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

Title	:	Reporting and Analysis Plan for GSK2983559 First time in human study 205021: A single-centre, randomised, double-blind (sponsor open), placebo controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK2983559, in single (in both fed and fasted states) and repeat oral doses in healthy participants
Compound Number	:	GSK2983559
Effective Date	:	25-NOV-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2017N322016_02.
- This RAP is intended to describe the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK2983559, in single (in both fed and fasted states) and repeat oral doses in healthy participants.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables.

RAP Author(s):

Approver	Date	Approval Method
PPD Statistics Leader (II Biostatistics)	14-Oct-2019	Author/Email
PPD Programming Manager (II Clinical Programming)	17-Oct-2019	Email

RAP Team Approvals:

Approver	Date	Approval Method
PPD Scientist Director (II Discovery Medicine)	14-Oct-2019	Email
PPD Director (II Clinical Pharmacology Modelling & Simulation)	17-Oct-2019	Email
PPD Global Clinical Development Manager (II Global Clinical Sciences and Delivery)	15-Oct-2019	Email

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Senior Statistics Director (II Clinical Statistics)	25-Nov-2019	eSignature CARS
PPD Programming Manager (II Clinical Programming)	22-Nov-2019	eSignature CARS

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 205021:

Revision Chronology:		
2017N322016_00	06-OCT-2017	Original
2017N322016_01	17-OCT-2017	Original Protocol Republishing
2017N322016_02	24-JUL-2018	Formulation change to enteric capsule

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

This study was terminated during Cohort 2 of Part A. Participants in Cohort 2 received only 2 of 4 planned single doses.

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

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	**Reporting & Analysis Plan**	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Part A (single dose): Dose proportionality will be assessed by visual inspection of dose normalised AUC(0 ∞) [or if not available AUC(0-t)] and Cmax values versus dose. Analysis of these loge-transformed parameters may be carried out, using the power model.	• Summary of dose normalised PK parameters will be replaced by summary of PK parameters • No analyses of log-transformed data will be conducted	• Study terminated prior to full dose escalation completion
• Part A (food effect): The ratio of fed state to fasted state may be assessed for the loge-transformed parameters AUC(0-∞) [or if not available AUC(0-t)] and Cmax. The effect of food will be assessed utilising a mixed effects model, with fed state (fasted or fed) as a fixed effect and participant as a random effect	• No food effect summaries or statistical analyses	• Study terminated prior to fed dosing period
• Part B: The extent of accumulation after repeat	• No Part B summaries or statistical analyses	• Study terminated prior to Part B multiple ascending

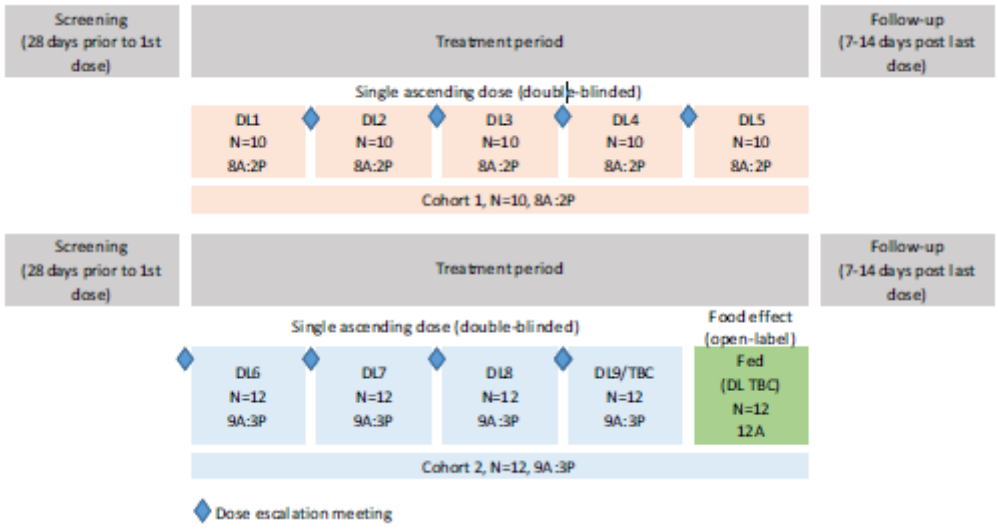
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
dosing, the observed accumulation ratio (Ro), may be determined. The plasma steady state ratio (Rs) and an assessment of plasma steady state across the trough concentrations may also be made. Dose proportionality may be assessed using similar methods to the single dose Part A.		dose cohorts
• For combined 5-ABT and NAc-5-ABT (corrected to 5-ABT), observed Cmax and Tmax will be determined using non-compartmental methods and will be summarised descriptively	• 5-ABT and NAc-5-ABT (corrected to 5-ABT) concentrations will be listed. No PK parameters will be produced	• Limited number of subjects with quantifiable 5-ABT and NAc-5-ABT PK concentrations to warrant summaries or PK parameter derivations
• To investigate the metabolic profile of GSK2983559 following single and/or repeat doses in healthy participants in urine	• No urine data will be reported	• Data is no longer planned due to study termination prior to urine samples being analysed

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the safety and tolerability of single (fed and fasted) and repeat doses of GSK2983559 in healthy participants.	• Safety and tolerability of GSK2983559 as assessed by clinical monitoring and reporting of adverse events and serious adverse events, change in laboratory values, ECG, vital signs, physical examinations.
Secondary Objectives	**Secondary Endpoints**
• To characterise the PK profile of single (fasted) doses of GSK2983559 and its active moiety GSK2668176 in healthy participants.	• Derived PK parameters for GSK2983559 and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single (fasted) doses, where data allow.
• To characterise the PK profile of repeat doses of GSK2983559 and its active	• Derived PK parameters for GSK2983559 and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$,

Objectives	Endpoints
moiety GSK2668176 in healthy participants.	$AUC_{(0-T)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single and repeat doses, and estimation of an accumulation ratio where data allow.
• To assess the effect of food on the pharmacokinetics of GSK2983559 and its active moiety GSK2668176 in fasted and fed state in healthy participants.	• Derived PK parameters for GSK2983559, and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single (fed and fasted) dose, where data allow.
Exploratory Objectives	**Exploratory Endpoints**
• To determine the PD effect of single and repeat doses of GSK2983559 in healthy participants.	• PD/biomarker endpoints may include, but not be limited to, assessments of pharmacologic effects through measurements of target engagement and pathway activation. These may include measurements of RIP-2 receptor occupancy, and levels of MIP1α, MIP1β and TNF proteins, following stimulation of whole blood, as data permit. (Cohort 1 subjects only)
• To investigate the metabolic profile of GSK2983559 following single and/or repeat doses in healthy participants in blood and urine	• Identification and quantitative estimates of GSK2983559 and its active moiety GSK2668176 and potential metabolites following single and repeat doses in plasma and urine.
• To characterize exposure to 5-ABT and NAc-5-ABT after single and repeated doses of GSK2983559 in healthy participants.	• Concentration of 5-ABT and NAc-5-ABT (adjusted to 5-ABT concentration based on molecular weight (MW)) and derive Cmax for the combined concentration curve of 5-ABT and MW adjusted NAc-5-ABT

2.3. Study Design

Overview of Study Design and Key Features – Part A Single Ascending Dose	
	
Design Features	• Separate participants will be enrolled into both cohorts of Part A. • **Cohort 1 Standard Capsule**: 5-way crossover design. Each participant will receive single ascending oral doses of either GSK2983559 or placebo in a 4:1 ratio according to the randomisation schedule, in study periods 1 to 5, in a blinded manner. • **Cohort 2 Enteric Capsule**: 4-way crossover design for single ascending dose, including an additional period for assessing GSK2983559 under fed conditions (period 5 – open-label). • During the blinded part, each participant will receive single ascending oral doses of either GSK2983559 or placebo in a 3:1 ratio according to the randomisation schedule, in study periods 1 to 4, in a blinded manner. • Cohorts 1 and 2 will be dosed sequentially, incorporating sentinel participants: Cohort 1 will complete all 5 dosing periods before Cohort 2 begins. • Following completion of Cohort 1 and before starting Cohort 2, a GSK internal safety board (independent of DEC) will be reviewing the data. • Based on emerging PK data, all doses may not be investigated. • There will be a at least 48-hour washout period between each dose escalation step but the washout period may be extended depending on emerging data.
Dosing	• Participants will be randomised on Day 1 followed by a single oral dose of GSK2983559 • Sentinel dosing will be employed within each ascending dose cohort and treatment period (except for when investigating the food effect). • On Day 1, one participant will receive GSK2983559 and one participant will receive matched-placebo, to evaluate tolerability and safety for at least 24 hours post-dose. • Dosing in the remaining 8 and 10 participants in Cohorts 1 and 2, and treatment period will occur at least 24 hours later after review of safety results from the initial

<table>
<tr><th colspan="2">Overview of Study Design and Key Features – Part A Single Ascending Dose</th></tr>
<tr><td></td><td>2 participants in a 7:1 and 4:1 ratios (GSK2983559: placebo) for Cohorts 1 and 2, respectively</td></tr>
<tr><td>Time & Events</td><td>• Refer to Appendix 2: Schedule of Activities</td></tr>
<tr><td>Treatment Assignment</td><td>
• At screening a unique number (case report form [CRF] number) will be assigned to any participant who has at least one Screening procedure performed, other than signed informed consent. The unique number will be used to identify individual participants during the course of the study.

• Participants who meet the screening eligibility criteria will be randomised to a treatment group through an Interactive Response Technology (IRT). The IRT will confirm the participants CRF number and provide the randomisation number, where, a randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other participant in the study.

• The randomisation is centrally controlled by the IRT.

Part A

Within Cohort 1, participants will be assigned to one of 5 dosing sequences in a 1:1:1:1:1 ratio.

Within Cohort 2, participants will be assigned to one of up to 4 dosing sequences in a 1:1:1:1 ratio.

<table>
<tr><th></th><th>Cohort 1</th><th>Cohort 2</th></tr>
<tr><td>Sequence</td><td>PBCDE
APCDE
ABPDE
ABCPE
ABCDP</td><td>PGHIJ
FPHIJ
FGPIJ
FGHPJ</td></tr>
</table>

Participants will be randomised to:
</td></tr>
</table>

<table>
<tr><th colspan="2">Overview of Study Design and Key Features – Part A Single Ascending Dose</th></tr>
<tr><td></td><td>
<table>
<tr><th>Treatment code</th><th>Original Planned Treatment Description</th><th>Cohort 1 Actual Treatment & Cohort 2 Planned Treatment Description</th></tr>
<tr><td>A</td><td>2 mg GSK2983559</td><td></td></tr>
<tr><td>B</td><td>10 mg GSK2983559</td><td>4 mg GSK2983559</td></tr>
<tr><td>C</td><td>30 mg GSK2983559</td><td>10 mg GSK2983559</td></tr>
<tr><td>D</td><td>75 mg GSK2983559</td><td>30 mg GSK2983559</td></tr>
<tr><td>E</td><td>150 mg GSK2983559</td><td>100 mg GSK2983599</td></tr>
<tr><td>F</td><td>300 mg GSK2983559</td><td>200 mg GSK2983599</td></tr>
<tr><td>G</td><td>600 mg GSK2983559</td><td>400 mg GSK2983559</td></tr>
<tr><td>H</td><td>800 mg GSK2983559</td><td>600 mg GSK2983559</td></tr>
<tr><td>I</td><td>Dose TBC GSK2983559</td><td>Dose TBC GSK2983559</td></tr>
<tr><td>J</td><td>GSK2983559 Fed</td><td>GSK2983559 Fed</td></tr>
<tr><td>P</td><td>Placebo</td><td></td></tr>
</table>
</td></tr>
<tr><td>Interim Analysis</td><td>• No Interim Analysis were conducted due to study termination</td></tr>
</table>

<table>
<tr><th colspan="2">Overview of Study Design and Key Features – Part B Multiple Ascending Dose</th></tr>
<tr><td></td><td>• Study terminated prior to Part B start, please refer to protocol for exact details</td></tr>
<tr><td>Treatment Assignment</td><td>• Part B treatment codes were planned to be:
<table>
<tr><th>Treatment code</th><th>Treatment Description</th></tr>
<tr><td>K</td><td>Dose 1 GSK2983559</td></tr>
<tr><td>L</td><td>Dose 2 GSK2983559</td></tr>
<tr><td>M</td><td>Dose 3 GSK2983559</td></tr>
<tr><td>N</td><td>Dose 4 GSK2983559</td></tr>
<tr><td>P</td><td>Placebo</td></tr>
</table>
</td></tr>
</table>

2.4. Statistical Hypotheses / Statistical Analyses

The objectives of this study are to assess the safety and tolerability of single and repeat ascending doses of GSK2983559 in healthy volunteers. No formal hypotheses will be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

Dose escalation meetings occurred after each period in Part A and were scheduled to occur following the completion of 14 days dosing of each cohort in Part B. The decision to proceed to the next cohort and next dose strength to be studied, was made by the Dose Escalation Committee (DEC) based on assessment of blinded safety (e.g., AEs, clinical laboratory results, vital signs and ECG), active moiety (GSK2668176) pharmacokinetic and 5-ABT concentrations obtained in all participants at the prior dose level. Individual safety data (adverse events, laboratory safety tests, ECGs and vital signs) was reviewed. This study was double blind (sponsor open), where the participant, investigator and site staff will remain blinded to the treatment allocation. Sponsor open refers only to those members of the DEC as required.

Following completion of Cohort 1: Part A and before starting Cohort 2: Part A, a GSK internal safety board (independent of DEC) reviewed the emerging PK and safety data.

A formal interim analysis was due to be performed during the study on completed cohorts in Part A of the study to aid internal decision making only. The study was terminated prior to completion of Part A.

3.2. Final Analyses

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

All participants have completed the study as defined in the protocol or the study is terminated.

All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

All criteria for unblinding the randomisation codes have been met.

Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility	Screen Failure Population Analysed.
Randomised	All participants who were randomly assigned to treatment in the study. This population will be based on the treatment the participant was randomised to.	Age ranges
Safety	All randomised participants who received at least one dose of study treatment. This population will be based on the treatment the subject actually received. Note: Participants who were not randomised but received at least one dose of study treatment should be listed.	All other Study Population Safety
Pharmacokinetic (PK)	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). This population will be based on the treatment the participant actually received.	PK

Refer to Appendix 10: List of Data Displays which details the population used for each display.

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 Version 2 (08-Feb-2018).

- 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

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	GSK2983559 single dose 1	GSK 2 mg	2
B	GSK2983559 single dose 2	GSK 4 mg	3
C	GSK2983559 single dose 3	GSK 10 mg	4
D	GSK2983559 single dose 4	GSK 30 mg	5
E	GSK2983559 single dose 5	GSK 100 mg	6
F	GSK2983559 single dose 6	GSK 200 mg E	7
G	GSK2983559 single dose 7	GSK 400 mg E	8
H	GSK2983559 single dose 8	GSK XX mg E [1]	Not used
I	GSK2983559 single dose 9	GSK XX mg E [1]	Not used
J	GSK2983559 fed single dose	Not Used	Not used
P	Placebo single dose	Placebo	1
K	GSK2983559 repeat dose 1	Not Used	Not used
L	GSK2983559 repeat dose 2	Not Used	Not used
M	GSK2983559 repeat dose 3	Not Used	Not used
N	GSK2983559 repeat dose 4	Not Used	Not used
Q	Placebo repeat dose	Not Used	Not used

1. Dose level not required as the study was terminated prior to being utilised

5.2. Baseline Definitions

- For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.
- For Part A, baseline definitions defined in the table are applicable to each treatment period.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing. The mean of triplicate measurements at any given time point will be used as the value for that time point unless otherwise stated.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Clinical Chemistry/ Haematology/ Urinalysis	X	X	X	Day 1
12-lead ECG	X	X [1]	X [1]	Day 1
Vital Signs	X	X	X [1]	Day 1
Pharmacokinetic				
PK Concentrations			X	Day 1
Pharmacodynamic				
PD Blood sample			X	Day 1
Target Engagement sample			X	Day 1

[1] ECG/Vital signs recordings will be performed in triplicate at visit. Use the mean of the triplicate measurements.

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

5.3. Multicentre Studies

This is a single centre study.

5.4. Examination of Covariates, Other Strata and Subgroups

There are no covariates, strata or subgroups to be investigated in this study.

5.5. Multiple Comparisons and Multiplicity

No adjustments for multiplicity will be required.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

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

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the “Screened” or “Randomised” population, unless otherwise specified.

Study population analyses including analyses of subject’s disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

7. SAFETY ANALYSES

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

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

8. PHARMACOKINETIC ANALYSES

8.1. Primary Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

PK plasma concentration-time data for the prodrug GSK2983559 and active moiety GSK2668176 will be listed, no statistical analysis will be conducted. Summary statistics of the prodrug GSK2983559 and active moiety GSK2668176 concentrations by nominal blood sampling time will be determined.

PK data will be summarised for Parts A by randomised treatment.

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

Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log-transformed			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Pharmacokinetic								
Plasma Drug concentration	Y	Y[1][2]	Y[1]	Y				

NOTES:

- T = Table, F = Figure, L = Listings, Y = 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 participant observed raw data.

1: Linear and Semi-Log plots will be created on the same display.
2: Separate Mean (± SE) and Median plots will be generated.

PK plasma concentrations for 5-ABT and N-Ac-5-ABT (adjusted to 5-ABT concentration based on molecular weight (MW)) will be listed, no statistical analysis will be conducted.

8.1.1.1. Drug Concentration Measures

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

8.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the prodrug GSK2983559 and active moiety GSK2668176 concentration-time data, as data permits.

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-inf)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / 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
t1/2	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**

NOTES:

- Additional parameters may be included as required.

8.1.2. Summary Measures

- The pharmacokinetic profile following a single dose of GSK2983559
- Derived PK parameters for GSK2983559 and active moiety GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single (fasted) doses, where data allow.
- Descriptive statistics (n, arithmetic mean, standard deviation [SD] standard error [SE], 95% CI, minimum, median and maximum) will be calculated by treatment for all PK concentrations over time and for the derived PK parameters.
- In addition, for loge-transformed PK parameter variables geometric mean, 95% CI and $\%CV_b$ ($100 * \sqrt{(\exp(SD^2) - 1)}$) will be provided, where the SD is the standard deviation of log-transformed data.

8.1.3. Population of Interest

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

8.1.4. Strategy for Intercurrent (Post-Randomisation) Events

- Study completion (i.e. as specified in the protocol) was defined as completing all phases of the study including the follow-up visit.
- Withdrawn participants may be replaced in the study. Replacement participants, enrolled will be dosed with the next planned treatment of the withdrawn participant, and they will not receive any treatment that the withdrawn participant has already received with the exception of the need to increase participants numbers to obtain the minimum number of evaluable participants required for interim decisions, and to obtain data in any other treatment that is required for a valid comparison. Replacement participants will receive the required treatments in the same order as planned for the original participant.

- All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

8.2. Secondary Pharmacokinetic Analyses

8.2.1. Endpoint / Variables

5-ABT and NAc-5-ABT (adjusted to 5-ABT concentration based on molecular weight (MW)) concentrations will be listed, no statistical analysis will be conducted.

8.2.1.1. Drug Concentration Measures

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

8.2.2. Summary Measure

- Listings of 5-ABT and NAc-5-ABT (adjusted to 5-ABT concentration based on molecular weight (MW)) will also be provided

8.2.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the “Pharmacokinetic” population, unless otherwise specified.

9. PHARMACODYNAMIC ANALYSES

9.1. Exploratory Pharmacodynamic Analyses

9.1.1. Endpoint / Variables

Levels of blood MIP1α, MIP1β and TNF proteins will be summarised and listed by randomised treatment for Cohort 1 only. No statistical analyses will be conducted.

9.1.2. Summary Measure

Actual values and percentage change from baseline of blood MIP1α, MIP1β and TNF proteins will be summarised.

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9.1.3. Population of Interest

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

10. REFERENCES

None

11. APPENDICES

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

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

Screening and Follow Up SOA

Procedure	Screening	Follow-up Visit	Notes
	(up to 28 days prior to Day 1)		
Outpatient Visit	X	X	Follow-up Visit to occur approximately 7 days or 5 half lives (as determined from Part A PK data), whichever is longer, and no greater than 14 days after last study drug administration.
Informed Consent	X		
Inclusion and Exclusion Criteria	X		
Medical/medication/drug/alcohol history	X		
Demographics	X		
Full Physical Examination	X		Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).
Brief Physical Examination		X	
Drug/alc./cotinine screen	X		Tests include alcohol breath test, urine cotinine and drug screen.
HIV, Hep B and Hep C screen	X		
Tuberculosis Test	X		Conducted as standard practice of the site.
Serum Pregnancy Test (all females)	X		
FSH and estradiol (all females)	X		
Hema/Chem/Urinalysis tests	X	X	
Coagulation Panel	X		
Lipid panel (Part B only)	X		
Height and weight	X		
Holter Monitoring (24-hour)	X		
12-lead ECG	T	X	T= Triplicate
Vital signs	X	X	Vital signs to include heart rate, blood pressure, respiration rate and temperature.
Concomitant Medication Review	X	X	
AE and SAE Review		X	

Part A SOA

Procedure		Study Day (each dosing session)																	Notes
		Day -1	Day 1 (time relative to dose) See Study Reference Manual for assessment time windows														Day 2	Day 3	*Participants to be admitted to the unit the day before dosing (Day -1), and remain in house until discharge after 48-hour post-dose assessments (Day 3) are completed.*
			Pre dose	0 h	15min	30min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4hr	5hr	6hr	8 hr	10 hr	12 hr	24 hr	48 hr	
Pregnancy test (all females)		X																	
Brief Physical Examination		X															X	X	*Additional exams./screens may be performed, or brief exams made full exams. by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).*
Drug/alc./cotinine screen		X																	*Additional assessments may be performed at the discretion of the Investigator. Tests will be conducted within site specified standards.*
Heam/Chem/Coags/Urinalysis		X	X												X			X	X	*Non-fasted samples will be collected on Day -1 and at 8 hours on Day 1. Non-fasted chemistry only will be collected at 8 hour time point.*
Neuro. examination		X							X									X	X	
Telemetry			<----------																	*Continuous at least 8 hours post-dose. Initiate at least 15 min. prior to dosing*
Vital signs		X	T			X		X	X	X		X			X		X	X	X	*Vital signs to include HR, BP, respiration rate and temperature. T = Triplicate (HR and BP only) single respiration rate and temperature. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.*
12-lead ECG		T	T					X	X	X		X			X		X	X	X	
Meals	**All**	D										Per site Schedule								*Prior to dosing, participants will fast for 8 hrs overnight; no food is allowed for at least 4 hrs post-dose. Water is permitted with dosing and at all times except 1 hour pre-dose through 2-hours post-dose. Participants will receive standardized meals scheduled at the same time in each period.*
	Cohort 2, fed period	D	B																	
Study Treatment dosing				X																*A minimum interval of 30 minutes will be observed between the dosing of the first 2 participants at each dose level. A minimum interval of 15 minutes will be observed between the dosing of the remaining 6 participants.*
PK Blood Sample			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	*The number and sampling times may be adjusted once the human PK data are available.*
Urine Collection for Metabolites			X	<----------0-24 hours---------->																*Participants will void bladder prior to dosing, a sample will be kept as control. 0-24-hr urine samples will be collected.*
PD Blood Sample			X						X				X		X			X	X	*Two samples will be drawn at pre-dose. The PD sampling time points may be updated based on emerging PK data. PD samples will not be collected in the food efect part of the study.*
TE Blood Sample			X						X				X		X			X	X	*TE samples will not be collected in the food effect part of the study*
Adverse Event Review			<----------X---------->																	*See section 10.1.1 for pre-dose SAE requirements*
Concomitant Med.		<----------X---------->																		
For ECG and vital signs T=Triplicate, For Meals B=Breakfast, D=Dinner																				

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of Assessment Windows for Analyses

No Assessment Windows will be defined for Analysis, and summaries and analyses will be based on nominal visits.

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

11.4.1. Study Phases

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

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

11.4.1.1. Study Phases for Concomitant Medication

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

NOTES:

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

11.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date +1. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 • For studies with greater than one treatment period (e.g., crossover study), if AE onset is during one period and worsens during a later period it would be counted in both periods. For the initial period the logic would be as above. For the later period the logic would use the treatment dates associated with the later period: • Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date +1 day

NOTES:

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

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	UK1SALX00175
HARP Compound	One reporting effort will be set up for this study \ arenv \ arprod \ gsk2983559 \ mid205021 \final_01
Analysis Datasets	
• Analysis datasets will be created according to Legacy Integrated Data Standards Library (IDSL) GSK A&R dataset standards	
Generation of RTF Files	
• RTF files will be generated for all tables within the final_01 reporting effort.	

11.5.2. Reporting Standards

General

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

Formats
• All data will be reported according to the actual treatment the participant 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, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP’s.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject’s listings.

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

11.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to PKOne Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	Not applicable
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to PKOne

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 11.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

11.6.2. Study Population

Treatment Compliance
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)** • Planned Treatment Duration is defined as 1 day in Part A in each period
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** • Participants who were randomised 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.

11.6.3. Safety

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

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

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

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as all phases of the study including the last scheduled procedure shown in the SoA (see Appendix 2). • Withdrawn subjects may have been replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.
Liver Chemistry Stopping Criteria	• Discontinuation of study treatment for abnormal liver tests is required when: o in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant. o ALT ≥ 3 x ULN. • Note: Refer to Appendix 7 of the protocol for details of the required assessments if a participant meets the above criteria.
QTc Stopping Criteria	• A participant that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment: o QTcF > 500 msec o Change from baseline: QTcF > 60 msec
Nervous System Stopping Criteria	• A participant will be withdrawn from the study if: o A Grade 3 or greater CTCAE Nervous System finding is observed or a significant neurologic change from a participant's baseline physical examination is observed. o Any adverse event included in the CTCAE for Nervous System, which is also considered to be clinically significant by the Principal Investigator, will be reviewed for potential participant withdrawal.

11.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o 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. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.

Element	Reporting Detail
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• 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.

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Haemoglobin	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	g/L		30	
Calcium	mmol/L		2	2.75
Creatinine	umol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Phosphorus	mmol/L		<0.8	>1.6
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

11.8.2. ECG

ECG Parameter	Units	Category	Clinical Concern Range	
			Lower	Upper
Absolute				
Absolute QTc Interval	msec	H1	> 450	< 480
		H2	≥ 480	≤ 500
		H3	> 500	
Absolute PR Interval	msec	L, H	< 110	> 220
Absolute QRS Interval	msec	L, H	< 75	> 110
Change from Baseline				
Increase from Baseline QTc	msec	H1	> 30	≤ 60
		H2	> 60	

Note: PCIs will be determined for QTcF. If QTcF not available, PCIs will be determined for QTcB instead

11.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110
Respiratory Rate	breaths/min	≤ 8	≥ 20
Temperature	ºC	≤ 35.5	≥37.8

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

11.9. Appendix 9: Abbreviations & Trade Marks

11.9.1. Abbreviations

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

Abbreviation	Description
TA	Therapeutic Area
TFL	Tables, Figures & Listings

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.11	
Efficacy		
Safety	3.1 to 3.22	3.1 to 3.7
Pharmacokinetic	4.1 to 4.6	4.1 to 4.8
Population Pharmacokinetic (PopPK)		
Pharmacodynamic and / or Biomarker	6.1	6.1
Pharmacokinetic / Pharmacodynamic		
Section	**Listings**	
ICH Listings	1 to 30	
Other Listings	31 to 37	

11.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

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

11.10.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

NOTES:

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

11.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES8A	Summary of Subject Status and Reason for Study Withdrawal: Part A	ICH E3, FDAAA, EudraCT Add footnote: Note: "Subjects" is used to refer to "Participants" in all data displays to reflect GSK display standards and CDISC SDTM/ADaM standards.	SAC
1.2.	Safety	ES4	Summary of Subject Disposition at Each Study Epoch: Part A	ICH E3 Page by cohort, include treatment column for Randomised Trt Sequence and Total Column	SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure: Part A	Journal Requirements	SAC
Protocol Deviation					
1.4.	Safety	DV1	Summary of Important Protocol Deviations: Part A	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Population Analysed					
1.5.	All Subjects	SP1	Summary of Study Populations: Part A	IDSL Add the following footnotes: [1] Subjects are included in the Randomised population if they were randomly assigned to treatment in the study. [2] Subjects are included in the Safety population if they have been randomised and received at least one dose of study treatment. [3] Subjects are included in the Pharmacokinetic population if they are in the Safety Population and a pharmacokinetic sample was obtained and analysed.	SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM1	Summary of Demographic Characteristics: Part A	ICH E3, FDAAA, EudraCT Overall and by cohort Include treatment column for randomised treatment sequence and total column	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.7.	Randomised	DM11	Summary of Age Ranges: Part A	EudraCT Only include age ranges applicable to the study ('Adult (18-64 years)' and '>=65-84 years')) Please add footnote to say that randomised population=enrolled population. Overall and by cohort Include treatment column for randomised treatment sequence and total column	SAC
1.8.	Safety	DM5	Summary of Race and Racial Combinations: Part A	ICH E3, FDA, FDAAA, EudraCT Overall and by cohort Include treatment column for randomised treatment sequence and total column	SAC
Prior and Concomitant Medications					
1.9.	Safety	MH4	Summary of Current/Past Medical Conditions: Part A	ICH E3 Separate summaries for Current & Past conditions, if collected.	SAC
1.10.	Safety	CM1	Summary of Concomitant Medications: Part A	ICH E3	SAC
Exposure and Treatment Compliance					
1.11.	Safety	EX5	Summary of Exposure to Study Treatment: Part A	ICH E3	SAC

11.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term: Part A	ICH E3	SAC
3.2.	Safety	AE5A	Summary of All Adverse Events by Maximum Grade / Intensity by System Organ Class and Preferred Term: Part A	ICH E3	SAC
3.3.	Safety	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity: Part A	ICH E3 .	SAC
3.4.	Safety	AE15	Summary of Common (>=10%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences) : Part A	FDAAA, EudraCT ‘	SAC
Serious and Other Significant Adverse Events					
3.5.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) : Part A	FDAAA, EudraCT	SAC
3.6.	Safety	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term /by Overall Frequency: Part A	IDSL	SAC
Laboratory: Chemistry					
3.7.	Safety	LB1	Summary of Chemistry Changes from Baseline: Part A	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.8.	Safety	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline: Part A	ICH E3	SAC
Laboratory: Hematology					
3.9.	Safety	LB1	Summary of Hematology Changes from Baseline: Part A	ICH E3	SAC
3.10.	Safety	LB17	Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline: Part A	ICH E3	SAC
Laboratory: Urinalysis					
3.11.	Safety	LB1	Summary of Urine Concentration Changes from Baseline: Part A	ICH E3	SAC
3.12.	Safety	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline: Part A	ICH E3	
Laboratory: Hepatobiliary (Liver)					
3.13.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting: Part A	IDSL	SAC
3.14.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities: Part A	IDSL	SAC
ECG					
3.15.	Safety	EG1	Summary of ECG Findings : Part A	IDSL	SAC
3.16.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category: Part A	IDSL	SAC
3.17.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit: Part A	IDSL	SAC
3.18.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category: Part A	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.19.	Safety	VS1	Summary of Change from Baseline in Vital Signs: Part A	ICH E3	SAC
3.20.	Safety	VS3 / VS6 / VS7	Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline: Part A	IDSL	SAC
Holter					
3.21.	Safety	HM1	Summary of Holter Interpretations: Part A		SAC
3.22.	Safety	HM2	Summary of Holter Abnormalities: Part A		SAC

11.10.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE10	Plot of Common (>=10%) Adverse Events and Relative Risk: Part A	IDSL	SAC
Laboratory					
3.2.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT: Part A	IDSL	SAC
3.3.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin: Part A	IDSL	SAC
3.4.	Safety	SAFE_01	Individual Profile Plots for Liver Function Tests : Part A	Page by liver function test (ALT, AST, ALKP, BILI) Scheduled & Unscheduled Visits to be presented Panel by subject Lower reference line ULN, High Reference Line PCI as y-axis allows. Label reference line clearly on figure or in legend	SAC
3.5.	Safety	SAFE_02	Box Plot of Liver Function Tests by Period: Part A	Page by liver function test (ALT, AST, ALKP, BILI) Scheduled visits only	SAC

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	Safety	SAFE_01	Individual Profile Plots for Renal Function Tests: Part A	Page by renal function test (Blood Urea Nitrogen, Calcium, Creatinine, Gamma GT, Potassium, Sodium, Blood Glucose – fasted, Urea) Scheduled & Unscheduled Visits to be presented Panel by subject LLN and ULN to be included as y-axis allows Label reference line clearly on figure or in legend	SAC
3.7.	Safety	SAFE_02	Box Plot of Liver Function Tests by Period: Part A	Page by renal function test (Blood Urea Nitrogen, Calcium, Creatinine, Gamma GT, Potassium, Sodium, Blood Glucose – fasted, Urea) Scheduled Visits Only	SAC

11.10.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
4.1.	PK	PK01	Summary of Plasma GSK2983559 Pharmacokinetic Concentration-Time Data: Part A	Include column for 95% CI.	SAC
4.2.	PK	PK01	Summary of Plasma GSK2668176 Pharmacokinetic Concentration-Time Data: Part A	Include column for 95% CI.	SAC
Pharmacokinetic Paramaters					
4.3.	PK	PK03	Summary of Derived Plasma GSK2983559 Pharmacokinetic Parameters: Part A	Include columns for parameter, period, treatment, N, n, mean, 95% CI, standard deviation [SD], standard error [SE], median, minimum and maximum.	SAC
4.4.	PK	PK05	Summary of Log-Transformed Derived Plasma GSK2983559 Pharmacokinetic Parameters: Part A	Include columns for parameter, period, treatment, N, n, geometric mean, 95% CI of geometric mean, standard deviation [SD] of logged data and %CVb. Do not summarise Tmax.	SAC
4.5.	PK	PK03	Summary of Derived Plasma GSK2668176 Pharmacokinetic Parameters: Part A	Include columns for parameter, period, treatment, N, n, mean, 95% CI, standard deviation [SD], standard error [SE], median, minimum and maximum.	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.6.	PK	PK05	Summary of Log-Transformed Derived Plasma GSK2668176 Pharmacokinetic Parameters: Part A	Include columns for parameter, period, treatment, N, n, geometric mean, 95% CI of geometric mean, standard deviation [SD] of logged data and %CVb. Do not summarise Tmax.	SAC

11.10.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
4.1.	PK	PK16b	Individual Plasma GSK2983559 Concentration-Time Plots (Linear and Semi-log) by Subject: Part A		SAC
4.2.	PK	PK24	Individual Plasma GSK2983559 Concentration-Time Plots (Linear and Semi-log) by Treatment : Part A	Set Y-axis maximum value close to maximum concentration for each treatment	SAC
4.3.	PK	PK19	Mean (+ SD) Plasma GSK2983559 Concentration-Time Plots (Linear and Semi-log) by Treatment: Part A	One plot / cohort	SAC
4.4.	PK	PK20	Median (Range) Plasma GSK2983559 Concentration-Time Plots (Linear and Semi-log) by Treatment: Part A	One plot / cohort	SAC
4.5.	PK	PK16b	Individual Plasma GSK2668176 Concentration-Time Plots (Linear and Semi-log) by Subject: Part A		SAC
4.6.	PK	PK24	Individual Plasma GSK2668176 Concentration-Time Plots (Linear and Semi-log) by Treatment : Part A		SAC
4.7.	PK	PK19	Mean (+ SD) Plasma GSK2668176 Concentration-Time Plots (Linear and Semi-log) by Treatment: Part A	One plot / cohort	SAC
4.8.	PK	PK20	Median (Range) Plasma GSK2668176 Concentration-Time Plots (Linear and Semi-log) by Treatment : Part A	One plot / cohort	

11.10.9. PharmacodynamicTables

PharmacodynamicTables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pathway Activation					
6.1.	Safety	PD_T1	Summary of Actual and Percentage Change from Baseline Pathway Activation Markers by Randomised Treatment	Page by TNFα, MIP-1α, MIP-1β	SAC

11.10.10. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pathway Activation					
6.1.	Safety		Mean(+-SE) of Actual and Percentage Change from Baseline Pathway Activation Markers by Randomised Treatment	Page by TNFα, MIP-1α, MIP-1β	SAC

11.10.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure: Part A	Journal Guidelines	SAC
2.	Safety	ES3	Listing of Reasons for Study Withdrawal Part A	ICH E3	SAC
3.	Safety	SD3	Listing of Reasons for Study Treatment Discontinuation: Part A	ICH E3	SAC
4.	Safety	BL2	Listing of Subjects for Whom the Treatment Blind was Broken: Part A	ICH E3	SAC
5.	Safety	TA1	Listing of Planned and Actual Treatments: Part A	IDSL	SAC
Protocol Deviations					
6.	Safety : Part A	DV2A	Listing of Important Protocol Deviations	ICH E3	SAC
7.	Safety : Part A	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
8.	All Subjects (Part A)	SP3a	Listing of Subjects Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
9.	Safety : Part A	DM4	Listing of Demographic Characteristics: Part A	ICH E3 Include Weight & BMI from vitals	SAC
10.	Safety : Part A	DM10	Listing of Race: Part A	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
11.	Safety : Part A	CP_CM4	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
12.	Safety : Part A	EX4	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
13.	Safety (Part A)	AE9CP	Listing of All Adverse Events: Part A	ICH E3	SAC
14.	Safety : Part A	AE7	Listing of Subject Numbers for Individual Adverse Events: Part A	ICH E3	SAC
15.	Safety : Part A	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text: Part A	IDSL	SAC
Serious and Other Significant Adverse Events					
16.	Safety : Part A	AE9CPa	Listing of Serious Adverse Events: Part A	ICH E3	SAC
17.	Safety (Part A)	AE14	Listing of Reasons for Considering as a Serious Adverse Event: Part A	ICH E3	SAC
18.	Safety (Part A)	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment: Part A	ICH E3	SAC
All Laboratory					
19.	Safety : Part A	LB6	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance: Part A	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
20.	Safety (Part A)	LB6	Listing of Laboratory Values of Potential Clinical Importance: Part A		SAC
21.	Safety : Part A	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
22.	Safety : Part A	UR2B	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC
ECG					
23.	Safety : Part A	EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	IDSL	SAC
24.	Safety : Part A	EG4	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
25.	Safety : Part A	EG4	Listing of All ECG Changes for Subjects with Any Value of Potential Clinical Importance	IDSL	SAC
26.	Safety : Part A	EG4	Listing of ECG Changes of Potential Clinical Importance	IDSL	SAC
27.	Safety (Part A)	EG6	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding	IDSL	SAC
28.	Safety : Part A	EG6	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
29.	Safety (Part A)	VS5	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
30.	Safety (Part A)	VS5	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC

11.10.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic					
31.	Pharmacokinetic	PK08	Listing of Plasma GSK2983559 Pharmacokinetic Concentration-Time Data: Part A		SAC
32.	Pharmacokinetic	PK08	Listing of Plasma GSK2668176 Pharmacokinetic Concentration-Time Data: Part A		SAC
33.	Pharmacokinetic	PK08	Listing of Plasma 5-ABT Pharmacokinetic Concentration-Time Data: Part A		SAC
34.	Pharmacokinetic	PK08	Listing of Plasma NAc-5-ABT Pharmacokinetic Concentration-Time Data: Part A		SAC
Pharmacodynamic					
35.	Safety		Listing of Pathway Activation Markers	TNFα, MIP-1α, MIP-1β	SAC