9 : Abbreviations & Trade Marks

10.9.1 Abbreviations

µg	Microgram
λz	Terminal phase rate constant
AE	Adverse Event
Ae	Excretion of unchanged drug
AIC	Akaike's Information Criteria
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve from time zero (pre-dose) during a dosage interval
AUC(Ro)	Observed Accumulation Ratio for AUC observed accumulation ratio for AUC
AUC[0-24]	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose
BMI	Body mass index
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Clearance
CLr	Renal Clearance
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling and Simulation
CPSR	Clinical Pharmacology Study Report
CPSSO	Clinical Pharmacology Sciences and Study Operations
CRF	Case Report Form
Cτ	Trough concentration (Cτ)
CV	Coefficient of variance
DBR	Database Release
DEC	Dose Escalation Committee
DP's	Decimal places
ECG	Electrocardiogram
ESS	Effective sample size
fe	Fraction of the dose excreted in urine
GSK	GlaxoSmithKline
h	Hour
HARP	Harmonized Analysis and Reporting Process
Hg	Mercury

ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
kg	Kilogram
L	Litres
MCMC	Markov Chain Monte Carlo
MCSE	Monte Carlo Standard Error
mg	Milligram
mL	Millilitre
mm	Millimetre
MM	Mixed Model
nm	Nanometer
NOAEL	No Observed Adverse Effect Level
PK	Pharmacokinetic
PTS	Platform Technologies and Science
QSI	Quantitative Sciences India
QTc	Electrocardiogram QT interval corrected for heart rate
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RCmax	Cmax Ratio
RAP	Reporting and Analysis Plan
RBC	Red blood cells
Rss	Steady-State Ratio
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SAS	Statistical Analysis System
SD	Standard Deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPDS	Statistics, Programming and Data Sciences
t½	Terminal phase half-life
Tmax	Time of occurrence of Cmax
TB	Tuberculosis
tmax	Time of occurrence of Cmax
ULN	Upper Limit of Normal
WBC	White blood cells

10.9.2 Trademarks

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
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10.10 Appendix 10: List of Data Displays

10.10.1 Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.23	N/A
Pharmacokinetic	2.1 to 2.15	2.1 to 2.8
Safety	3.1 to 3.32	N/A
Dose Escalation	4.1 to 4.2	4.1 to 4.4
Section	**Listings**	
ICH Listings	1 to 32	
Other Listings	33 to 41	

10.10.2 Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Pharmacokinetic		PK_Tn	
Dose Escalation	DE_Fn	DE_Tn	

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.10.3 Deliverable

Delivery	Description
DE	Dose Escalation
SAC	Statistical Analysis Complete

10.10.4 Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Enrolled	ES4	Summary of Subject Disposition – Part A		SAC
1.2.	Enrolled	ES4	Summary of Subject Disposition – Part B		SAC
1.3.	Enrolled	ES6	Summary of Screening Status and Reasons for Screen Failure – Part A		SAC
1.4.	Enrolled	ES6	Summary of Screening Status and Reasons for Screen Failure – Part B		SAC
1.5.	Safety	SD1	Summary of Reasons for Study Treatment Discontinuation – Part B		SAC
1.6.	Safety	ES1	Summary of Reasons for Study Withdrawal during the Study – Part A		SAC
1.7.	Safety	ES1	Summary of Reasons for Study Withdrawal during the Study – Part B		SAC
1.8.	Safety	IE1	Summary of Inclusion/Exclusion Criteria Deviations – Part A		SAC
1.9.	Safety	IE1	Summary of Inclusion/Exclusion Criteria Deviations – Part B		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Protocol Deviation					
1.10.	Safety	DV1	Summary of Important Protocol Deviations – Part A		SAC
1.11.	Safety	DV1	Summary of Important Protocol Deviations – Part B		SAC
Population Analysed					
1.12.	Safety	SP1	Summary of Study Populations – Part A		SAC
1.13.	Safety	SP1	Summary of Study Populations – Part B		SAC
Demography					
1.14.	Safety	DM1	Summary of Demographic Characteristics – Part A	Include BMI	SAC
1.15.	Safety	DM1	Summary of Demographic Characteristics – Part B	Include BMI	SAC
1.16.	Safety	DM5	Summary of Race and Racial Combinations – Part A		SAC
1.17.	Safety	DM5	Summary of Race and Racial Combinations – Part B		SAC
Concomitant Medications					
1.18.	Safety	CM1	Summary of Concomitant Medications – Part A		SAC
1.19.	Safety	CM1	Summary of Concomitant Medications – Part B		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
1.20.	Safety	EX1	Summary of Exposure to Study Drug – Part A		SAC
1.21.	Safety	EX1	Summary of Exposure to Study Drug – Part B		SAC
1.22.	Safety	COMP1	Summary of Overall Compliance Based on Exposure – Part A		SAC
1.23.	Safety	COMP1	Summary of Overall Compliance Based on Exposure – Part B		SAC

10.10.5 Pharmacokinetic Tables

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic					
2.1.	PK	PK01	Summary of Plasma GSK3036656 Pharmacokinetic Concentration-Time data – Part A		SAC
2.2.	PK	PK01	Summary of Plasma GSK3036656 Pharmacokinetic Concentration-Time data – Part B		SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	PK	PK02	Summary of Pharmacokinetic Urine Excretion Rate-Time Data – Part A		SAC
2.4.	PK	PK02	Summary of Pharmacokinetic Urine Excretion Rate-Time Data – Part B		SAC
2.5.	PK	PK03	Summary of Derived Plasma GSK3036656 Pharmacokinetic Parameters (untransformed data) – Part A		SAC
2.6.	PK	PK03	Summary of Derived Plasma GSK3036656 Pharmacokinetic Parameters (untransformed data) – Part B		SAC
2.7.	PK	PK05	Summary of Derived Plasma GSK3036656 Pharmacokinetic Parameters (log-transformed data)– Part A		SAC
2.8.	PK	PK05	Summary of Derived Plasma GSK3036656 Pharmacokinetic Parameters (log-transformed data)– Part B		SAC
2.9.	PK	Non-Standard PK_T1	Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part A	AUC(0-t), AUC(0-∞) and Cmax	SAC
2.10.	PK	Non-Standard PK_T1	Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model) – Part B	AUC(0-τ) and Cmax	SAC
2.11.	PK	Non-Standard PK_T2	Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Food Effect– Part A	Only for Single Dose Study Phase: AUC(0-t), AUC(0-∞), Cmax and t1/2	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	PK	Non-Standard PK_T3	Non-Parametric Analysis of Pharmacokinetic Parameter Assessing Food Effect -Tmax – Part A	Only for Single Dose Study Phase: T-max	SAC
2.13.	PK	Non-Standard PK_T4	Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Time Invariance– Part B	Only for Repeat Dose Study Phase	SAC
2.14.	PK	Non-Standard PK_T5	Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Accumulation Ratio– Part B	Only for Repeat Dose Study Phase; AUC(Ro) and RCmax	SAC
2.15.	PK	Non-Standard PK_T6	Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Steady State– Part B	Only for Repeat Dose Study Phase	SAC

10.10.6 Pharmacokinetic Figures

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic					
2.1.	PK	PK16a	Individual Subject Plasma GSK3036656 Concentration-time Plot (Linear and Semi-log) by Subject	By part	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.2.	PK	PK24	Individual Subject Plasma GSK3036656 Concentration-time Plot (Linear and Semi-log) by Treatment	By part	SAC
2.3.	PK	PK17	Mean Plasma GSK3036656 Concentration-Time Plots (Linear and Semi-log) by treatment	By part	SAC
2.4.	PK	PK18	Median Plasma GSK3036656 Concentration-Time Plots (Linear and Semi-log) by treatment	By part	SAC
2.5.	PK	PK21	Individual Urine Excretion Rate-Time Plots (Linear and Semi-log) by subject	By part	SAC
2.6.	PK	PK22	Mean Urine Excretion Rate-Time Plots (Linear and Semi-log) by treatment	By part	SAC
2.7.	PK	PK23	Median Urine Excretion Rate-Time Plots (Linear and Semi-log) by treatment	By part	SAC
2.8.	PK	PK25	Comparative Plot of Individual Subject Plasma GSK3036656 Pharmacokinetic Parameter Versus Treatment	By part	SAC

10.10.7 Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term – Part A		SAC
3.2.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term – Part B		SAC
3.3.	Safety	AE3	Summary of Serious Adverse Events – Part A		SAC
3.4.	Safety	AE3	Summary of Serious Adverse Events – Part B		SAC
3.5.	Safety	AE3	Summary of Drug Related Adverse Events – Part A		SAC
3.6.	Safety	AE3	Summary of Drug Related Adverse Events – Part B		SAC
3.7.	Safety	AE3	Summary of Adverse Events Leading Withdrawal from Study – Part A		SAC
3.8.	Safety	AE3	Summary of Adverse Events Leading Withdrawal from Study – Part B		SAC
3.9.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) - Part A		SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.10.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) - Part B		SAC
3.11.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part A		SAC
3.12.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – Part B		SAC
Laboratory Measurements					
3.13.	Safety	LB1	Summary of Clinical Chemistry Values – Part A		SAC
3.14.	Safety	LB1	Summary of Clinical Chemistry Values – Part B		SAC
3.15.	Safety	LB1	Summary of Change from Baseline for Clinical Chemistry Values – Part A		SAC
3.16.	Safety	LB1	Summary of Change from Baseline for Clinical Chemistry Values – Part B		SAC
3.17.	Safety	LB1	Summary of Haematology Values – Part A		SAC
3.18.	Safety	LB1	Summary of Haematology Values – Part B		SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.19.	Safety	LB1	Summary of Change from Baseline for Haematology Values – Part A		SAC
3.20.	Safety	LB1	Summary of Change from Baseline for Haematology Values – Part B		SAC
3.21.	Safety	UR3	Summary of Urinalysis Dipstick Results – Part A		SAC
3.22.	Safety	UR3	Summary of Urinalysis Dipstick Results – Part B		SAC
ECG					
3.23.	Safety	EG1	Summary of ECG Findings – Part A		SAC
3.24.	Safety	EG1	Summary of ECG Findings – Part B		SAC
3.25.	Safety	EG2	Summary of ECG Values – Part A		SAC
3.26.	Safety	EG2	Summary of ECG Values – Part B		SAC
3.27.	Safety	EG2	Summary of Change from Baseline for ECG Values – Part A		SAC
3.28.	Safety	EG2	Summary of Change from Baseline for ECG Values – Part B		SAC
Vital Signs					
3.29.	Safety	VS1	Summary of Vital Signs – Part A		SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.30.	Safety	VS1	Summary of Vital Signs – Part B		SAC
3.31.	Safety	VS1	Summary of Change from Baseline for Vital Signs – Part A		SAC
3.32.	Safety	VS1	Summary of Change from Baseline for Vital Signs – Part B		SAC

10.10.8 Dose Escalation Tables

Dose Escalation Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Dose Escalation Meetings					
4.1.	PK	Non-Standard DE_T1	Summary of PK parameters for Part A – Bayesian Prediction	Example given for Part A, same outputs will be produced for Part B	DE
4.2.	PK	Non-Standard DE_T2	Summary of PK Parameters for Part A – Bayesian Predictive Probability of Exceeding Threshold	Example given for Part A, same outputs will be produced for Part B	DE

10.10.9 Dose Escalation Figures

Dose Escalation Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Dose Escalation Meetings					
4.1.	PK	Non-Standard DE_F1	Dose Response Curve of Predictive Distributions for AUC[0-24] - Part A	Example given for Part A, same outputs will be produced for Part B	DE
4.2.	PK	Non-Standard DE_F2	Density Plot of Predictive Distributions for AUC[0-24] - Part A	Example given for Part A, same outputs will be produced for Part B	DE
4.3.	PK	Non-Standard DE_F1	Dose Response Curve of Predictive Distributions for Cmax - Part A	Example given for Part A, same outputs will be produced for Part B	DE
4.4.	PK	Non-Standard DE_F2	Density Plot of Predictive Distributions for Cmax - Part A	Example given for Part A, same outputs will be produced for Part B	DE

10.10.10 ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Randomization					
1.	Safety	CP_TA1	Listing of Randomized and Actual Treatments	By part	SAC
Subject Disposition					
2.	Safety	SD2	Listing of reasons for study treatment discontinuation	Only for Part B	SAC
3.	Safety	ES2	Listing of Reasons for Study Withdrawal	By part	SAC
4.	Enrolled	ES7	Listing of Reasons for Screening Failure	By part	SAC
5.	Safety	DV2	Listing of Important Protocol Deviations	By part	SAC
6.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	By part	SAC
Demography					
7.	Safety	DM2	Listing of Demographic Characteristics	By part	SAC
8.	Safety	DM9	Listing of Race	By part	SAC
9.	Safety	SP3	Listing of Subjects Excluded from Any Population	By part	SAC
Medical/Surgical History & Concomitant Medications					
10.	Safety	SP1	Listing of Medical/Surgical Procedures	By part	SAC
11.	Safety	CM3	Listing of Concomitant Medications	By part	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure and Treatment Compliance					
12.	Safety	EX3	Listing of Exposure Data	By part	SAC
13.	Safety	COMP2	Listing of Overall Compliance	By part	SAC
Adverse Events					
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	By part	SAC
15.	Safety	AE8	Listing of All Adverse Events	By part	SAC
16.	Safety	AE8	Listing of Serious Adverse Events	By part	SAC
17.	Safety	AE8	Listing of Drug-Related Adverse Events	By part	SAC
18.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study	By part	SAC
19.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Laboratory Measurements					
20.	Safety	LB5	Listing of Clinical Chemistry Values	By part	SAC
21.	Safety	LB5	Listing of Change from Baseline for Clinical Chemistry Values	By part	SAC
22.	Safety	LB5	Listing of Haematology Values	By part	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
23.	Safety	LB5	Listing of Change from Baseline for Haematology Values	By part	SAC
24.	Safety	UR2b	Listing of Urinalysis Data	By part	SAC
ECGs					
25.	Safety	EG5	Listing of ECG Findings	By part	SAC
26.	Safety	EG3	Listing of ECG Values	By part	SAC
27.	Safety	EG3	Listing of Change from Baseline for ECG Values	By part	SAC
28.	Safety	CP_EG4	Listing of ECG Values Of Potential Clinical Importance	By part	SAC
29.	Safety	CP_EG6	Listing of Telemetry	By part	SAC
Vital Signs					
30.	Safety	CP_VS5	Listing of Vital Signs	By part	SAC
31.	Safety	CP_VS5	Listing of Change from Baseline for Vital Signs	By part	SAC
32.	Safety	CP_VS5	Listing of Vital Sign Values of Potential Clinical Importance	By part	SAC

10.10.11 Non-ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic					
33.	PK	PK07	Listing of Plasma Pharmacokinetic Concentration-Time Data	By part	SAC
34.	PK	PK09	Listing of Urine Sample Collections	By part	SAC
35.	PK	PK11	Listing of Urine Excretion Rate Data	By part	SAC
36.	PK	PK13	Listing of Derived Plasma Pharmacokinetic Parameters	By part	SAC
37.	PK	N/A	RAW SAS Output from Summary of Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model)	By part	SAC
38.	PK	N/A	RAW SAS Output from Summary of Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Food Effect	By part	SAC
39.	PK	N/A	RAW SAS Output from Summary of Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Accumulation	By part	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
40.	PK	N/A	RAW SAS Output from Summary of Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Steady State	By part	SAC
41.	PK	N/A	RAW SAS Output from Non-Parametric Analysis of Pharmacokinetic Parameter-Tmax	By part	SAC

10.11 Appendix 11: Example Mock Shells for Data Displays

Example : DE_T1
Protocol : GSK3036656
Population : Pharmacokinetic

Table DE_T1
Summary of PK Parameters for Part A – Bayesian Prediction

PK Parameter Statistics	XX mg	XX mg	XX mg	XX mg	XX mg	XX mg
AUC[0-24] (µg.h/mL)						
N	X	X	X	NA	NA	NA
Observed Mean	X.XX	X.XX	X.XX	NA	NA	NA
Predictive Distribution						
Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
5th Percentile	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
Median	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
95th Percentile	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
Cmax (µg/mL)						
N	X	X	X	NA	NA	NA
Observed Mean	X.XX	X.XX	X.XX	NA	NA	NA
Predictive Distribution						
Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
5th Percentile	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
Median	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
95th Percentile	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX

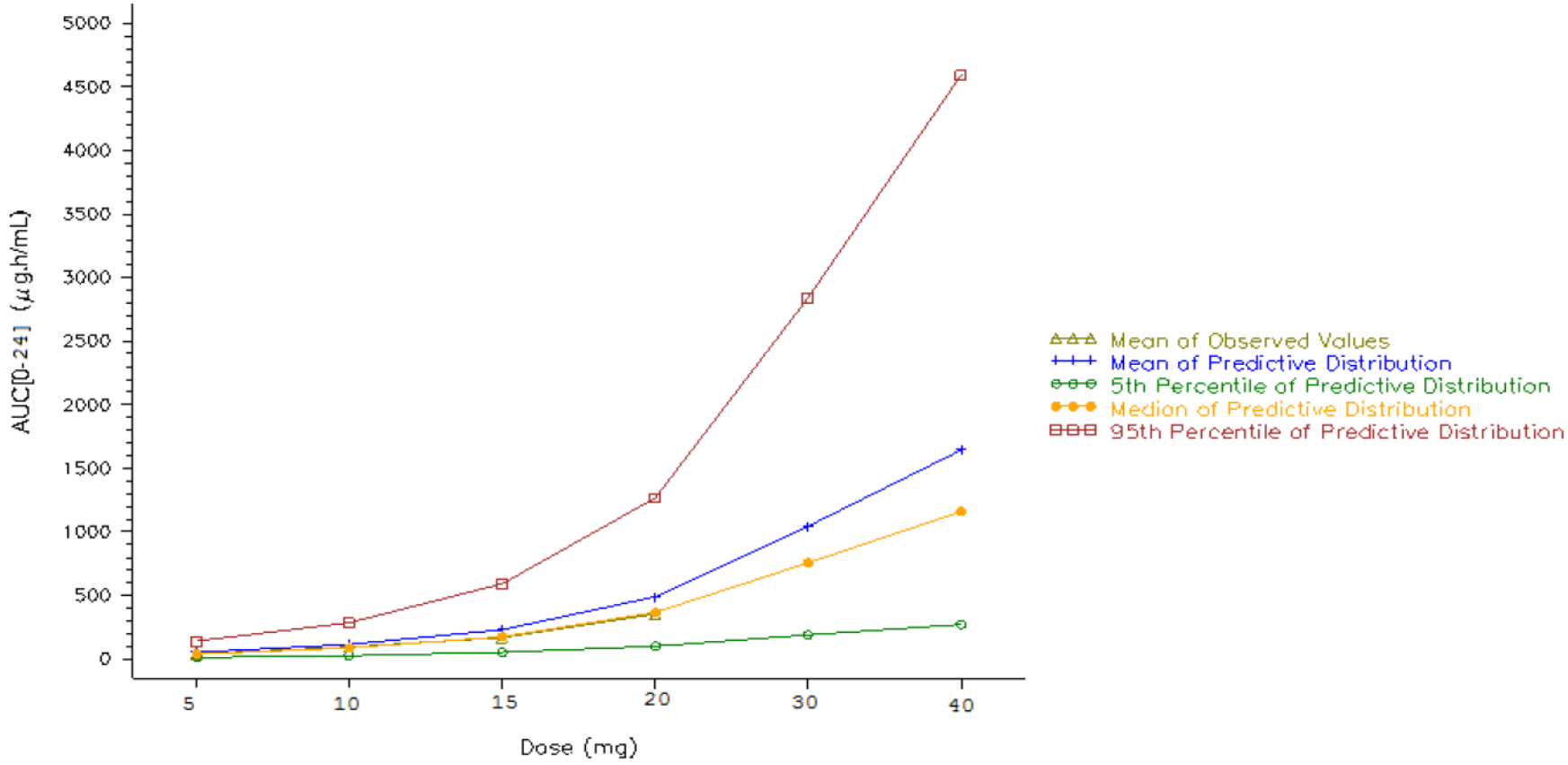
Example : DE_T2
Protocol : GSK3036656
Population : Pharmacokinetic

Table DE_T2
Summary of PK Parameters for Part A – Bayesian Predictive Probability of Exceeding Threshold

PK Parameter		Probability (greater than threshold | observed data)					
	Threshold	XX mg	XX mg	XX mg	XX mg	XX mg	XX mg
AUC[0-24] (µg.h/mL)	4.9	0.XX	0.XX	0.XX	0.XX	0.XX	0.XX
Cmax (µg/mL)	0.443	0.XX	0.XX	0.XX	0.XX	0.XX	0.XX

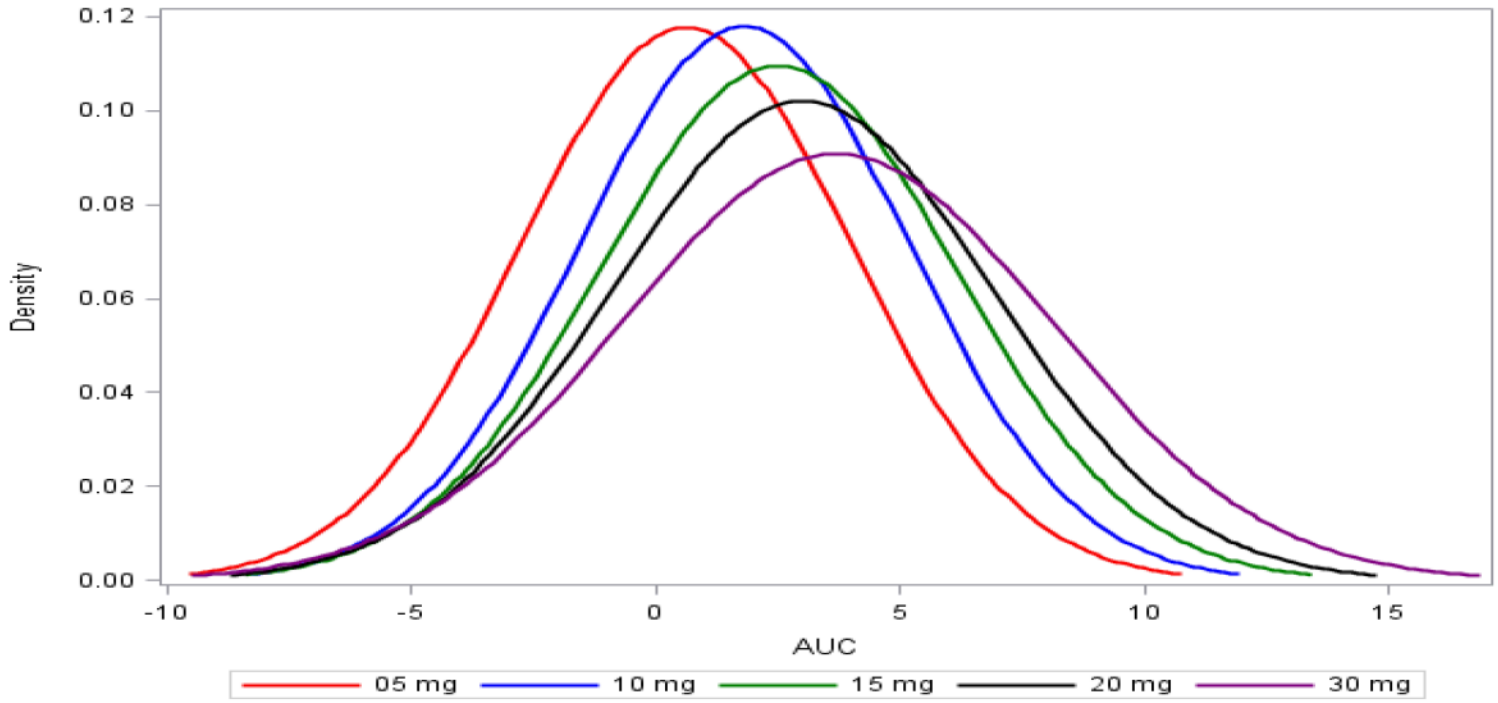
Example : DE_F1
Protocol : GSK3036656
Population : Pharmacokinetic

Table DE_F1
Dose Response Curve of Predictive Distributions for AUC[0-24] Part A



Example : DE_F2
Protocol : GSK3036656
Population : Pharmacokinetic

Table DE_F2
Density Plot of Predictive Distributions for AUC[0-24] Part A



Example : PK_T1
Protocol : GSK3036656
Population : Pharmacokinetic

Table PK_T1
Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model)
Part A / Part B

Parameter (units)	Slope Log Parameter vs Log Dose	90% CI of the Slope
AUC(0-t) (µg.h/mL)	x.xx	(x.xxx, x.xxx)
AUC(0-∞) (µg.h/mL)	x.xx	(x.xxx, x.xxx)
AUC(0-τ) (µg.h/mL)	x.xx	(x.xxx, x.xxx)
Cmax (µg/mL)	x.xx	(x.xxx, x.xxx)

Example : PK_T2
Protocol : GSK3036656
Population : Pharmacokinetic

Table PK_T2
Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Food Effect Part A

Parameter (units)	Treatment	Comparison	Geom.LsMean				Ratio	90% Confidence Interval	
			n	Test	n	Ref			
AUC(0-t) (µg.h/mL)	XXmg	Fed vs Fasted	xx	x.xxx	xx	x.xxx	x.xxx	(x.xxx,	x.xxx)
AUC(0-∞) (µg.h/mL)	XXmg	Fed vs Fasted	xx	x.xxx	xx	x.xxx	x.xxx	(x.xxx,	x.xxx)
Cmax (µg/mL)	XXmg	Fed vs Fasted	xx	x.xxx	xx	x.xxx	x.xxx	(x.xxx,	x.xxx)
T1/2 (µg/mL)	XXmg	Fed vs Fasted	xx	x.xxx	xx	x.xxx	x.xxx	(x.xxx,	x.xxx)

Example : PK_T3
Protocol : GSK3036656
Population : Pharmacokinetic

Table PK_T3
Non-Parametric Analysis of Pharmacokinetic Parameter Assessing Food Effect -Tmax Part A

Parameter (units)	Treatment	Comparison	Median				Diff	90% Confidence Interval
			n	Test	n	Ref		
Tmax (µg/mL)	XXmg	Fed vs Fasted	xx	x.xxx	xx	x.xxx	x.xxx	(x.xxx, x.xxx)

Example : PK_T4
Protocol : GSK3036656
Population : Pharmacokinetic

Table PK_T4
Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Time Invariance Part B

Parameter (units)	Treatment	Comparison	Ratio	90% Confidence Interval
AUC(0-τ)(µg.h/mL) Vs AUC(0-inf)(µg.h/mL)	XXmg	Day 14 vs Day	x.xxx	(x.xxx, x.xxx)

Example : PK_T5
Protocol : GSK3036656
Population : Pharmacokinetic

Table PK_T5
Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Accumulation Ratio Part B

Parameter (units)	Treatment	Comparison	Geom.LsMean				Ratio	90% Confidence Interval
			n	Test	n	Ref		
AUC(Ro)(µg.h/mL)	XXmg	Day 14 vs Day 1	XX	x.xxx	xx	x.xxx	x.xxx	(x.xxx, x.xxx)
Cmax(RCmax)(µg/mL)	XXmg	Day 14 vs Day 1	XX	x.xxx	xx	x.xxx	x.xxx	(x.xxx, x.xxx)

Example : PK_T6
Protocol : GSK3036656
Population : Pharmacokinetic

Table PK_T6
Statistical Analysis of log transformed plasma GSK3036656 Pharmacokinetic Parameters Assessing Steady State Part B

Parameter	Treatment	Day	Back-Transformed Slope	90% Confidence Interval
Ctrough	xxmg	1-14	x.xxx	(x.xxx, x.xxx)