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

Title	:	Reporting and Analysis Plan for Study 207674: A randomised, double-blind, parallel group study to evaluate the safety, tolerability and pharmacokinetics of a single dose of GSK2269557 administered via the ELLIPTA™ dry powder inhaler to healthy participants.
Compound Number	:	GSK2269557
Effective Date	:	08-JUN-2017

Description :

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

- Describe the safety, tolerability, and pharmacokinetics 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).

Author's Name and Functional Area:

PPD Manager, Statistics (Clinical Statistics)	19-MAY-2017

Reviewed by:

PPD	Manager, (Clinical Pharmacology)
	Programming
	Clinical Investigation Lead
	Global Clinical Safety & Pharmacovigilance
	Safety physician
	Medical Writer
	Data Manager
	Drug Metabolism and Pharmacokinetics

Approved via e-mail by:

PPD Director (Clinical Statistics)	07-JUN-2017
PPD Manager, Programming	08-JUN-2017

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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: • Planned analyses and output for the study.
Protocol	• Reporting and Analysis Plan is based on original protocol (Dated: 04-APR-2017) for study GSK2269557/207674 [GlaxoSmithKline Document Number: 2017N316562_00].
Primary Objective / Endpoint	• Primary objective is to assess the pharmacokinetic profile of a single dose of GSK2269557 administered via the ELLIPTA™ dry powder inhaler to healthy participants by derived pharmacokinetic parameters including: Area under the plasma drug concentration versus time curve from zero to time t AUC(0-t), Area under the plasma drug concentration versus time curve from zero to 24 hours AUC(0-24), Area under the plasma drug concentration versus time curve from zero to infinity AUC(0-inf∞), Maximum observed plasma drug concentration (Cmax), Time to maximum observed plasma drug concentration (Tmax), Concentration at trough (Ctrough), Terminal half-life (T1/2), where data allow.
Study Design	• Randomised, double-blind, parallel group, single dose study in healthy participants. • Approximately 12 participants will be randomised to receive a single dose of GSK2269557 750 µg or a single dose of GSK2269557 500 µg in a 1:1 ratio.
Analysis Population	• Primary: Pharmacokinetic Population (Comprised of All randomised participants who take at least 1 dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed. Participants will be analysed according to the treatment they received).
Hypothesis	• There are no formal hypotheses being tested in the study; instead an estimation and inference approach will be adopted to evaluate the objectives.
Primary Analyses	• Pharmacokinetic data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Individual GSK2269557 plasma concentration-time profiles (by treatment and subject) and median/mean (±SD) profiles by treatment group will be plotted and listed. Plasma concentration time data for GSK2269557 will be analyzed by non-compartmental methods using WinNonlin and derived PK parameters summarised and listed. No formal statistical analyses will be conducted.
Secondary Analyses	• Safety data will be presented in tabular format and summarized descriptively.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol [Dated: 04-APR-2017].

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

Objectives	Endpoints
Primary (Pharmacokinetic)	**Primary (Pharmacokinetic)**
• To assess the pharmacokinetic profile of a single dose of GSK2269557 administered via the ELLIPTA dry powder inhaler to healthy participants.	• GSK2269557 plasma concentration data and derived pharmacokinetic parameters including area under the plasma drug concentration versus time curve from zero to time t (AUC(0-t)), area under the plasma drug concentration versus time curve from zero to 24 hours (AUC(0-24)), area under the plasma drug concentration versus time curve from zero to infinity (AUC(0-inf∞)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), Concentration at trough (Ctrough), terminal half-life (T1/2), where data allow.
Secondary Objectives (Safety)	**Secondary Endpoints (Safety)**
• To assess the safety and tolerability of a single dose of GSK2269557 administered via the ELLIPTA dry powder inhaler to healthy participants.	• Safety and tolerability of GSK2269557 as assessed by clinical monitoring of: • Vital Signs • Electrocardiogram (ECG) • Spirometry • Laboratory safety data • Adverse events (AEs)

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	• Randomised, double-blind, parallel group single centre study to investigate the safety, tolerability, and pharmacokinetics of a single dose of GSK2269557 administered via the ELLIPTA^{T} dry powder inhaler to healthy participants.
Dosing	• Patients dosed within 28 days of screening. • Study treatment will be administrated on Day 1. Participants will be discharged after completion of all 24h post dose assessments on Day 2 and if there are no safety concerns
Treatment Assignment	• Approximately 12 participants will be randomised to receive a single dose of GSK2269557 750 µg or a single dose of GSK2269557 500 µg in a 1:1 ratio.

2.4. Statistical Hypotheses

There are no formal hypotheses being tested in the study; instead an estimation and inference approach will be adopted to evaluate the objectives.

3. PLANNED ANALYSES

3.1. 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
All Participants Enrolled (APE) Population	• All participants for whom a record exists on the study database; includes both screen participants and participants who are not screened but sign the informed consent form	• Study Population
Safety	• All randomised participants who receive at least one dose of study treatment. Participants will be analysed according to the treatment they actually received.	• Study Population • Safety

Population	Definition / Criteria	Endpoint(s) Evaluated
Pharmacokinetic	• All randomised participants in the Safety population and for whom a pharmacokinetic sample was obtained and analysed.	• PK

NOTES :

- Please refer to Appendix 7 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 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: Time & Events
10.2	Appendix 2: Treatment States and Phases
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 8: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Randomisation			
Randomisation			Y
Subject Disposition			
Subject Disposition		Y	
Reasons for Screening Failures		Y	Y
Reasons for Withdrawals			Y
Important Protocol Deviations		Y	Y
Inclusion and Exclusion Criteria Deviations			Y
Demography			
Demographics Characteristics		Y	Y
Age Ranges		Y	
Race & Racial Combinations		Y	Y
Study Populations		Y	
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)			Y
Concomitant Medication			Y

NOTES:

- Y = Yes display generated.

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacokinetic Analyses

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

7.1.1. Overview of Planned Pharmacokinetic Analyses

Table 3 provides an overview of the planned pharmacokinetic analyses with full details of data displays being presented in Appendix 8: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Plasma Concentrations	Y	Y	Y	Y	Y	Y	Y	
Derived PK Parameters		Y		Y		Y		

NOTES :

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

7.1.2. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).

7.1.3. Pharmacokinetic Parameters

7.1.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).
- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Win Nonlin Pro.
- All calculations of non-compartmental parameters will be based on actual sampling times recorded during the study.
- Pharmacokinetic parameters described in Table 4 will be determined from plasma GSK2269557 concentration-time data, as data permits.

Table 4 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(0-24)	Area under the concentration-time curve will be calculated to fixed nominal time 24 hours after administration (AUC(0-24)),using the combination of linear and logarithmic trapezoidal methods (i.e., Linear Up/Log Down calculation method in Phoenix WinNonlin Professional). If a sampling time deviation occurred at nominal time 24 hours after administration (and 24 < t), AUC(0-24) will be calculated using the concentration at time 24 hours after administration post-dose estimated by the method of interpolation. If nominal time 24 hours after administration > t (or if the concentration at time 24 hours after administration was below then limit of quantification), then the concentration (y) at time 24 hours after administration is estimated using lambda_z and last observed Ct according to the formula: y=Ct(obser) x e-lambda_z(24-t) Then the following equation will be used to calculate (AUC(0-24)) where t is the time of last quantifiable plasma concentration. AUC(0-24) = AUC(0-t) + AUC(t-24) If lambda_z is not estimable, a partial AUC is not calculated (when 24 > t).
AUC(0-inf∞)	Area under the concentration-time curve from zero time (pre-dose) extrapolated to infinite time (AUC(0-inf)) will be calculated as follows: AUC(0-inf) = AUC(0-t) + Ct / lambda_z.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
Ctrough	Trough observed concentration, will be obtained directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **$t_{1/2} = \ln 2 / \lambda_z$** (NOTE: λz is the terminal phase rate constant).

NOTES:

- Additional parameters may be included as required.

7.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

There are no planned statistical analyses.

8. SECONDARY STATISTICAL ANALYSES

8.1. Safety Analyses

8.1.1. Overview of Planned Safety Analyses

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

Table 5 provides an overview of the planned analyses, with full details being presented in Appendix 8: List of Data Displays.

Table 5 Overview of Planned Safety Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events								
All AE's	Y			Y				
All Drug-Related AE's	Y							
Serious AE's	Y			Y				
Non Serious AE's	Y							
Withdrawal AE's	Y			Y				
Laboratory Values								
Clinical Chemistry					Y			
Hematology					Y			
Urinalysis	Y							
ECG's								
ECG Findings	Y							
ECG Values	Y				Y			
Vital Signs								
Vitals Values					Y			
Emergent Vital Signs				Y	Y			
Spirometry								
FEV1	Y			Y	Y			
FVC	Y			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.

8.1.1.1. Statistical Analysis of Safety Parameters

There are no planned statistical analyses.

9. REFERENCES

GlaxoSmithKline Document Numbers 2017N316562_00 (Original 04-APR-2017): A randomised, double-blind, parallel group study to evaluate the safety, tolerability and pharmacokinetics of a single dose of GSK2269557 administered via the ELLIPTA dry powder inhaler to healthy participants).

10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Time and Events
Section 10.2	Appendix 2: Treatment States & Phases
Section 10.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.4	Appendix 4: Derived and Transformed Data • General • Study Population • Safety
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
Section 10.6	Appendix 6: Values of Potential Clinical Importance • Laboratory Values • ECG • Vital Signs
Other RAP Appendices	
Section 10.7	Appendix 7: Abbreviations & Trade Marks
Section 10.8	Appendix 8: List of Data Displays

10.1. Appendix 1: Time & Events

10.1.1. Protocol Defined Time & Events

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
Informed consent	X							
Inclusion and exclusion criteria	X							Recheck clinical status before randomization
Demography	X							
Full physical examination including height and weight	X							
Medical history (includes substance usage and current medical conditions)	X							Substances: Drugs, Alcohol, tobacco and caffeine
Urine pregnancy test (WOCBP only)	X	X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
HIV, Hepatitis B and C screening	X							If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Admission to unit		X						
Outpatient visit					X	X		
Discharge				X				
Laboratory assessments (include liver chemistries)	X	X		X				
Urine Drug, Alcohol and Smoking breath test	X	X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
12-lead ECG	X		X	X				Screening only: ECG in triplicate Day 1: pre-dose, 5 mins & 6 hrs post-dose Day 2: before discharge
Vital signs	X		X	X				Screening only: VS in triplicate Day1: pre-dose, 1h and 6h post-dose
FEV1 and FVC (triplicate)	X		X					Day 1: pre-dose, 30 min post-dose
Brief physical examination		X						

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
Inhaler training		X						Training conducted by reviewing the Patient Information Leaflet with the participant. Additional training may be conducted at the discretion of the investigator.
Dosing study treatment			X					
AE review			←==========	==========	==========	==========	==========→	
SAE review	←==========	==========	==========	==========	==========	==========	==========→	
Concomitant medication review			X	X	X	X	X	
Pharmacokinetic blood sample			X	X	X	X		Day 1: pre-dose, 5 min and 0.5, 2, 6 and 12 hours post-dose. Day 2: 24 hours post-dose. Day 3: 48 hours post-dose Day 6: 120 hours post dose.

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

- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF

10.2. Appendix 2: Treatment States and Phases

10.2.1. Treatment Phases

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

Treatment Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start date < Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

10.2.2. Treatment States

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

10.2.2.1. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before the treatment stop date Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date [+ 1]
Post-Treatment	If AE onset date is after the treatment stop date AE Start Date > Study Treatment Stop Date
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
Duration (Days)	AE Resolution Date – AE Onset Date + 1
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.

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	GSK2269557 500 mcg	GSK2269557 500 mcg	1
B	GSK2269557 750 mcg	GSK2269557 750 mcg	2

NOTES:

1. Order in which treatments are to be presented in Tables, Figures and Listings.

10.3.2. Baseline Definition & Derivations

10.3.2.1. Baseline Definitions

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

10.3.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.3.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.3.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: \arprod\gsk2269557\mid207674\final_01
QC Spreadsheet	: \ARWORK\gsk2269557\ mid207674\Final_01\Documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards	
Generation of RTF Files	
• RTF files for tables will be generated.	

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	
• 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 and figures: o Planned time relative to dosing will be used in figures and summaries 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. 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 and summaries.	
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 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary	N, n, geometric mean, 95% CI of geometric mean, standard deviation

Reporting Standards	
Statistics. (Log Transformed)	(SD) of logged data and between geometric coefficient of variation (CVb (%)) will be reported. CVb (%) = √ (exp(SD2) - 1) * 100 [NOTE: SD = SD of log transformed data]
Parameters Not Being Log Transformed	tmax, first point, last point and number of points used in the determination of Lambda_z.
Parameters Not Being Summarised	Additionally include tmax, first point, last point and number of points used in the determination of Lambda_z.
Listings	Include the first point, last point and number of points used in the determination of Lambda_z.
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

10.4. Appendix 4: Derived and Transformed Data

10.4.1. 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.

FEV1 and FVC measurements

- FEV1 and FVC measurements are to be taken in triplicate, the maximum of the values entered at one time point will be used for the summaries and listings of FEV1 and FVC

Study Day

- Calculated as the number of days from randomisation date :
  - Ref Date = Missing → Study Day = Missing
  - Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  - Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

10.4.2. Study Population

Demographics

Age

- GSK standard algorithms will be used for calculating age where birth date is imputed as:
  - 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.

10.4.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : $$RR = \left[\left(\frac{QT}{QTcB}\right)^{2}\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcB}\right)^{3}\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be collected values THEN do not derive.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals using Bazett's (QTcB) and Fridericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Adverse Events
• MedDRA version 20.0 will be used for coding of AE's.

10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion is defined as subjects who receive study treatment and complete all post dose assessments, including the Follow Up Phone Call. • Withdrawn subjects maybe replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.5.2. 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.

10.5.2.1. 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 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

Element	Reporting Detail
	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. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

10.5.2.2. 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:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
	  • However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date.
	  • The AE will then be considered to start on-treatment (worst case).
	  • 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.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. 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)**
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

10.6.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
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	
	msec	> 30	≤ 59

10.6.3. 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

10.7. Appendix 7 - Abbreviations & Trade Marks

10.7.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
APE	All Participants Enrolled
AUC(0-24)	Area Under the Plasma Drug Concentration versus Time Curve from zero to 24 hours
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
BMI	Body mass index
CI	Confidence Interval
Cmax	Maximum observed concentration
Ctrough	Concentration at trough
CV	Coefficient of variance
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
hrs	Hours
IDSL	Integrated Data Standards Library
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Micrograms
msec	Milliseconds
NQ	Non Quantifiable
PK	Pharmacokinetic
QTc	Corrected QT interval
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event(s)
SAS	Statistical Analysis Software
SD	Standard Deviation
T1/2	Terminal Half-life
Tmax	Time to maximum observed plasma drug concentration
WOCBP	Women of Child Bearing Potential

10.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ELLIPTA
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

10.8. Appendix 8: List of Data Displays

10.8.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.8	N/A
Safety	2.1 to 2.17	N/A
Pharmacokinetic	3.1 to 3.4	3.1 to 3.2
Section	**Listings**	
ICH Listings	1 to 28	
Other Listings	N/A	

10.8.2. Deliverable [Priority]

Delivery [Priority] [1]	Description
SAC [1]	Statistical Analysis Complete

NOTES:

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

10.8.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1	Safety	ES1	Summary of Subject Disposition		SAC [1]
1.2	APE	ES6	Summary of Reasons for Screening Failure		SAC [1]
1.3	Safety	DV1	Summary of Important Protocol Deviations		SAC [1]
Demographics					
1.4	Safety	SP1	Summary of Study Populations		SAC [1]
1.5	Safety	DM1	Summary of Demographic Characteristics		SAC [1]
1.6	Safety	DM11	Summary of Age Ranges		SAC [1]
1.7	Safety	DM5	Summary of Race and Racial Combinations		SAC [1]

10.8.4. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1	Safety	CP_AE1p	Summary of All Adverse Events		SAC [1]
2.2	Safety	CP_AE1p	Summary of All Drug-Related Adverse Events	Include total column.	SAC [1]
2.3	Safety	CP_AE1p	Summary of Serious Adverse Events		SAC [1]
2.4	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC [1]
2.5	Safety	CP_AE1p	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study		SAC [1]
Labs					
2.6	Safety	LB1	Summary of Chemistry Changes from Baseline		SAC [1]
2.7	Safety	LB17	Summary of Emergent Chemistry Results by Potential Clinical Importance (PCI) Criteria		SAC [1]
2.8	Safety	LB1	Summary of Haematology Changes from Baseline		SAC [1]
2.9	Safety	LB17	Summary of Emergent Haematology Results by Potential Clinical Importance (PCI) Criteria		SAC [1]

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10	Safety	UR3b (LB1)	Summary of Urinalysis Results by Planned Timepoint	Use shell UR3b for: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase as these are collected by dipstick Use shell LB1 for: Specific gravity	SAC [1]
ECGs					
2.11	Safety	EG1	Summary of ECG Findings		SAC [1]
2.12	Safety	EG2	Summary of ECG Values		SAC [1]
2.13	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC [1]
Vital Signs					
2.14	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC [1]
2.15	Safety	VS7	Summary of Emergent Vital Signs Results by Potential Clinical Importance (PCI) Criteria		SAC [1]
Spirometry					
2.16	Safety		Summary of Spirometry (FVC and FEV1)	See example: uk1salx00175/gsk2269557/mid205759/final/ Table 2.35	SAC [1]
2.17	Safety		Summary of Change from Baseline in Spirometry (FVC and FEV1)	See example: uk1salx00175/gsk2269557/mid205759/final/ Table 2.38	SAC [1]

10.8.5. Pharmacokinetic Tables

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1	PK	PK01	Summary of Plasma GSK2269557 Pharmacokinetic Concentration-Time Data		SAC [1]
3.2	PK	PK01	Summary of Plasma GSK2269557 Pharmacokinetic Concentration-Time Data (log transformed)		SAC [1]
PK Derived Parameters					
3.3	PK	PK03	Summary of Derived Plasma GSK2269557 Pharmacokinetic Parameters	Parameters with units	SAC [1]
3.4	PK	PK05	Summary of Log-Transformed Derived Plasma GSK2269557 Pharmacokinetic Parameters	Parameters with units	SAC [1]

10.8.6. Pharmacokinetic Figures

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1	PK	PK16	Individual GSK2269557 Plasma Concentration-Time Plot by Subject (Linear and Semi-log)	Paginate by Subject	SAC [1]
Mean / Median Concentration Plots					
3.2	PK	PK20	Median (range) Plasma GSK2269557 Concentration-Time Plots (Linear and Semi-log)	Paginate by Treatment	SAC [1]

10.8.7. ICH Listings

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomisation					
1	Safety	CP_TA1	Listing of Randomised and Actual Treatments		SAC [1]
Subject Disposition					
2	Safety	ES2	Listing of Reasons for Study Withdrawal		SAC [1]
3	APE	ES7	Listing of Reasons for Screening Failure		SAC [1]
4	Safety	BL1	Listing of Subjects for Whom the Treatment Blind was Broken		SAC [1]
5	Safety	SP3	Listing of Subjects Excluded from PK Population		SAC [1]
6	Safety	DV2	Listing of Important Protocol Deviations		SAC [1]
7	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC [1]
Demographics					
8	Safety	DM2	Listing of Demographic Characteristics		SAC [1]
9	Safety	DM9	Listing of Race		SAC [1]
Prior and Concomitant Medications					
10	Safety	CP_CM3	Listing of Concomitant Medications		SAC [1]
11	Safety	MH2	Listing of Current and/or Past Medical Conditions		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
12	Safety	EX3	Listing of Exposure Data		SAC [1]
Adverse Events					
13	Safety	AE7	Listings of Subject Numbers for Individual Adverse Events		SAC [1]
14	Safety	AE8	Listing of All Adverse Events		SAC [1]
15	Safety	AE8	Listing of Serious Adverse Events		SAC [1]
16	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC [1]
LABS					
17	Safety	CP_LB5	Listing of All Clinical Chemistry Laboratory Data for Subjects with PCI Abnormalities		SAC [1]
18	Safety	CP_LB5	Listing of All Haematology Laboratory Data for Subjects with PCI Abnormalities		SAC [1]
19	Safety	CP_LB5	Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance		
20	Safety	CP_LB5	Listing of Haematology Abnormalities of Potential Clinical Importance		
ECGs					

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
21	Safety	CP_EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC [1]
22	Safety	CP_EG3	Listing of ECG Values of Potential Clinical Importance		SAC [1]
23	Safety	CP_EG5	Listing Abnormal ECG Findings		SAC [1]
Vital Signs					
24	Safety	CP_VS4	Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance		SAC [1]
25	Safety	CP_VS4	Listing of Vital Signs of Potential Clinical Importance		SAC [1]
Spirometry					
26	Safety		Listing of Spirometry (FEV1 and FVC)	See example: uk1salx00175/gsk2269557/mid205759/final/ Listing 61	SAC [1]
PK					
27	PK	PK07	Listing of GSK2269557 Plasma Pharmacokinetic Concentration-Time Data		SAC [1]
28	PK	PK13	Listing of Derived Plasma GSK2269557 Pharmacokinetic Parameters		SAC [1]