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

Title	:	Reporting and Analysis Plan for Study 201570: Randomized, Double-blind, Placebo Controlled Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Doses (Intravenous bolus) and constant intravenous infusion over 7 Days of GSK3335065 in Healthy Adult Subjects.
Compound Number	:	GSK3335065
Effective Date	:	22-Oct-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201570
- This RAP is intended to describe the safety, tolerability, pharmacokinetic and pharmacodynamic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) for the end of study final reporting deliverable.

RAP Author(s):

Approver	Date	Approval Method
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PPD Statistician (FPD, Clinical Statistics)	10-Oct-2018	CARS eSignature
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Approver	Date	Approval Method
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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 201570 (Amendment 3):

Revision Chronology:		
2015N261138_00	14-JUN-2017	Original
2015N261138_01	11-JUL-2017	Correction of Inconsistency in text between Appendix 5 and protocol body. For further details, please see the protocol.
2015N261138_02	21-AUG-2017	Change in washout period window in Part A and minor administrative changes. For further details, please see the protocol.
2015N261138_03	29-Nov-2017	Change in post dose safety observation period, PK and PD assessment time points based on emerging PK data. For further details, please see the protocol.

Following safety review after sentinel dosing of Part A Cohort 3 (08-Feb-2018), the study was terminated because a relationship between GSK3335065 and ventricular tachycardia in a subject could not be excluded. The development of ventricular tachycardia in this subject significantly changed the risk: benefit profile.

Please note that although the RAP will use the terminology “participants”, all displays (Tables, Figures & Listings) will use the term 'Subjects'.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

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

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• To determine the safety and tolerability of GSK3335065 administered as a single IV bolus (Part A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers	• To determine the safety and tolerability of GSK3335065 administered as a single IV bolus (Part A) in healthy volunteers	• As the study is terminated following the safety review in Part A Cohort 3 Sentinel dosing, only available Part A data will be reported
• To determine the pharmacokinetic characteristics of GSK3335065 administered as a single IV bolus (Part A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers	• To determine the pharmacokinetic characteristics of GSK3335065 administered as a single IV bolus (Part A) in healthy volunteers	
• Determine dose/exposure effects of GSK3335065 on KMO inhibition (pharmacodynamics) in healthy volunteers (Part A)	• Determine dose/exposure effects of GSK3335065 on KMO inhibition (pharmacodynamics) in healthy volunteers (Part A)	

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To determine the safety and tolerability of GSK3335065 administered as a single IV bolus (Part A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers	• Adverse event / Serious Adverse event monitoring • Laboratory parameters (hematology, clinical chemistry, urinalysis) • 12-lead ECG parameters (PR, QRS, QT, QTcF, etc.) • Vital signs (systolic and diastolic blood pressure, heart rate)
Secondary Objectives	**Secondary Endpoints**
• To determine the pharmacokinetic characteristics of GSK3335065 administered as a single IV bolus (Part	• Pharmacokinetic Parameters: AUC(0 – t), AUC(0 – ∞), tlast, Cmax, Cavg, tmax, CL, V, t½

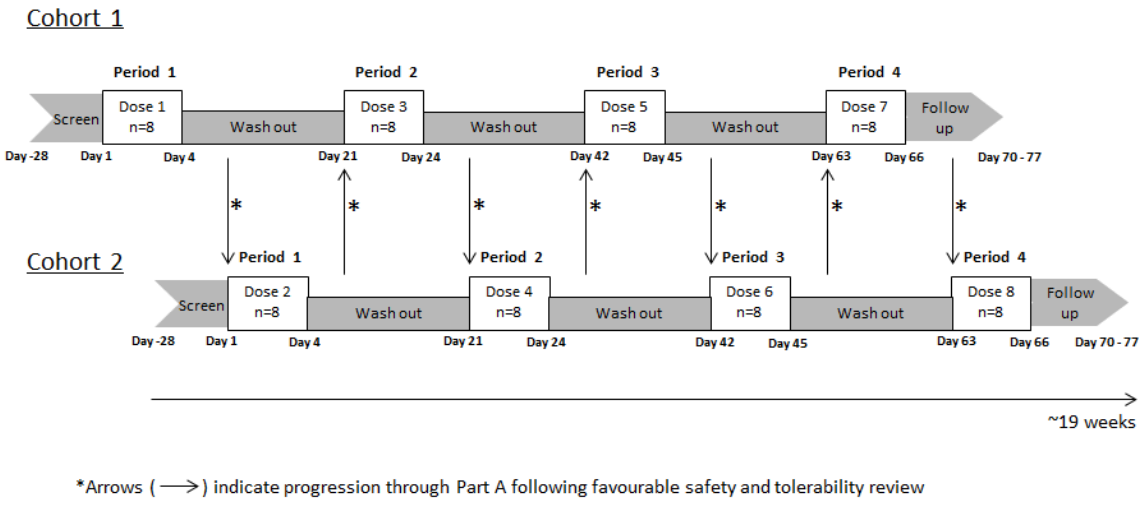
Objectives	Endpoints
A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers • Determine dose/exposure effect of GSK3335065 on KMO inhibition (pharmacodynamics) in healthy volunteers (All Parts)	• Evaluate changes in levels of TRP metabolites (3HK and KYN)
Exploratory Objectives	**Exploratory Endpoints**
• Determine the effect of KMO inhibition on other components of the KYN pathway of TRP metabolism (All Parts) • To investigate the plasma, urinary (Parts B & C) and biliary (Part B) metabolic pathways of GSK3335065 in healthy subjects	• Evaluate changes in TRP, KYNA, 3-HAT, XA, QA and other pathway components. • GSK335065-related material in plasma, urine and bile

2.3. Study Design

In Protocol Amendment 3 the design of Part A changed. As such the RAP will refer to the most recent protocol. Please refer to Protocol Amendment 2 for details of the original design.

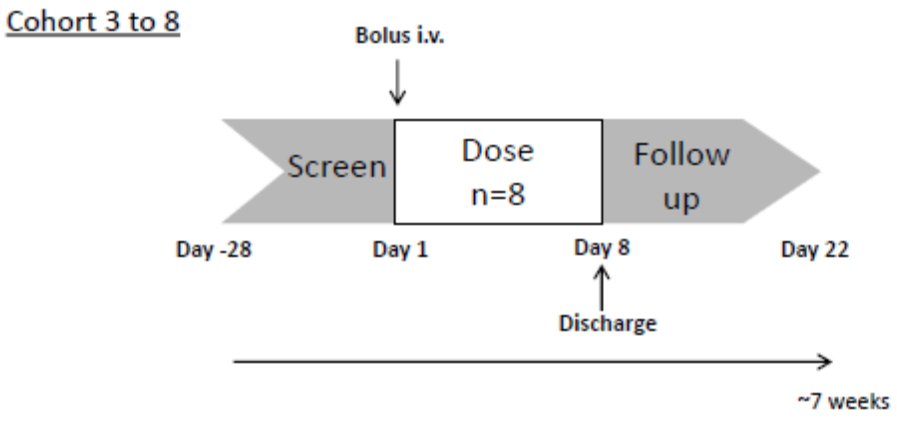
Overview of Study Design and Key Features

Part A:



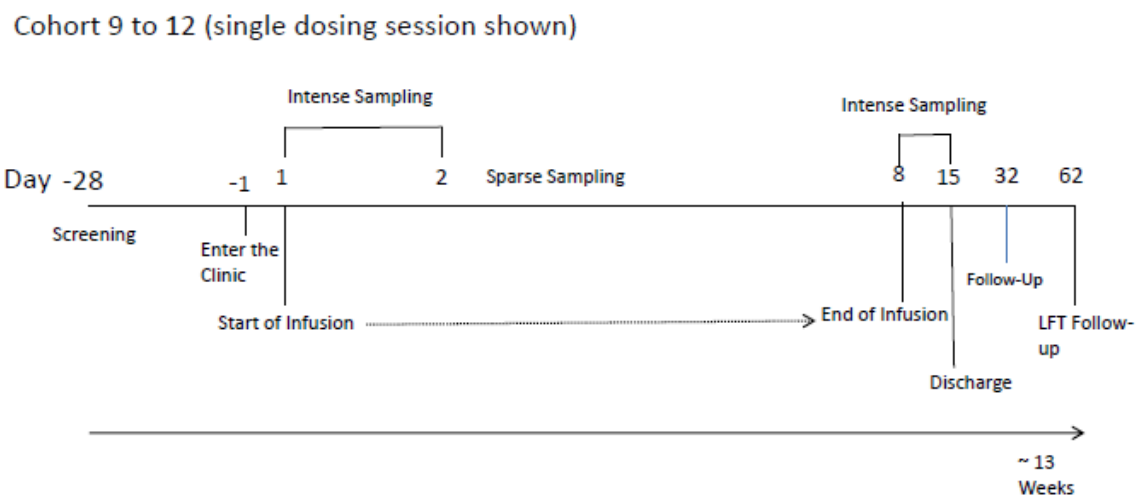
*Arrows (⟶) indicate progression through Part A following favourable safety and tolerability review

Revised Part A Schematic:

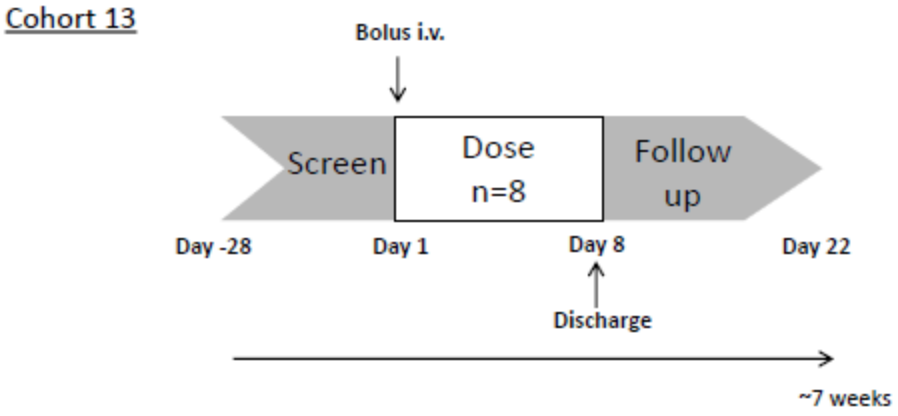


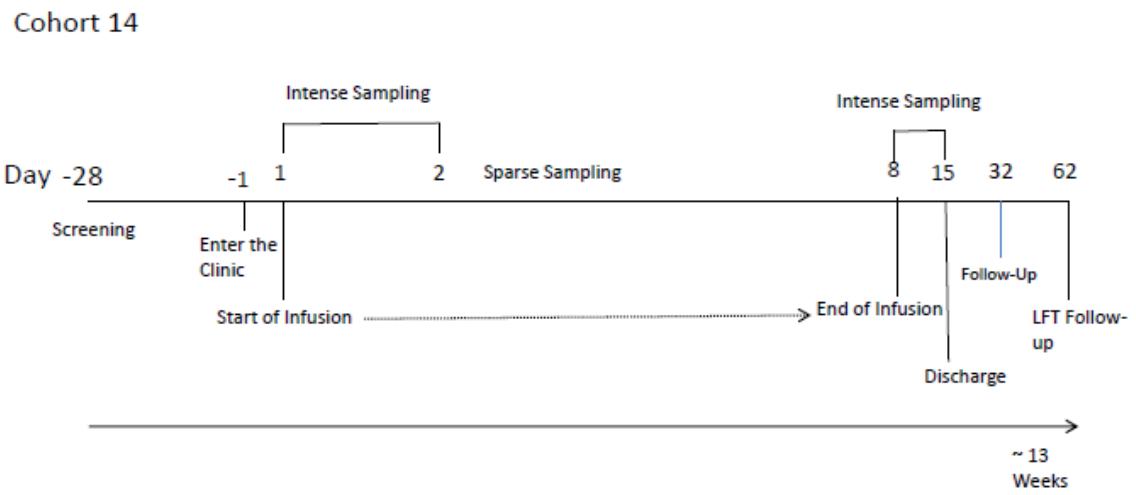
Overview of Study Design and Key Features

Part B:



Part C:



Overview of Study Design and Key Features	
	
Design Features	• Three part, randomized, placebo-controlled double blind (Sponsor unblind) dose escalation study • Adaptive design to combine Single Ascending Dose (SAD) by IV bolus (Part A) with Ascending Doses by IV constant infusion dosing for 7 days (Part B) in healthy volunteers. • Part A Cohorts 1– 8 are in a parallel group design in male participants. • Part B Cohorts are in a parallel group design in male participants • Part C will recruit WONCBP only, and a single dose by IV bolus will be investigated prior to multiple dose (7 day) being investigated, with both cohorts in a parallel group design
Dosing	**Part A:** • The first 2 subjects in each cohort will act as sentinels. • One of these subjects will be randomized to active treatment, and the other will receive placebo. At least 24 hours will elapse (relative to the start of dosing) before administration of GSK3335065 to the subsequent subjects at the same dose level to allow for assessment of potential adverse experiences. • If there are no clinically relevant safety or tolerability concerns, the remaining 6 subjects will receive the dose. • In each cohort subjects are randomized to placebo or active dose in a parallel design • Doses are administered through IV bolus

Overview of Study Design and Key Features	
	Part B: (as the study is terminated this is now not applicable) • Constant infusion dosing in Part B will be initiated after completion of dosing in Part A using an initial dose level that is considered safe and well tolerated and expected not to exceed the highest exposures safely achieved in Part A. • In all cohorts, each dose level will consist of an IV bolus subsequently followed by a continuous IV infusion for seven days. • There will be 2 sentinel subjects such that each new ascending dose will be staggered in Part B. One subject will be randomized to receive active treatment, and the other placebo. • Once these subjects have completed the 7 day dosing, the safety and tolerability data will be reviewed. If there are no clinically relevant safety or tolerability concerns, the remaining 6 subjects will be dosed. **Part C: (as the study is terminated this is now not applicable)** • Cohort 13 will investigate a single intravenous dose, and Cohort 14 will investigate a multiple dose (continuous IV infusion over 7 days) both in WONCBP only. • Cohort 13 and 14 can commence once safety, tolerability and PK data from the equivalent dose group is available from the healthy male cohort. • Cohort 13 will complete prior to cohort 14 initiation.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Subjects will be randomized to achieve a total of 112 evaluable participants • Part A will consist of 64 healthy male participants over eight cohorts. • Part B will consist of 32 healthy male participants over four cohorts • Part C will consist of 16 participants that are WONCBP over two cohorts. • Each cohort will consist of 8 participants, with 6 randomized to GSK3335065 and 2 randomized to placebo in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Overview of Study Design and Key Features	
	• For further details refer protocol for the study.
Interim Analysis	• Informal data review will be performed between dose escalation of each cohort in part A and between dose escalation in part B (multiple dose ascending phase) to support (i) whether the dose should be escalated and (ii) the next dose level. • A formal interim analysis will also occur after the completion of Part A • After the study was terminated – the interim analysis will no longer go ahead
Final Analysis	• Final analysis is planned for participants who were screened for the study prior to its termination. All data available prior to termination of the study will be reported.

2.4. Statistical Hypotheses

The main purpose of this study is to assess the safety and tolerability of single and repeated intravenous doses of GSK3335065 in healthy volunteers. No formal hypotheses are being tested and no statistical testing will be performed on the safety data.

3. PLANNED ANALYSES

3.1. Interim Analyses

Informal data review was performed between dose escalation of cohort 1 - 8 in part A and was due to be performed between dose escalation in part B (multiple dose ascending phase) to support (i) whether the dose should be escalated and (ii) the next dose level. PK and safety data (including any available PD data) was/will be reviewed. The GSK pharmacokineticist extracts PK data (including treatment information) from SMS2000 via PKHARP. Standard concentration-time graphs were/will be derived for each participant by the GSK pharmacokineticist. These parameters were/will be summarised by each dose level and will be overlaid with initial model's predictions for a comparison. The safety data was/will be listed and presented for each individual participant by treatment group.

A formal interim analysis was also planned to occur after the completion of Part A. However, a safety review was performed for cohort 3 sentinel dosing and the decision was taken to terminate the study due to the occurrence of a Suspected Unexpected Serious Adverse Reaction (SUSAR). It was clear that the risk: benefit profile for GSK3335065 in healthy volunteers had significantly altered. All data available for Part A will now be used in the final reporting.

3.2. Final Analyses

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

1. All participants screened for the study prior to its termination will be part of the final analysis.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

3.3. Changes to the Protocol Defined Statistical Analysis Plan

Table 2 details the changes and deviations to the originally planned statistical analysis specified in the protocol [(Dated: 29-Nov-2017)].

Table 2 Changes to Protocol Defined Statistical Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• An exploratory statistical analysis may be performed on the biomarker data if deemed appropriate.	• Biomarker data will be summarized	• Lack of data following study termination

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• PK/PD analysis of the biomarkers will be conducted between PD biomarkers and PK, other exploratory PK/PD analysis of the biomarkers may be conducted should changes in biomarkers be detected	• PK/PD analysis will not be conducted	

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Enrolled Population	• Defined as all subjects who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exists on the study database.	• Study Population
Screened Subjects	• Screened Subjects population will be defined as all subjects who were screened regardless of whether they were successful	• Screen failures
All Subjects	• All Subjects population will be defined as all subjects randomised to treatment who receive at least one dose of study treatment. • Subjects will be reported based on the treatment they actually received	• Study Population • Safety • PD
PK Concentration	• PK Concentration population will be defined as all subjects for whom a pharmacokinetic sample was obtained and analysed.	• PK • PK/PD
PK Parameter	• PK Parameter population will be defined as all subjects in the 'PK Concentration' population who provide pharmacokinetic parameters.	• PK

NOTES:

- Please refer to 11.10: List of Data Displays which details the population to be used for each display being generated.
- Additional populations (to those described in the protocol) have been created for the purpose of required displays

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 1 dated: 2nd August 2017.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of PIMS.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Details Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description[1]	Order[2]
Part A			
A1	Part A. Cohort 1 GSK3335065 (IV) Active Dose 1	GSK3335065 0.1 mg	2
A2	Part A. Cohort 2 GSK3335065 (IV) Active Dose 2	GSK3335065 0.25 mg	3
AA3	Part A. Cohort 3 GSK3335065 (IV) Active Dose 3	GSK3335065 1.3 mg	4
AA4	Part A. Cohort 4 GSK3335065 (IV) Active Dose 4	GSK3335065 Dose 4	5
AA5	Part A. Cohort 5 GSK3335065 (IV) Active Dose 5	GSK3335065 Dose 5	6
AA6	Part A. Cohort 6 GSK3335065 (IV) Active Dose 6	GSK3335065 Dose 6	7
AA7	Part A. Cohort 7 GSK3335065 (IV) Active Dose 7	GSK3335065 Dose 7	8
AA8	Part A. Cohort 8 GSK3335065 (IV) Active Dose 8	GSK3335065 Dose 8	9
PA1/ PA2/ PA3/ PA4/ PA5/ PA6/ PA7/ PA8[3]	Part A. Placebo Cohort 1/ Part A. Placebo Cohort 2/ Part A. Placebo Cohort 3/ Part A. Placebo Cohort 4/ Part A. Placebo Cohort 5/ Part A. Placebo Cohort 6/ Part A. Placebo Cohort 7/ Part A. Placebo Cohort 8	Placebo	1
Part B			
B9	Part B. Cohort 9 GSK3335065 (IV) Active Dose 9	GSK3335065 Dose 9	2
B10	Part B. Cohort 10 GSK3335065 (IV) Active Dose 10	GSK3335065 Dose 10	3

Treatment Details Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description[1]	Order[2]
B11	Part B. Cohort 11 GSK3335065 (IV) Active Dose 11	GSK3335065 Dose 11	4
B12	Part B. Cohort 12 GSK3335065 (IV) Active Dose 12	GSK3335065 Dose 12	5
PB9/ PB10/ PB11/ PB12	Part B. Placebo Cohort 9 / Part B. Placebo Cohort 10/ Part B. Placebo Cohort 11/ Part B. Placebo Cohort 12	Placebo	1
Part C			
C13	Part C. Cohort 13 GSK3335065 (IV) Active Dose 13	GSK3335065 Dose 13	2
C14	Part C. Cohort 14 GSK3335065 (IV) Active Dose 14	GSK3335065 Dose 14	3
PC13/ PC14	Part C. Placebo Cohort 13/ Part C. Placebo Cohort 14	Placebo	1

NOTES:
[1] As the study was terminated during Part A Cohort 3 the remaining doses are not completed
[2] Order represents treatments being presented in TFL, as appropriate.
[3] Placebo is pooled by part for all analysis except the pharmacodynamic analysis

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. GSK3335065 X.X mg vs Placebo
2. GSK3335065 Y.Y mg vs Placebo etc.

5.2. Baseline Definitions

For all endpoints apart from the PD biomarkers, the baseline value will be the latest pre-dose assessment. For the PD data, the baseline will be the average of all pre-dose measurements (incl. Day -1). Unless otherwise stated in the schedule of activities, the mean of replicate assessments at any given time point will be used as the value for that time point (e.g. for ECGs).

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

5.2.1. Derivations and Handling of Missing Baseline Data

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

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 5.2 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.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

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

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

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "Screened", "Enrolled" and "All Subjects" 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 and Table 3 provides an overview of the analysis required during interim and final reporting.

Table 3 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Status and Reason for Study Withdrawal	Y		
Reasons for Subject Withdrawal			Y
Screening Status and Reasons for Screen Failure	Y		Y
Subjects for Whom the Treatment Blind was Broken			Y
Randomized and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y
Populations Analysed			
Study Populations	Y		
Participants Excluded from any population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Age Ranges	Y		
Race and Racial Combinations	Y		Y [1]
Prior and Concomitant Medications			
Current Medical Conditions	Y		
Past Medical Conditions	Y		
Concomitant Medications	Y		Y
Exposure and Treatment Compliance			
Exposure to Study Treatment	Y		Y

NOTES:

- Y = Yes display generated at end of study only

[1] Listing of race.

7. SAFETY ANALYSES

The safety analyses will be based on the "All Subjects" 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. Table 4 provides an overview of the planned analyses.

Table 4 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by Maximum Intensity and SOC and PT	Y		Y
Common AEs (2 or more subjects) by Overall Frequency	Y		
Common Non-serious AEs (2 or more subjects) by SOC and PT (Number of Participants and Occurrences)	Y		
Drug-Related AEs by SOC and PT and Maximum Intensity	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT and Verbatim Text			Y
Assessment at Infusion site			Y
Serious and Other Significant AEs			
All SAEs	Y		Y
All SAEs by SOC and PT (Number of Participants and Occurrences)	Y		
Fatal Serious AEs			Y
Drug-Related Serious AEs	Y		
Drug-Related Fatal Serious AEs			Y
Reasons for Considering as a Serious AE			Y
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT	Y		Y

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.

Table 5 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Changes from Baseline				Y		
Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	Y					
Chemistry Results by PCI	Y					
Hematology						
Hematology Changes From Baseline				Y		
Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	Y					
Hematology Results by PCI	Y					
Urinalysis						
Urine Concentration Changes from Baseline				Y		
Worst Case Urinalysis Results Relative to Normal Range Post-Baseline Relative to Baseline	Y					
Urinalysis Results by PCI	Y					
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting	Y					
Hepatobiliary Laboratory Abnormalities	Y					
All Laboratory						
All Laboratory Data for Subjects with any Value of PCI			Y			
Laboratory Values of PCI			Y			
Laboratory Data with Character Results [1]			Y			
Urinalysis Data for Participants with Any Value of PCI			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated at end of study only, YI = Yes display generated at end of study and at interim, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Urine dipstick results

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.

Table 6 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y					
Maximum QTc Values Post-Baseline Relative to Baseline by Category	Y					
ECG Values by Visit [1]	Y		Y	Y		Y
Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	Y					
All ECG Values for Subjects with any Value of PCI			Y			
ECG Values of PCI			Y			
All ECG Findings for Participants with an Abnormal ECG Finding			Y			
Abnormal ECG Findings			Y			
Echocardiogram and Continuous ECG monitoring						
Echocardiogram Findings			Y			
ECG monitoring and Telemetry Findings			Y			
Vital Signs						
Vital Signs by Visit	Y		Y	Y		Y
Worst Case Vital Signs Results Relative to Normal Range Post-Baseline Relative to Baseline	Y					
All Vital Signs for Subjects with any Value of PCI			Y			Y
Vital Signs of PCI			Y	Y		Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated at the end of the study, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Includes continuous cardiac monitoring results

8. PHARMACOKINETIC ANALYSES

8.1. Primary Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

The pharmacokinetic (PK) parameters of interest are: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, t_{last}, C_{max}, C_{avg}, t_{max}, CL, V, and $t_{½}$.

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

The analysis will be performed by, or be under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline. PK parameters will be calculated by standard non-compartmental analysis in WinNonLin, using concentration-time data based on actual sample times, as described in the standard operating procedure SOP-314000. All derived PK parameters will be listed and summarized according to SOP-BMD-4002 (Standard Statistical Methods for the analysis of Pharmacokinetic Data).

Table 7 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: AUC = AUC(0-t) + C(t) / lambda_z
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: [AUC(0-inf) – AUC(0-t)] / AUC(0-inf) x 100
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: t½ = ln2 / lambda_z
Clearance (CL)	CL = Dose / AUC (0-inf)
Volume of Distribution at Steady State (Vdss)	Vdss = CL x MRTiv where MRTiv is Mean Residence Time and Mean Absorption Time and is given by MRTiv = (AUMC(0-inf)/AUC(0-inf)) – T/2 where T is the infusion duration

Parameter	Parameter Description
tlast	Time of the last measurable concentration, determined directly from the concentration-time data.

NOTES:

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

8.1.2. Summary Measure

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

Individual plasma GSK3335065 concentration-time profiles will be plotted by treatment (linear and semi-linear profiles). Blood sampling times will be related to the start of the infusion procedure. Actual sampling times will be used to calculate all the non-compartmental pharmacokinetic parameters. Individual concentrations of GSK3335065 in plasma will be listed and summarised by treatment and nominal time.

8.1.3. Population of Interest

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

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

No statistical analysis will be completed for the pharmacokinetic endpoints, only summary statistics. Only the single dose data is available for analysis so this section is irrelevant to the PK analysis.

8.1.5. Statistical Analyses / Methods

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

For each of the parameters mentioned above the following summary statistics will be calculated and tabulated by dose group for Part A:

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

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

9. PHARMACODYNAMIC BIOMARKER ANALYSES

9.1. Primary and Exploratory Pharmacodynamic Analyses

9.1.1. Endpoint / Variables

For KMO inhibition, the key endpoint of interest are the TRP metabolites (i.e. 3HK and KYN). As part of the exploratory analysis other metabolites such as TRP, KYNA, 3-HAT, XA, QA and other pathway components are of interest.

To investigate the metabolic pathway of GSK335065 in healthy participants, GSK335065-related material in plasma, urine and bile will be considered.

9.1.2. Summary Measure

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

9.1.3. Population of Interest

The pharmacodynamic analyses and biomarker will be based on the "All Subjects" population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

No statistical analysis will be completed for the pharmacokinetic endpoints, only summary statistics. Only the single dose data is available for analysis so this section is irrelevant to the PD analysis.

9.1.5. Other details

Due a procedural issue in analysing cohort 3 pharmacodynamic samples, cohort 3 pharmacodynamic levels cannot be compared against cohort 1 and cohort 2.

For the pharmacodynamic related displays only: participants in cohort 3 (placebo or active) will be presented separately from cohorts 1 and 2 (i.e. placebo will not be pooled across cohorts). In cohorts 1 and 2, placebo PD samples were not collected.

Please note that the Anthranilic acid (AA) and quinolinic acid (QA) metabolites were not measured and as such they will not be reported.

10. REFERENCES

PPD GlaxoSmithKline, Greenford UK, Statistics and Pharmacokinetics in Clinical Pharmacology Studies PhUSE 2006 Paper ST03

GlaxoSmithKline Document Number 2015N261138_03 201570, Randomized, Double-blind, Placebo Controlled Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Doses (Intravenous bolus) and constant intravenous infusion over 7 Days of GSK3335065 in Healthy Adult Subjects (Amendment 3 – 29-Nov-2017)

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

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

SOP_314000, Non-Compartmental Analysis of Clinical Pharmacokinetic Data

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

11. APPENDICES

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

Inclusion Criteria

Number	Inclusion Description
1	Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent. In Part C (WONCBP) participants must be between 18 and 60 years of age.
2	Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3	A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor if required agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
4	Body weight >50kg and body mass index (BMI) within the range 18.5 – 32 kg/m2 (inclusive).
5	Abstinence/contraceptives: Length of time required for abstinence or use of contraceptives should take into account the reproductive toxicity profile including genotoxicity and teratogenicity, the size of the molecule, and the number of doses. **Male participants:** A male participant must agree to use contraception as detailed in Appendix 5 of the protocol during the treatment period and for at least 2 days after the last dose of study treatment and refrain from donating sperm during this period. **Female participants:** Only female participants of non childbearing potential (WONCBP) as defined in the protocol Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information are eligible to participate.
6	Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion Criteria

Number	Inclusion Description
1	Alanine transaminase (ALT) and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
2	Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
3	QTcF >450 msec from a mean of triplicate readings taken no more than 2 minutes apart
4	Clinically significant abnormal echocardiogram
5	The participant has a history or current evidence of depression, bipolar disorder, suicidal ideation and behaviour, or a lifetime history of suicide attempt.
6	cTn or BNP >ULN
7	Use of prohibited medication (Section 7.7 & Section 7.8) of protocol
8	The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
9	Exposure to more than four new chemical entities within 12 months prior to the first dosing day
10	Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. For potent immunosuppressive agents, subjects with presence of hepatitis B core antibody (HBcAb) should also be excluded.
11	A positive pre-study drug/alcohol screen.
12	A positive test for human immunodeficiency virus (HIV) antibody.
13	Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 84 days.
14	Poor or unsuitable venous access
15	History of regular alcohol consumption within 6 months of the study defined as: An average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint

Number	Inclusion Description
16	History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
17	History of smoking within 6 months of the study.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

Please refer to Protocol Amendment 3 Section 2 for full details of the Schedule of Activities.

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of Assessment Windows for Analyses

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

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 start and/or stop date and time of the study treatment

Study 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

11.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before enrolment
Concomitant	Any medication that is not a prior

NOTES:

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

11.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date. (plus, washout or protocol-specified time limit (e.g. half-life of drug, certain number of days, etc.). • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date [+ 5 x half-life].

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

Reporting Process	
Software	
• The currently supported versions of SAS software 9.4 will be used.	
Reporting Area	
HARP Server	UK1SALX00175
HARP Area	arenv/arprod/GSK3335065/mid201570/final_01
QC Spreadsheet	arenv/arprod/GSK3335065/mid201570/final_01/documents
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards	
Generation of RTF Files	
• RTF files will be generated for the end of study SAC	

11.5.2. Reporting Standards

Reporting Standards
General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  • 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

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. • 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 participant's listings.

Reporting Standards	
• Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data) (MSE = mean square error from mixed effect model of loge-transformed data).
Parameters Not Being Log Transformed	Tmax, t1/2, tlast
Summary Tables	Cmax, tmax, AUC(0-t), AUC (0-∞), CL, V, t1/2, and tlast as data permit
Listings	All parameters collected in the dataset will be listed
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 the [PKOne standards] 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 SOP_3140000
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

11.6. Appendix 6: Derived and Transformed Data

11.6.1. 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. • Participants with both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from 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

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)** • Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) at each visit will be calculated. • Planned Treatment Duration is defined as the number of days planned on study treatment. As Part A is single dose this would be one day.
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 randomized but did not report a treatment start date will be categorised as having zero days of exposure.
Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any participant with a missing day will have this imputed as day '15'.
  ○ Any participant 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**

11.6.3. Safety

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

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 indicated as less than x in the comment field) is present, the corresponding numeric value will be imputed as 0.5 * x

11.6.4. Pharmacokinetic

PK Parameters
• Please see Table 7 for derived Pharmacokinetic parameters

11.6.5. Pharmacodynamic

PD Parameters
• The concentrations and change from baseline values (with baseline defined as the average of all pre-dose measurements (incl. Day -1)) will be summarized by planned time points.

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• All participants who withdraw prematurely from the study/study drug will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). • Withdrawn participants may be replaced in the study except in Part A Cohorts (3-8). • 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.

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 using a "blank" in participant 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 participant 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: o 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: Treatment States and Phases. o 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

Element	Reporting Detail

	missing.
	• AE time will be collected and if it is missing the following imputation will be applied:
	  o If AE start time is missing then time is imputed as 00:00 unless the AE occurs on the first day of dosing in which case it has been imputed as the time of first dose.
	  o If AE end time is missing then time is imputed as 23:59.
	• Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

11.7.2.2. Handling of Partial Dates

Element	Reporting Detail

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  o 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:
	  o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
	  o 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.
	  o The AE will then be considered to start on-treatment (worst case).
	  o 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.

11.7.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Imputation	• There will be no imputation in any statistical analysis

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	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

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

Please review the IDSL standards for the Urinalysis PCI criteria.

11.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450 [1]	
		> 450 [2]	≤ 479 [2]
		≥ 480 [2]	≤ 499 [2]
		≥ 500 [2]	
Absolute PR Interval	msec	< 110 [1]	> 220 [1]
Absolute QRS Interval	msec	< 75 [1]	> 110 [1]
Change from Baseline			
Increase from Baseline QTc	msec	> 60 [1]	
	msec	> 30 [2]	≤ 59 [2]
	msec	≥ 60 [2]	

NOTES:
1. To be used to flag ECG values of PCI for tables not split by category
2. To be used to flag ECG values of PCI for tables which **are** split by category

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

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
3-HAA (3-HAT)	3-hydroxyanthranilic acid
µg	Microgram
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
AUC	AUC Area under concentration-time curve
AUC(0-inf)	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 participant across all treatments
AUC(0-tau)	Area under the concentration-time curve from time zero (pre-dose) during a dosage interval
AUC (Ro)	Observed Accumulation Ratio for AUC observed accumulation ratio for AUC
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Clearance
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
(C_T)	Trough concentration (C_T)
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
GSB	Global Safety Board
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

Abbreviation	Description
ITT	Intent-To-Treat
KYNA	kynurenic acid
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PKCNC	Pharmacokinetic concentration
PP	PK Parameter
PopPK	Population PK
QA	quinolinic acid
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	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TRP	Tryptophan
XA	xanthurenic acid

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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Trademarks not owned by the GlaxoSmithKline Group of Companies
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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	N/A
Safety	2.1 to 2.28	N/A
Pharmacokinetic	3.1 to 3.3	3.1
Pharmacodynamic	4.1 to 4.2	4.1 to 4.4
Section	**Listings**	
ICH Listings	1 to 34	
Other Listings	35 to 41	

11.10.2. Mock Example Shell Referencing

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

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic	PD_Fn	PD_Tn	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
DR	Dry Run
SAC	Statistical Analysis Complete

11.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Subjects	ES8	Summary of Subject Status and Reason for Study Withdrawal (Part A)	ICH E3, FDAAA, EudraCT	DR, SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure (Part A)	Journal Requirements	DR, SAC
Demographic and Baseline Characteristics					
1.3.	All Subjects	DM1	Summary of Demographic Characteristics (Part A)	ICH E3, FDAAA, EudraCT	DR, SAC
1.4.	Enrolled	DM11	Summary of Age Ranges (Part A)	EudraCT	DR, SAC
1.5.	All Subjects	DM5	Summary of Race and Racial Combinations (Part A)	ICH E3, FDA, FDAAA, EudraCT	DR, SAC
Protocol Deviations					
1.6.	All Subjects	DV1	Summary of Important Protocol Deviations (Part A)	ICH E3	DR, SAC
Populations Analysed					
1.7.	Screened	SP1	Summary of Study Populations (Part A)	IDSL	DR, SAC
Prior and Concomitant Medications					
1.8.	All Subjects	MH1	Summary of Current Medical Conditions (Part A)	ICH E3	SAC
1.9.	All Subjects	MH1	Summary of Past Medical Conditions (Part A)	ICH E3	SAC
1.10.	All Subjects	CM1	Summary of Concomitant Medications (Part A)	ICH E3	SAC
Exposure and Treatment Compliance					
1.11.	All Subjects	EX5	Summary of Exposure to Study Treatment (Part A)	ICH E3	DR, SAC

11.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	All Subjects	AE5A	Summary of All Adverse Events by Maximum Intensity and System Organ Class and Preferred Term (Part A)	ICH E3	DR, SAC
2.2.	All Subjects	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity (Part A)	ICH E3	SAC
2.3.	All Subjects	AE3	Summary of Common (2 or more subjects) Adverse Events by Overall Frequency (Part A)	ICH E3	SAC
2.4.	All Subjects	AE15	Summary of Common (More than 2 occurrences) 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					
2.5.	All Subjects	CP_AE1p	Summary of All Serious Adverse Events (Part A)	Sort Adverse Event Displays by SOC	DR, SAC
2.6.	All Subjects	CP_AE1p	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term (Part A)	IDSL	SAC
2.7.	All Subjects	CP_AE1p	Summary of all Drug Related Serious Adverse Events (Part A)	ICH E3 Sort Adverse Event Displays by SOC	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	All Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
Laboratory: Chemistry					
2.9.	All Subjects	LB1	Summary of Chemistry Changes from Baseline (Part A)	ICH E3 Includes Baseline values. Includes pre-specified parameters repeated in conventional units.	SAC
2.10.	All Subjects	LB3	Summary of Chemistry Results by PCI (Part A)	Include Baseline planned timepoint and category instead of change category	SAC
2.11.	All Subjects	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline (Part A)	ICH E3	SAC
Laboratory: Hematology					
2.12.	All Subjects	LB1	Summary of Hematology Changes from Baseline (Part A)	ICH E3 Includes baseline values.	SAC
2.13.	All Subjects	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline (Part A)	ICH E3	SAC
2.14.	All Subjects	LB3	Summary of Hematology Results by PCI (Part A)	As per 2.10	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Urinalysis					
2.15.	All Subjects	LB1	Summary of Urine Concentration Changes from Baseline (Part A)	ICH E3 Includes Baseline values.	SAC
2.16.	All Subjects	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline (Part A)	ICH E3 Define change categories according to actual values expected from lab dataset	SAC
2.17.	All Subjects	LB3	Summary of Urinalysis Results by PCI (Part A)	As per 2.10	SAC
Laboratory: Hepatobiliary (Liver)					
2.18.	All Subjects	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting (Part A)	IDSL	SAC
2.19.	All Subjects	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities (Part A)	IDSL	SAC
ECG					
2.20.	All Subjects	EG1	Summary of ECG Findings (Part A)	IDSL	SAC
2.21.	All Subjects	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category (Part A)	IDSL	DR, SAC
2.22.	All Subjects	EG2	Summary of ECG Values by Visit (Part A)	IDSL Includes continuous cardiac monitoring results	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	All Subjects	EG2	Summary of Change from Baseline in ECG Values by Visit (Part A)	IDSL Includes Baseline values. Includes continuous cardiac monitoring results	SAC
2.24.	All Subjects	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category (Part A)	IDSL	SAC
Vital Signs					
2.25.	All Subjects	VS1	Summary of Vital Signs by Visit (Part A)	ICH E3 Includes Baseline values.	SAC
2.26.	All Subjects	VS1	Summary of Change from Baseline in Vital Signs by Visit (Part A)	Includes Baseline values.	SAC
2.27.	All Subjects	VS3	Summary of Worst Case Vital Signs Results Relative to Normal Range Post-Baseline Relative to Baseline (Part A)	IDSL	SAC
2.28.	All Subjects	VS8	Summary of Change from Baseline Vital Signs by PCI (Part A)	Include Baseline planned timepoint and category instead of change category	SAC

11.10.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentration/Parameters					
3.1.	PKCNC	PK01	Summary of Plasma GSK3335065 Pharmacokinetic Concentration-Time Data (Part A)		SAC
3.2.	PP	PK03	Summary of Derived Plasma GSK3335065 Pharmacokinetic Parameters (Part A)		SAC
3.3.	PP	PK05	Summary of Log-Transformed Derived Plasma GSK3335065 Pharmacokinetic Parameters (Part A)		SAC

11.10.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentration/Parameters					
3.1.	PKCNC	PK16a	Individual Plasma GSK3335065 Concentration-Time Plots (Linear and Semi-log)		SAC

11.10.8. Pharmacodynamic Tables

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
KMO inhibition					
4.1.	All Subjects	PD1	Summary of primary TRP Metabolite Data by Treatment Group and Time (Part A)	3HK and KYN	SAC
4.2.	All Subjects	PD3	Summary of change from baseline in primary TRP Metabolite Data by Treatment Group and Time (Part A)	3HK and KYN	SAC

11.10.9. Pharmacodynamic Figures

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
KMO inhibition					
4.1.	All Subjects	PK16a	Individual primary TRP Metabolite Plots by Time (Part A)	3HK and KYN Programming Notes: Only use the linear scale, replace concentration units as appropriate and create plots for each metabolite on a new page	SAC
4.2.	All Subjects	PK16a	Individual change from baseline in primary TRP Metabolite Plots by Time (Part A)	3HK and KYN Programming Notes: As per Figure 4.1	SAC
4.3.	All Subjects	PK16a	Individual exploratory TRP Metabolite Plot by Time (Part A)	TRP, KYNA, AA, 3-HAT, XA, QA and any other pathway components Programming Notes: As per Figure 4.1	SAC
4.4.	All Subjects	PK16a	Individual change from baseline in exploratory TRP Metabolite Plots by Time (Part A)	TRP, KYNA, AA, 3-HAT, XA, QA and any other pathway components Programming Notes: As per Figure 4.1	SAC

11.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Subjects	ES2	Listing of Reasons for Study Withdrawal	ICH E3	DR, SAC
2.	Screened Subjects	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
3.	All Subjects	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	DR, SAC
4.	All Subjects	TA1	Listing of Randomised and Actual Treatments	IDSL	DR, SAC
Protocol Deviations					
5.	All Subjects	DV2	Listings of Important Protocol Deviations	ICH E3	DR, SAC
6.	All Subjects	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	DR, SAC
Demographic and Baseline Characteristics					
7.	All Subjects	DM2	Listing of Demographic Characteristics	ICH E3	SAC
8.	All Subjects	DM9	Listing of Race	ICH E3	SAC
Populations Analysed					
9.	Screened	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Prior and Concomitant Medications					
10.	All Subjects	CP_CM3	Listing of Concomitant Medications	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
11.	All Subjects	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
12.	All Subjects	AE8CP	Listing of All Adverse Events	ICH E3	DR, SAC
13.	All Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
14.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Serious and Other Significant Adverse Events					
15.	All Subjects	AE8CPa	Listing of Serious Adverse Events	ICH E3	DR, SAC
16.	All Subjects	AE8CPa	Listing of Fatal Serious Adverse Events	ICH E3	SAC
17.	All Subjects	AE8CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	DR, SAC
18.	All Subjects	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
19.	All Subjects	AE8CP	Listing of All Drug-Related Fatal Serious Adverse Events		SAC
All Laboratory					
20.	All Subjects	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3 Display ALL labs for a subject who experienced a value of potential clinical importance. Include time with date	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
21.	All Subjects	LB5	Listing of Laboratory Values of Potential Clinical Importance	Include time with date	SAC
22.	All Subjects	LB14	Listing of Laboratory Data with Character Results	ICH E3 Dipstick results	SAC
23.	All Subjects	UR2A	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3 Display ALL data for a subject who experienced a value of potential clinical importance.	SAC
ECG					
24.	All Subjects	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL Display ALL ECGs for a subject who experienced a value of potential clinical importance.	SAC
25.	All Subjects	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
26.	All Subjects	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
27.	All Subjects	EG5	Listing of Abnormal ECG Findings	IDSL	SAC
28.	All Subjects	EG3	Listing of All ECG Values		SAC
29.	All Subjects	EG3	Listing of All Change from Baseline ECG Values		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
30.	All Subjects	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL Display ALL Vital Signs for a subject who experienced a value of potential clinical importance. Include participants flagged with change from baseline vital sign values of PCI	SAC
31.	All Subjects	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC
32.	All Subjects	VS4	Listing of Change from Baseline in Vital Signs of Potential Clinical Importance	IDSL	SAC
33.	All Subjects	VS4	Listing of All Vital Signs Values		SAC
34.	All Subjects	VS4	Listing of All Change from Baseline Vital Signs Values		SAC

11.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other Adverse Events Listings					
35.	All Subjects	SAFE_L1	Listing of Assessment at Infusion Site		SAC

Other ECG Listings					
36.	All Subjects	SAFE_L2	Listing of Echocardiogram Findings		SAC
37.	All Subjects	SAFE_L2	Listing of ECG monitoring and Telemetry Findings		SAC
Pharmacokinetic Concentration/Parameters					
38.	PKCNC	PK07	Listing of Plasma GSK3335065 Pharmacokinetic Concentration-Time Data		SAC
39.	PP	PK13	Listing of Derived Plasma GSK3335065 Pharmacokinetic Parameters		SAC
Pharmacodynamic analysis					
40.	All Subjects	PK07	Listing of primary TRP Metabolite Data by Treatment Group and Time	3HK and KYN Include change from baseline as well as concentration	SAC
41.	All Subjects	PK07	Listing of exploratory TRP Metabolite Data by Treatment Group and Time	TRP, KYNA, AA, 3-HAT, XA, QA and any other pathway components Include change from baseline as well as concentration	SAC

11.11. Appendix 11: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request