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

Title	:	Reporting and Analysis Plan for A three-part open-label, non-randomised, dose-escalation study to investigate the safety and tolerability of GSK3039294 administered as a single dose to healthy volunteers, and as repeat dose to healthy volunteers and patients with systemic amyloidosis.
Compound Number	:	GSK3039294
Effective Date	:	09-NOV-2017

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2014N218204_03.
- This RAP is intended to describe the safety and PK/PD analyses of GSK3039294 administered as a single dose to healthy volunteers, and as repeat dose to healthy volunteers and patients with systemic amyloidosis.
- This RAP will be provided to study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable for the interim and final analysis for this study.

Author's Name and Functional Area:

PPD Associate Statistician, QSI	
PPD Principal Statistician, Clinical Statistics	06-NOV-2017 (approval captured electronically within CARS system)
PPD Principal Statistician, Clinical Statistics	
PPD Director, Clinical Pharmacology Modelling & Simulation	01-NOV-2017 (approval captured electronically within CARS system)

Approved by:

PPD Director, Clinical Statistics	01-NOV-2017 (approval captured electronically within CARS system)
PPD Programming Manager, Clinical Statistics	31-OCT-2017 (approval captured via email)

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

<table>
<tr><th>Overview</th><th>Key Elements of the Reporting and Analysis Plan</th></tr>
<tr><td>Purpose</td><td>• The purpose of this reporting and analysis plan (RAP) is to describe all interim and final analyses for this study.</td></tr>
<tr><td>Protocol</td><td>• Reporting and Analysis Plan is based on amended protocol (Dated: 30-NOV-2016) for study GSK3039294/RAD201664 [GlaxoSmithKline Document Number: 2014N218204_03].</td></tr>
<tr><td>Objectives / Endpoints</td><td>Part A: Single ascending dose in healthy volunteers
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>Evaluate safety and tolerability of single doses of GSK3039294</td><td>Adverse events, laboratory measurements, ECG, vital signs</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>Evaluate pharmacokinetics of single doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)</td><td>PK parameters of GSK2315698 and GSK3039294</td></tr>
</table>
Part B: Repeat dose in healthy volunteers
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>Evaluate safety and tolerability of repeat doses of GSK3039294</td><td>Adverse events, laboratory measurements, ECG, vital signs and cardiac telemetry (where applicable)</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>Evaluate pharmacokinetics of repeat doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)</td><td>PK parameters of GSK2315698 and GSK3039294</td></tr>
<tr><td>Pharmacodynamic effect of repeat doses of GSK3039294 on plasma SAP levels</td><td>Plasma SAP levels</td></tr>
<tr><td>Explore correlation of dose of GSK3039294, blood concentration of GSK2315698 and plasma SAP levels</td><td>PK parameters of GSK2315698 and GSK3039294
Plasma SAP levels</td></tr>
<tr><td colspan="2">Exploratory</td></tr>
<tr><td>Determine the effect of food on a single dose of GSK3039294</td><td>PK parameters of GSK2315698 and GSK3039294 under fasted and fed conditions.</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>Part C: Repeat dose in patients with systemic amyloidosis
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>Evaluate safety and tolerability of repeat doses of GSK3039294</td><td>Adverse events, laboratory measurements, ECG, vital signs and cardiac telemetry (where applicable)</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>Evaluate pharmacokinetics of repeat doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)</td><td>PK parameters of GSK2315698 and GSK3039294</td></tr>
<tr><td>Pharmacodynamic effect of multiple doses of GSK3039294 on plasma SAP levels</td><td>Plasma SAP levels and time to repletion of SAP.</td></tr>
<tr><td>Explore correlation of dose of GSK3039294, blood concentration of GSK2315698 and plasma SAP levels</td><td>PK parameters of GSK2315698 and GSK3039294
Plasma SAP levels</td></tr>
</table></td></tr>
<tr><td>Study Design</td><td>• This is a three-part, open-label, non-randomised study. In Part A, sufficient healthy volunteers will be enrolled to ensure 6 subjects per cohort have completed the in-patient phases. In Part B, sufficient healthy volunteers will be enrolled to ensure 6 subjects per cohort have completed each of the in-patient phases. In Part C, a minimum of 12 patients with systemic amyloidosis will be enrolled.</td></tr>
<tr><td>Analysis Population</td><td>• Screened
• Enrolled
• Safety
• PK
• PD
• PK/PD</td></tr>
<tr><td>Hypothesis</td><td>• There are no formal hypotheses being tested in the study.</td></tr>
<tr><td>Interim Analyses</td><td>• Data will be reviewed on an ongoing basis throughout the study by the study team and investigator in order to inform dosing decisions for subsequent dosing sessions, cohorts and study parts. Dose escalation meetings will be held prior to increasing the dose. Key data to inform dosing decisions will include but not be limited to: safety (AEs, clinical laboratory data, vital signs and ECGs), PK (concentrations of GSK2315698, and if possible, GSK3039294 and the intermediate molecule GSK3037412), and plasma SAP levels (Part B data to inform Part C dosing regimen only).
• In addition to the ongoing review of data throughout the study, at the end of Part B, individual profiles over time will be presented graphically for</td></tr>
</table>

	selected urine and plasma laboratory parameters pertaining to the kidney. Individual profiles will be presented for both single and repeat-dose healthy volunteer data to further inform the evaluation of renal safety and the decision to progress to repeat dosing in systemic amyloidosis patients in Part C.
Primary Analyses	• Safety data will be summarized according to GSK's Integrated Data Standards Library (IDSL) standards in tabular and/or graphical format.
Secondary Analyses	• Pharmacokinetic: Individual GSK2315698 plasma concentration-time profiles (by treatment and subject) will be plotted. GSK3039294 and GSK2315698 plasma concentration data will also be summarised and listed. Plasma concentration time data for GSK2315698 will be analyzed by non-compartmental methods using WinNonlin and derived PK parameters will be presented graphically, summarised and listed. No formal statistical analyses will be conducted. • Pharmacodynamic: Individual plasma SAP profiles over time will be listed and presented graphically. Plasma SAP levels will be log-transformed or other transformation if appropriate, and summarised over time by cohort/dosing regimen, together with corresponding 95% confidence intervals.
Exploratory Analyses	• A food effect exploration will be conducted at Days 4 and 5 of Part B Cohort 3. On these days GSK3039294 will be administered under fasted and then under fed conditions, and the food effect on the PK parameter will be summarised and presented graphically.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Clarifications to the Protocol Defined Statistical Analysis Plan

Clarifications to the originally planned statistical analysis specified in the protocol (Dated: 30-NOV-2016, GSK Document Number 2014N218204_03) are as follows:

- Reviews of PK data to inform dosing decisions for subsequent dosing sessions/cohorts/study parts will be during Part A, at the end of Part A and on completion of each cohort in Part B.
- A review of the SAP data to inform the Part C dosing regimen will be at the end of Part B only (ie not during Part B). Note: SAP data not collected in Part A.
- Doses will be selected such that the upper limit of the 95% prediction interval for Cmax and AUC will not exceed preclinical limits.
- Analysis of the intermediate molecule GSK3037412 will be reported separately from the Clinical Pharmacology Study Report.

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

Part A: Single ascending dose in healthy volunteers

Objectives	Endpoints
Primary	
Evaluate safety and tolerability of single doses of GSK3039294	Adverse events, laboratory measurements, ECG, vital signs
Secondary	
Evaluate pharmacokinetics of single doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)	PK parameters of GSK2315698 and GSK3039294

Part B: Repeat dose in healthy volunteers

Objectives	Endpoints
Primary	
Evaluate safety and tolerability of repeat doses of GSK3039294	Adverse events, laboratory measurements, ECG, vital signs and cardiac telemetry (where applicable)
Secondary	
Evaluate pharmacokinetics of repeat doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)	PK parameters of GSK2315698 and GSK3039294

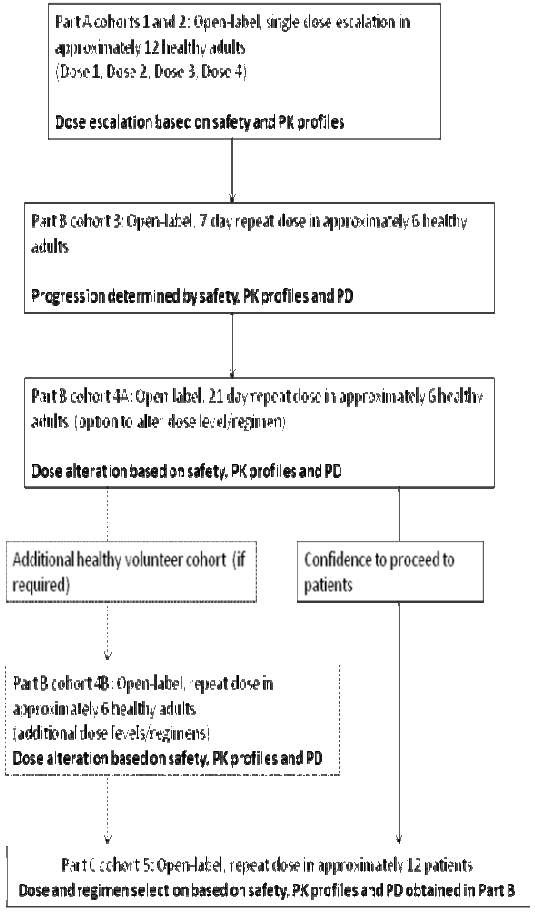
Objectives	Endpoints
Pharmacodynamic effect of repeat doses of GSK3039294 on plasma SAP levels	Plasma SAP levels
Explore correlation of dose of GSK3039294, blood concentration of GSK2315698 and plasma SAP levels	PK parameters of GSK2315698 and GSK3039294 Plasma SAP levels
Exploratory	
Determine the effect of food on a single dose of GSK3039294	PK parameters of GSK2315698 and GSK3039294 under fasted and fed conditions.

Part C: Repeat dose in patients with systemic amyloidosis

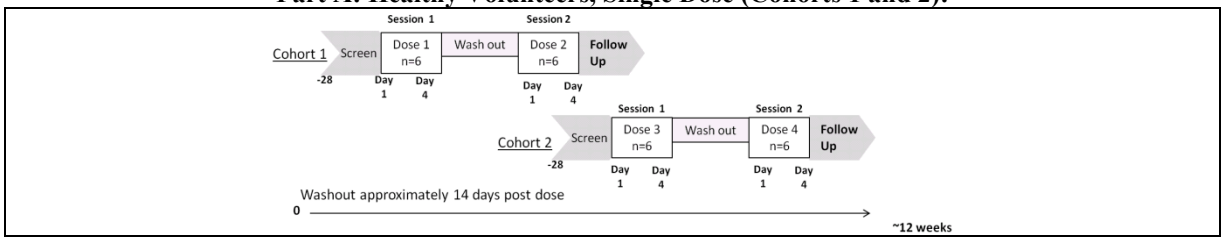
Objectives	Endpoints
Primary	
Evaluate safety and tolerability of repeat doses of GSK3039294	Adverse events, laboratory measurements, ECG, vital signs and cardiac telemetry (where applicable)
Secondary	
Evaluate pharmacokinetics of repeat doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)	PK parameters of GSK2315698 and GSK3039294
Pharmacodynamic effect of multiple doses of GSK3039294 on plasma SAP levels	Plasma SAP levels and time to repletion of SAP.
Explore correlation of dose of GSK3039294, blood concentration of GSK2315698 and plasma SAP levels	PK parameters of GSK2315698 and GSK3039294 Plasma SAP levels

2.3. Study Design

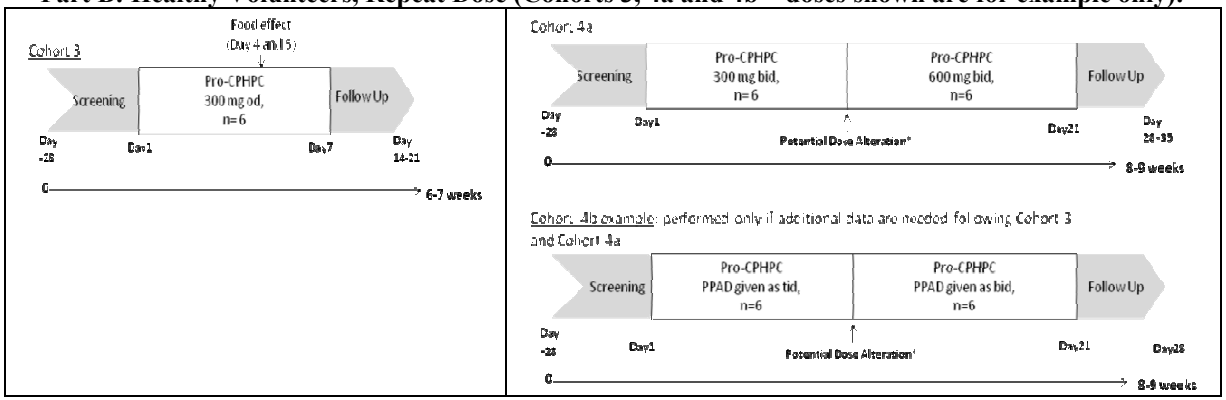
Overall Design:



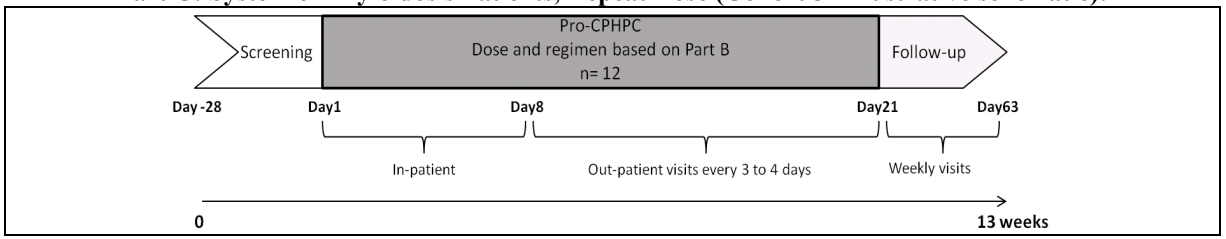
Part A: Healthy Volunteers, Single Dose (Cohorts 1 and 2):



Part B: Healthy Volunteers, Repeat Dose (Cohorts 3, 4a and 4b – doses shown are for example only):



Part C: Systemic Amyloidosis Patients, Repeat Dose (Cohort 5 - illustrative schematic):



Design Features	This will be a three-part open-label, non-randomised, dose-escalation study with no active or placebo control. Part A will allow assessment of safety, tolerability and PK including biotransformation of GSK3039294 into active CPHPC of single doses of GSK3039294. If the absorption of GSK3039294 and subsequent biotransformation of GSK3039294 to CPHPC is sufficient then repeat dosing will be investigated in Part B. Part B will allow assessment of safety, tolerability and PK including evaluation of food-effect and biotransformation of GSK3039294 into active CPHPC of repeat doses of GSK3039294 and PD (depletion of plasma SAP). PK and PD data will be compared within a subject following repeat dosing and dose escalation and regimen adjustments. If the exposure to CPHPC and the resulting depletion of SAP is sufficient and well tolerated, then repeat dosing of patients with systemic amyloidosis will be investigated in Part C. Part C will confirm the ability of GSK3039294 (dosing regimen determined from Part B) to decrease plasma SAP to a level suitable for mAb administration in subsequent studies and its ability to maintain this level over 21 days in patients with systemic amyloidosis. Also, safety and tolerability of the optimal clinical dose of GSK3039294 will be evaluated in systemic amyloidosis patients which may include those with known cardiac amyloid involvement.
Dosing	This study is planned to test single doses of GSK3039294 and repeat doses up to the maximum tolerated dose or the maximum allowable dose based on pre-clinical findings. **Part A** • The starting dose in Part A is planned to be 200mg of GSK3039294. This dose has been selected using the PK/PD model that was developed for CPHPC (active molecule), adjusted for the oral absorption of GSK3039294 and the conversion of GSK3039294 to CPHPC. • The next doses in Part A will be determined based on the data of the preceding dosing sessions. All available PK data will be analysed and the next dose will be such that the predicted median Cmax will be about 6 μg/mL, and the upper limit of the 95% prediction interval will not exceed preclinical Cmax and AUC limits. • The highest dose in Part A will not exceed pre-clinical safety exposure limits of AUC[0-24] of 250 μg.hr/mL and Cmax of 22.1μg/mL. **Part B** • The dose levels for Cohort 3 in Part B will be determined based on the PK data obtained in Part A, by analysing all available PK data

	from Part A and subsequently predicting concentration-time profiles at steady state after repeat dosing. • The dose levels for subsequent cohorts in Part B will be determined based on the PK data from Part A (single dose) and cohort 3 in Part B (multiple dose). The dose levels and dosing frequencies will be chosen such that the upper limit of the 95% prediction interval for Cmax and AUC at steady state will not exceed preclinical Cmax and AUC limits (22.1 μg/mL and 250 μg.hr/mL, respectively). **Part C** • GSK3039294 will be administered at the predicted optimal clinical dose for 21 days. This dose will be determined using the PK/PD model that was developed for CPHPC (active molecule) and using all available PK and plasma SAP (PD) data from Parts A and B, the model will be adjusted for the oral absorption of GSK3039294 and the conversion of GSK3039294 to CPHPC. The dose level and frequency will be chosen such that the upper limit of the 95% prediction interval for Cmax and AUC at steady state will not exceed preclinical Cmax and AUC limits (22.1 μg/mL and 250 μg.hr/mL, respectively).
Treatment Assignment	• This is an open-label, non-randomised study with no active or placebo control. • GSK3039294 doses will be administered sequentially and will be based on the review of safety, PK and PD data (as applicable) from previous cohorts, dosing sessions and study parts.
Interim Analysis	• The planned protocol-defined unblinded interim analyses are: [1] Ongoing data reviews throughout the study [2] Data reviews to inform dosing decisions for subsequent dosing sessions, cohorts and study parts [3] At the end of Part B, interim analysis of selected renal safety data.

2.4. Statistical Hypotheses

No formal hypotheses will be tested in this study.

3. PLANNED ANALYSES

3.1. Interim Analyses

Data will be reviewed on an ongoing basis throughout the study by the study team and investigator in order to inform dosing decisions for subsequent dosing sessions, cohorts and study parts. Dose escalation meetings will be held prior to increasing the dose. Key data to inform dosing decisions will include but not be limited to: safety (AEs, clinical laboratory data, vital signs and ECGs), PK (concentrations of GSK2315698, and if possible GSK3039294), and plasma SAP levels.

Data listings direct from the PIMS (Patient Information Management System) data capture system will facilitate ongoing reviews of safety data.

To inform dosing decisions for subsequent dosing sessions in Part A, individual values of Cmax and AUC[0-inf] will be derived by means of non-compartmental analysis. Assuming linear kinetics, the next dose will be such that the upper limit of the 95% prediction interval for Cmax and AUC will not exceed preclinical safety limits (22.1 μg /mL and 250 μg.hr/mL, respectively).

To inform dosing decisions for subsequent study parts, GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698 [Sahota, 2015]. Based on pre-clinical data it is expected that the conversion of GSK3039294 to GSK2315698 is very fast. Therefore, it can be assumed that this conversion will occur mainly during the absorption phase, and that the distribution and elimination of GSK2315968 are not altered. Hence, all distribution and elimination parameters (PK/PD) will be fixed to the reported parameter estimates, and only bioavailability (F) and absorption related parameters (e.g. Ka) will be estimated. Nominal time points will be used. This updated model will be used to simulate concentration-time data and plasma SAP levels using different dose levels and dosing regimens, which will be used to inform dosing decisions for subsequent dosing sessions, cohorts and study parts.

In addition to the ongoing review of data throughout the study, at the end of Part B, individual profiles over time will be presented graphically for selected urine and plasma laboratory parameters pertaining to the kidney (including, but not limited to: blood & urine glucose, urine protein, serum creatinine, urine protein/urine creatinine ratio, serum phosphate, urine pH, and arterial blood gas test results (blood pH and blood bicarbonate) if available. Note, an arterial blood gas test will only be performed if urine pH is abnormal, i.e. acidic. Individual profiles will be presented for both single (Part A) and repeat-dose (Part B) healthy volunteer data to further inform the evaluation of renal safety and the decision to progress to repeat dosing in patients in Part C.

3.2. Final Analyses

The final planned analyses will be performed at the end of Part C after the completion of the following sequential steps:

[1] All subjects have completed the study as defined in the protocol.

[2] All required database cleaning activities have been completed and final database release and database freeze have been declared by Data Management.

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Endpoint(s) Evaluated
Screened	• All subjects who signed the Informed Consent	• Study Population
Enrolled	• Subjects who ultimately pass screening	• Study Population
Safety	• All subjects who received at least one dose of study medication. • This will be the primary population for assessing safety.	• Study Population • Safety
Pharmacokinetic	• All subjects administered at least one dose of study medication and who have at least one PK sample taken and analysed. • This will be the primary population for assessing PK. Subjects will be classified by the actual dose received.	• PK
Pharmacodynamic:	• All subjects who received at least one dose of study medication and at least one post-treatment PD measure. • This will be the primary population for assessing PD. • Subjects will be classified by the actual dose received.	• PD
PK/PD:	• All subjects included in both the PK and PD populations. • This will be the primary population for PK/PD modelling. • Subjects will be classified by the actual dose received.	• PK/PD

NOTES :

- Please refer to Appendix 9: List of Data Displays which details the population to be used for each display.

4.1. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed prior to freezing the database to ensure all important deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) are captured and categorised on the protocol deviations dataset.
  - This dataset will be the basis for the listing of protocol deviations.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided, based on data recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Time & Events
10.2	Appendix 2: Treatment States and Phases
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Pharmacokinetic / Pharmacodynamic Analyses
10.8	Appendix 8: Abbreviations & Trade Marks
10.9	Appendix 9: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated	
	Table	Listing
Randomisation		
Treatment Allocation		Y
Subject Disposition		
Subject Disposition	Y	
Reasons for Screening Failures	Y	Y
Reasons for Withdrawals		Y
Protocol Deviations		
Important Protocol Deviations	Y	Y
Inclusion and Exclusion Criteria Deviations		Y
Subjects Excluded from Analysis Populations		Y
Demographic and Baseline Characteristics		
Demographics Characteristics	Y	Y
Race & Racial Combinations	Y	Y
Age Ranges	Y	
Prior and Concomitant Medications		
Concomitant Medication		Y
Current/Past Medical Conditions	Y	

Y = Yes display generated.

7. PRIMARY STATISTICAL ANALYSES

7.1. Safety Analyses

Safety data will be listed and presented in tabular and/or graphical format, as appropriate, and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. The primary safety analyses will be based on the "Safety" population, unless otherwise specified.

Table 3 provides an overview of the planned safety analyses with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 3 Overview of Planned Safety Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure and Treatment Compliance								
Exposure to Study Treatment	Y			Y				
Adverse Events								
All AE's by SOC and PT	Y			Y				
Serious AE's				Y				
Drug Related AEs	Y							
Withdrawal AE's				Y				
Relationship Between System Organ Class and Verbatim Text				Y				
Subject Numbers for Individual Adverse Events				Y				
Common Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y							
Laboratory Values								
Clinical Chemistry				Y	Y			
Emergent Chemistry Results by PCI Criteria	Y			Y				
Emergent Chemistry Results Relative to Normal Range	Y							
Haematology				Y	Y			
Emergent Hematology Results by PCI Criteria	Y			Y				
Emergent Hematology Relative to Normal Range	Y							
Urinalysis	Y			Y				
Urinalysis Data Outside the PCI Range				Y				
Renal Parameters			Y					
ECG's								
Abnormal ECG Findings				Y				
ECG Values Outside the PCI Range				Y				

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Vital Signs								
Vitals Values	Y				Y			
Vital Signs Measurements Outside the PCI Range				Y				
Holter								
Telemetry Interpretations	Y							
Telemetry Abnormalities	Y							

NOTES:

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

8. SECONDARY STATISTICAL ANALYSES

8.1. Pharmacokinetic Analyses

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Clinical Pharmacology Science and Study Operations (CPSSO), GlaxoSmithKline.

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

Derivation of pharmacokinetic parameters will be performed by Clinical Pharmacology Modelling and Simulation (CPMS), QSci, GlaxoSmithKline.

8.1.1. Overview of Planned Pharmacokinetic Analyses

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

Table 4 provides an overview of the planned analyses, with full details being presented in Appendix 9: List of Data Displays.

Table 4 Overview of Planned Pharmacokinetic Analyses

Part / Endpoint	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Part A								
GSK3039294 concentrations	Y			Y				
GSK2315698 concentrations	Y	Y	Y	Y				
GSK3039294 parameters	Y			Y	Y			

Part / Endpoint	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
GSK2315698 parameters	Y		Y	Y	Y			
Part B								
GSK3039294 concentrations	Y			Y				
GSK2315698 concentrations	Y	Y	Y	Y				
GSK3039294 parameters	Y[1]			Y[1]	Y[1]			
GSK2315698 parameters	Y[1]		Y[1]	Y[1]	Y[1]			
Part C								
GSK3039294 concentrations	Y			Y				
GSK2315698 concentrations	Y	Y	Y	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 subject observed raw data.

[1] PK parameters from Part B Cohort 3 Days 4&5 (exploration of food effect) only.

8.1.2. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).

8.1.3. Pharmacokinetic Parameters

- Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).
- The pharmacokinetic parameters (Part A, and Days 4 and 5 of Cohort 3 in Part B only) will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin version 5.0 or higher.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 5 will be determined from the blood (GSK3039294) or plasma (GSK2315698) concentration-time data, as data permit.

Table 5 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-6)	Area under the concentration-time curve from time zero to 6 hours post dose NOTE: this parameter is derived for Days 4&5 of Part B Cohort 3 only.
AUC(0-inf)	Area under the concentration-time curve extrapolated to infinity.
AUC(0-inf)/D	AUC(0-inf) corrected for dose of prodrug.
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (Clast).
AUC(0-t)/D	AUC(0-t) corrected for dose of prodrug.

Parameter	Parameter Description
Clast	Last quantifiable concentration.
Cmax	Maximum observed concentration.
Cmax/D	Cmax corrected for dose of prodrug.
t1/2	Terminal half-life.
Lambda_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
Lambda_z_lower	First time point used in computing Lambda_z.
Lambda_z_upper	Last time point used in computing Lambda_z.
#pts	Number of points used in computing Lambda_z.
r-squared	R-squared of Lambda_z computation.
tlast	Time of the last quantifiable concentration.
tmax	Time to reach Cmax.

8.2. Pharmacodynamic Analyses

8.2.1. Overview of Planned Pharmacodynamic Analyses

The pharmacodynamic analyses will be based on the "Pharmacodynamic" population, unless otherwise specified. Table 6 provides an overview of the planned pharmacodynamic analyses, with full details of data displays being presented in Appendix 9: List of Data Displays. Table 7 provides a list of pharmacodynamic parameters to be derived.

Table 6 Overview of Planned Pharmacodynamic Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Parts B&C				
Plasma SAP concentrations	Y[1]	Y	Y	Y
Plasma SAP parameters	Y			Y

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] For summary table, data will be transformed if required as appropriate. Table will include 95% CI.

Table 7 Derived Pharmacodynamic Parameters

Parameter	Parameter Description
$Cmin_{SAP}$	The first occurrence of the minimum observed plasma SAP concentration determined directly from the raw SAP concentration-time data; for Part B and C only; by dosing regimen in Part B
$tmin_{SAP}$	The time at which $Cmin_{SAP}$ is observed will be determined directly from the raw plasma SAP concentration-time data; for Part C only
$Trep_{SAP\_80\%}$	The earliest time a subject returns to at least 80% of their baseline plasma SAP levels after maximum depletion has been achieved and without any subsequent decrease in plasma SAP levels; for Part C only
$Trep_{SAP\_90\%}$	The earliest time a subject returns to at least 90% of their baseline plasma SAP levels after maximum depletion has been achieved and without any subsequent decrease in plasma SAP levels; for Part C only
$Trep_{SAP\_100\%}$	The earliest time a subject returns to at least 100% of their baseline plasma SAP levels after maximum depletion has been achieved and without any subsequent decrease in plasma SAP levels; for Part C only

8.3. Pharmacokinetic / Pharmacodynamic Analyses

- The primary goal of this analysis is to recommend the dose regimen that adequately reduces plasma SAP levels when the active moiety, GSK2315698, is administered as an oral prodrug, GSK3039294, to subjects with amyloidosis.
- A summary of the planned population pharmacokinetic/pharmacodynamic analyses is outlined below:
  - GSK2315698 plasma concentration – pharmacodynamic data (plasma SAP) obtained from healthy volunteers and patients with systemic amyloidosis will be analysed using the PK/PD model that was developed for GSK2315698 [Sahota, 2015] using the program NONMEM to develop a population PK/PD model.
  - This PK/PD model will be adjusted for oral absorption of GSK3039294 and conversion into GSK2315698.
  - Actual time points will be used for the PK/PD analysis.
  - To support this analysis a NONMEM-ready dataset will be generated, for which dataset specifications are provided in Appendix 7: Pharmacokinetic / Pharmacodynamic Analyses, which also contains detailed methodology for the analysis.

9. REFERENCES

- GlaxoSmithKline Document Number 2014N218204_00 (Original – 06-AUG-2015): A three-part open-label, non-randomised, dose-escalation study to investigate the safety and tolerability of GSK3039294 administered as a single dose to healthy volunteers, and as repeat dose to healthy volunteers and patients with systemic amyloidosis.
- GlaxoSmithKline Document Number 2014N218204_01 (Amendment 1 – 07-OCT-2015): A three-part open-label, non-randomised, dose-escalation study to investigate the safety and tolerability of GSK3039294 administered as a single dose to healthy volunteers, and as repeat dose to healthy volunteers and patients with systemic amyloidosis.
- GlaxoSmithKline Document Number 2014N218204_02 (Amendment 2 – 01-MAR-2016): A three-part open-label, non-randomised, dose-escalation study to investigate the safety and tolerability of GSK3039294 administered as a single dose to healthy volunteers, and as repeat dose to healthy volunteers and patients with systemic amyloidosis.
- GlaxoSmithKline Document Number 2014N218204_03 (Amendment 3 – 30-NOV-2016): A three-part open-label, non-randomised, dose-escalation study to investigate the safety and tolerability of GSK3039294 administered as a single dose to healthy volunteers, and as repeat dose to healthy volunteers and patients with systemic amyloidosis.
- GUI_137354 (2.0, 30-JUL-2014), Information for Authors: Reporting and Analysis Plan (RAP), Global
- GUI_51487 (4.0, 29-OCT-2014), Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global
- Sahota T, Berges A, Barton S, Cookson L, Zamuner S, Richards D. Target mediated drug disposition model of CPHPC in patients with systemic amyloidosis. CPT Pharmacometrics Syst Pharmacol 2015;4:e15
- SOP_54838 (5.0, 30-JUL-2014), Development, Review & Approval of Reporting & Analysis Plan (RAP), Global

10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Time & Events
Section 10.2	Appendix 2: Treatment States and Phases
Section 10.3	Appendix 3: Data Display Standards & Handling Conventions • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.4	Appendix 4: Derived and Transformed Data • General • Study Population • Safety
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • General • Study Population & Safety
Section 10.6	Appendix 6: Values of Potential Clinical Importance • Laboratory Values • ECG • Vital Signs
Section 10.7	Appendix 7: Pharmacokinetic / Pharmacodynamic Analyses
Other RAP Appendices	
Section 10.8	Appendix 8: Abbreviations & Trade Marks
Section 10.9	Appendix 9: List of Data Displays

10.1. Appendix 1: Time & Events

10.1.1. Part A – Cohorts 1 and 2, single dose, healthy volunteer subjects

Procedure	Screening (within 28 days of Day1)	Treatment Period Day -1	Day 1	Day 2	Day 3	Day 4	Wash out 5-13	Follow-up Day 14	Notes
Outpatient Visit	X							X	Outpatient visit at the end of second treatment.
Admission to Clinical Unit		X						X	Admission if due to start next dose level on the following day.
Inpatient Stay at Clinical Unit			←----------	----------	----------	----------→			
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Demography	X								
Full physical exam including height and weight	X								
Brief Physical		X						X	
Medical history (includes substance usage)	X								
Past and current medical conditions	X								
Urine Drug/Alcohol Breath Test	X	X							
FSH and oestradiol (women)	X								
Clinical Safety Laboratory Assessments *(HIV, Hep B and Hep C Screen at screening only[1])* – except Core Urine Monitoring Assessments	X	X		X	X			X	On dosing days, samples to be taken in the morning pre-dose. [1]If performed within 3 months prior to first dose of study treatment, testing at screening is not required.
Clinical Chemistry Only			X						
Core Urine Monitoring Assessments	X	X	X	X[1]	X			X	On dosing days, samples to be taken in the morning. [1]24 hrs post-dose
Urine Sample (for storage)		X							
24hr Urine collection			X						Collection from dose until 24hrs post-dose

Procedure	Screening (within 28 days of Day1)	Treatment Period Day -1	Day 1	Day 2	Day 3	Day 4	Wash out Day 5-13	Follow-up Day 14	Notes
12-lead ECG and Vital sign	X	X	X	X	X	X		X	Triplicate for all Pre dose and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 72hrs post-dose
24hr Holter	X		X						Continuous from 1hr predose to 24hr post dose
Study Treatment			X						Single administration
Blood Sampling for pharmacokinetics			←----------→						For sampling time points, see Section 7.4.1 in protocol
Discharge from Clinical Unit						X			Following completion of all assessments
PGx Sample			←----------→						Pre-dose if possible. Informed consent for optional genetics research must be obtained before collecting a sample
AE/SAE review		X	←----------→					X	
Concomitant medication review		X	←----------→					X	

10.1.2. Part B – Cohort 3, 7 day repeat dose healthy volunteer subjects

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)										Follow-up (7-14 days following last dose)	Notes
		-2	-1	1	2	3	4	5	6	7	8		
Outpatient Visit	X											X	
Admission to Clinical Unit		X											
Inpatient Stay at Clinical Unit				←----------							→|		
Informed consent	X												
Inclusion and exclusion criteria	X	X											
Demography	X												
Full physical exam incl height and weight	X												
Brief Physical		X										X	
Medical history (includes substance usage)	X												Substances: Drugs, Alcohol, tobacco and caffeine
Past and current medical conditions	X												
FSH and oestradiol (women)	X												
Clinical Safety Laboratory Assessments *(HIV, Hep B and Hep C Screen at screening only[1])* – except Core Urine Monitoring Assessments	X	X			X			X			X	X	On dosing days, samples to be taken in the morning pre-dose. [1]If performed within 3 months prior to first dose of study treatment, testing at screening is not required.
Clinical Chemistry Only				X		X							
High-sensitivity cardiac Troponin	X			X									Pre-dose
Core Urine Monitoring Assessments	X		X	X		X		X			X	X	Samples for Urine pH to be taken in the morning
Urine Sample (for storage)			X										
Urine Drug/Alcohol Breath Test	X	X											
12-lead ECG and vital signs	X		X	X	X	X	X	X	X	X	X	X	Triplicate for all. Pre-dose and 1hr post-dose
48hr Holter	X												

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)									Follow-up (7-14 days following last dose)	Notes
		-2	-1	1	2	3	4	5	6	7	8	
Telemetry		←----------									→----------			Temporary removal of telemetry (e.g. for showering) is permitted
Evaluation of Food Effect							X	X						Fasted on Day 4, Fed on Day 5. Not to be performed in sentinel subjects.
Study Treatment				←----------							→----------			
Blood Sampling (PK)				For sampling time points, see Section 7.4.1 in protocol								X		For 1st dose and escalation See Section 7.4.1 in protocol
Blood Sampling (PD)				For sampling time points, see Section 7.5 in protocol								X		
Discharge from Clinical Unit											X			Following completion of all assessments
PGx Sample		X												Pre-dose if possible. Informed consent for optional genetics research must be obtained before collecting a sample
AE/SAE review		←----------									→----------	X		
Concomitant medication review	X	←----------									→----------	X		

10.1.3. Part B – Cohort 4a and 4b, 21 day repeat dose healthy volunteer subjects

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																						Follow-up (7-14 days following last dose)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Outpatient Visit	X																X[2]						X	X	[2]Visit day ± 2 days is allowed
Admission to Clinical Unit		X																							
Inpatient Stay at Clinical Unit			←----------					----------→																	
Informed consent	X																								
Inclusion and exclusion criteria	X	X																							
Demography	X																								
Full physical exam incl height and weight	X																								
Brief Physical		X																						X	
Medical history (includes substance usage)	X																								Substances: [Drugs, Alcohol, tobacco and caffeine]
Past and current medical conditions	X																								
SH and oestradiol (women)	X																						X		

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																						Follow-up (7-14 days following last dose)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Clinical Safety Laboratory Assessments *(HIV, Hep B and Hep C Screen at screening only[1])* – except Core Urine Monitoring Assessments	X	X		X			X		X								X[2]						X	X	On dosing days, samples to be taken in the morning pre-dose. [1]If performed within 3 months prior to first dose of study treatment, testing at screening is not required. [2]Visit day ± 2 days is allowed
Clinical Chemistry Only			X		X																				
Core Urine Monitoring Assessments	X	X	X		X		X		X								X[2]						X	X	Samples for Urine pH to be taken in the morning. [2]Visit day ± 2 days is allowed
Urine Sample (for storage)		X																							
Urine Drug/Alcohol Breath Test	X	X																					X		
12-lead ECG and vital signs	X	X	X	X	X	X	X	X	X								X[2]						X	X	Triplicate for all. Pre-dose and 1hr post-dose. [2]Visit day ± 2 days is allowed
Home Dosing Record									←----------→																
Study Treatment			**Cohort 4a:** Dose and dosing frequency may be altered once during treatment period ←----------→ **Cohort 4b:** dosing regimen will be determined based on information from Cohort 4a																						D21 a.m. dosing only

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																					Follow-up (7-14 days following last dose)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Blood Sampling (PK)			For sampling time points, see Section 7.4.1 in protocol																				X	For 1st dose and escalation See Section 7.4.1 in protocol
Blood Sampling (PD)			For sampling time points, see Section 7.5 in protocol																				X	
Discharge from Clinical Unit									X															Following completion of all assessments
PGx Sample			X																					Pre-dose if possible. Informed consent for optional genetics research must be obtained before collecting a sample
AE/SAE review		←----------→																					X	
Concomitant medication review	X	←----------→																					X	

10.1.4. Part B – Cohort 4, 21 day repeat dose healthy volunteer subjects – dose alteration (only if dose alteration is required)

Should a dose alteration be required, subjects will be re-admitted to the clinical unit and the procedures be administered as stated below. **Note:** The 'Dose Day' relates to the first day of the adjusted dose, and not the study day.

Procedure	Dose Days								Notes
	-1	1	2	3	4	5	6	7	
Admission to Clinical Unit	X								
Inpatient Stay at Clinical Unit		←----------→							
SH and oestradiol (women)									
Clinical Safety Laboratory Assessments – except Core Urine Monitoring Assessments	X		X			X		X	On dosing days, samples to be taken in the morning pre-dose.
Clinical Chemistry Only		X		X					
Core Urine Monitoring Assessments	X	X		X		X		X	Samples for Urine pH to be taken in the morning
Urine Drug/Alcohol Breath Test	X								
12-lead ECG and vital signs	X	X	X	X	X	X	X	X	Triplicate for all. Pre-dose and 1hr post-dose
Study Treatment		←----------→							
Blood Sampling (PK)		For sampling time points, see Section 7.4.1 in protocol							
Blood Sampling (PD)		For sampling time points, see Section 7.5 in protocol							
Discharge from Clinical Unit								X	Following completion of all assessments
AE/SAE review	←----------→								
Concomitant medication review	←----------→								

10.1.5. Part C – Cohort 5, repeat dose, patient subjects

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																Safety Follow-up (7-14 days after last dose)	PD Follow-up (weekly up to D63)
		-1	1	2	3	4	5	6	7	8	9-11	12	13+14	15	16+17	18	19+20	21	
Outpatient Visit	X											X		X		X		X	X	
Admission to Clinical Unit		X																		
Inpatient Stay at Clinical Unit			←----------																	
Informed consent	X																			
Inclusion and exclusion criteria	X	X																		
Demography	X																			
Full physical exam incl height and weight	X																			
Medical history (includes substance usage)[1]	X																			
Past and current medical conditions	X																			
FSH and oestradiol (women)	X											X		X		X		X	X	
Clinical Safety Laboratory Assessments[2] *(HIV, Hep B and Hep C Screen at screening only[3])* – except Core Urine Monitoring Assessments	X	X		X			X			X		X		X		X		X	X	X
Clinical Chemistry Only			X		X				X											
High-sensitivity cardiac Troponin[3]	X		X																	

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																Safety Follow-up (7-14 days after last dose)	PD Follow-up (weekly up to D63)
		-1	1	2	3	4	5	6	7	8	9-11	12	13+14	15	16+17	18	19+20	21	
Core Urine Monitoring Assessments (except Spot UPC ratio)[4]	X		X		X		X		X	X		X		X		X		X	X	X
Urine Sample (for storage)		X																		
Urine Drug/Alcohol Breath Test	X	X										X		X		X		X	X	
Echocardiogram[5]	X																			
12-lead ECG and vital signs	X	X	X	X			X			X		X		X		X		X	X	
Lead II monitoring[6]	X[8]	←---------- →																		
Home Dosing Record											X	X	X	X	X	X	X	X		
Study Treatment			←----------															→		
Blood Sampling (PK)			For sampling time points, see Section 7.4.1 in protocol																	
Blood Sampling (PD)			For sampling time points, see Section 7.5 in protocol																X	X
Brief Physical		X																	X	
Discharge from Clinical Unit										X										
PGx Sample[7]			X																	
AE/SAE review		←----------																→	X	X
Concomitant medication review	X	←----------																→	X	

1. Substances: Drugs, Alcohol, tobacco and caffeine
2. On dosing days, samples to be taken in the morning pre-dose.
3. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
4. Samples to be taken in the morning pre-dose.
5. Patients with known cardiac amyloid involvement only. If test otherwise performed within 3 months of screening, and the patient has remained overall symptomatically stable during that time, then no testing at screening is required; otherwise, an echocardiogram is required at Screening
6. Patients with known cardiac involvement only. It is permissible to temporarily remove Telemetry from the subject for activities of daily living (e.g. showering) during patient monitoring
7. Informed consent for optional genetics research must be obtained before collecting a sample, sample to be collected pre-dose if possible
8. 7 day out-patient cardiac monitoring (Body Guardian or similar) only in patients with known cardiac involvement.

10.2. Appendix 2: Treatment States and Phases

10.2.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to dosing for the given study part. Treatment phase classifications will be by study part.

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

10.2.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment for the given study part. AE summaries and hence the classification of treatment states for AE data will be by study part.

10.2.2.1. Treatment States for AE Data

Treatment State	Definition
Onset Time Since First Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF

NOTES:

- If the study treatment stop date is missing and study treatment start date ≤ AE start date then the AE will be considered to be On-Treatment.
- Treatment start/stop dates relate to the start/end of treatment for a given study part.

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

		Treatment Group Descriptions		
		RandAll NG		Data Displays for Reporting
Part	Cohort	Code	Description	Description
A	1	A	Regimen A	GSK3039294 xxx mg
A	1	B	Regimen B	GSK3039294 xxx mg
A	2	C	Regimen C	GSK3039294 xxx mg
A	2	D	Regimen D	GSK3039294 xxx mg
B	3	E	Regimen E	GSK3039294 xxx mg XX
B	4a	F	Regimen F	GSK3039294 xxx mg XX
B	4a	G	Regimen G	GSK3039294 xxx mg XX
B	4b	H	Regimen H	GSK3039294 xxx mg XX
B	4b	I	Regimen I	GSK3039294 xxx mg XX
C	5	J	Regimen J	GSK3039294 xxx mg XX

xxx to be imputed with dose level
XX to be imputed with dosing frequency
The decision to proceed to each subsequent dose level will be made by the Dose Escalation Committee (DEC)

10.3.2. Baseline Definition & Derivations

10.3.2.1. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-dose assessment within a given study part, i.e. Day 1 (pre-dose) if available, or Day -1 if Day 1 (pre-dose) not available, or Screening if Day -1 and Day 1 (pre-dose) not available.

10.3.2.2. Derivations and Handling of Missing Baseline Data

Change from Study Part Baseline = Post-Dose Visit Value – Study Part Baseline.

If baseline data is missing no derivation will be performed and it will be set to missing.

10.3.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: \ARPROD\GSK3039294\RAD201664\Final_01
QC Spreadsheet	: \ARWORK\ GSK3039294\RAD201664\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.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: o Planned time relative to dosing will be used in summary figures and tables. o Actual time relative to dosing will be used in individual profile plots over time. o The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned results will be presented within the subject's listings.

Reporting Standards	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • All unscheduled visits will be included in listings and figures of individual profiles over time.	
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 geometric coefficient of variation (CVb (%)) will be reported. CVb (%) = √ (exp(SD2) - 1) * 100 [NOTE: SD = SD of log transformed data]
Parameters Not Being Log Transformed	tmax (note: tmax will be summarised).
Parameters Not Being Summarised	Clast, Lambda_z, Lambda_z_lower, Lambda_z_upper, #pts, r-squared, tlast.
Listings	All PK parameters (see Table 5).
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

10.4. Appendix 4: Derived and Transformed Data

10.4.1. General

'Any Visit Post-Baseline' Timepoint for Summaries
• Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Part Day

• Calculated as the number of days from randomisation date for given study part:
  • Ref Date = Missing → Study Part Day = Missing
  • Ref Date < Randomisation Date → Study Part Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Part Day = Ref Date –(Randomisation Date)+1

10.4.2. Study Population

Demographics
Age

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

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2]**

Extent of Exposure
• Exposure will be calculated/presented by study part. • Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

10.4.3. Safety

ECG Parameters
Corrected QT an RR Intervals
• QTcB will be provided directly in the eCRF. • QTcF and RR will not be derived or provided directly in the eCRF.

Non-Quantifiable Laboratory and Biomarker Parameters
For laboratory values < lower limit of quantification: • the character value ('<x') will be listed; • the numeric value will be imputed as half the limit of quantification (x/2) for figures and tables. For laboratory values > upper limit of quantification: • the character value ('>x') will be listed; • the numeric value will be imputed as the limit of quantification (x) for figures and tables.

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

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.5.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.5.2.1. Handling of Missing/Partial Dates

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

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  • Missing Start Day: First of the month will be used unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered On-treatment as per Appendix 2: Treatment States and Phases).
	  • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Element	Reporting Detail

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. Values of Potential Clinical Importance (Healthy Volunteers)

Laboratory Values of Potential Clinical Importance (Healthy Volunteers)

Hematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count		0.67	1.82
Neutrophil Count		0.83	
Hemoglobin	Male		1.03
	Female		1.13
Hematocrit	Male		1.02
	Female		1.17
Platelet Count		0.67	1.57
Lymphocytes		0.81	

Chemistry Analyte	Low	High	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
Albumin (g/L)	30		0.86	
Calcium (mmol/L)	2	2.75	0.91	1.06
Glucose (mmol/L)	3	9	0.71	1.41
Magnesium (mmol/L)	0.5	1.23	0.63	1.03
Phosphorus (mmol/L)	0.8	1.6	0.80	1.14
Potassium (mmol/L)	3	5.5	0.86	1.10
Sodium (mmol/L)	130	150	0.96	1.03
Total CO_2 (mmol/L)	18	32	0.86	1.14
△ Creatinine (µmol/L)		↑44.2		

Liver Function Test Values of Potential Clinical Importance (Healthy Volunteers)

Liver Function Test Analyte	Effect	Potential Clinical Importance (PCI) Range	Unit
ALT/SGPT	High	≥ 2x ULN	U/L
AST/SGOT	High	≥ 2x ULN	U/L
AlkPhos	High	≥ 2x ULN	U/L
T. Bilirubin	High	≥ 1.5x ULN	μmol/L
T. Bilirubin + ALT	High	≥ 1.5x ULN T.Bilirubin + ≥ 2x ULN ALT	μmol/L U/L

ECG Values of Potential Clinical Importance (Healthy Volunteers)

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc Interval	>450	msec
Increase from Baseline QTc	>60	msec
PR Interval	<110 and >220	msec
QRS Interval	<75 and >110	msec

Vital Sign Values of Potential Clinical Importance (Healthy Volunteers)

VS Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	<85 and >160	mmHg
Diastolic Blood Pressure	<45 and >100	mmHg
Heart Rate	<40 and >110	bpm
Systolic Blood Pressure (Change from Baseline)	Decrease ≥20 and ≥40	mmHg
	Increase ≥20 and ≥40	mmHg
Diastolic Blood Pressure (Change from Baseline)	Decrease ≥10 and ≥20	mmHg
	Increase ≥10 and ≥20	mmHg
Heart Rate (Change from Baseline)	Decrease ≥15 and ≥30	bpm
	Increase ≥15 and ≥30	bpm

10.6.2. Values of Potential Clinical Importance (Systemic Amyloidosis Patients)

Laboratory Values of Potential Clinical Importance (Systemic Amyloidosis Patients)

Haematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count		0.60	1.82
Neutrophil Count		0.60	
Haemoglobin	Male	0.75	1.2
	Female	0.70	1.2
Haematocrit	Male		1.2
	Female		1.2
Platelet Count		0.60	1.50
Lymphocytes		0.60	

Chemistry Analyte	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
Albumin (g/L)	0.70	
Calcium (mmol/L)	0.80	1.20
Glucose (mmol/L)	0.60	2.00
Magnesium (mmol/L)	0.60	1.20
Phosphorus (mmol/L)	0.60	1.30
Potassium (mmol/L)	0.86	1.10
Sodium (mmol/L)	0.92	1.10
Total CO_2 (mmol/L)	0.75	1.30

Liver Function Test Values of Potential Clinical Importance (Systemic Amyloidosis Patients)

Liver Function Test Analyte	Effect	Potential Clinical Importance (PCI) Range	Unit
ALT/SGPT	High	>3x ULN	U/L
AST/SGOT	High	>3x ULN	U/L
AlkPhos	High	>3x ULN	U/L
T. Bilirubin	High	>2x ULN	μmol/L
T. Bilirubin + ALT	High	> 1.5x ULN T.Billirubin + > 3x ULN ALT	μmol/L U/L

ECG Values of Potential Clinical Importance (Systemic Amyloidosis Patients)

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc Interval	>500	msec
Increase from Baseline QTc	>60	msec
PR Interval	<110 and >220	msec
QRS Interval	<75 and >110	msec

Vital Sign Values of Potential Clinical Importance (Systemic Amyloidosis Patients)

VS Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	<100 and > 180	mmHg
Diastolic Blood Pressure	<30 and > 110	mmHg
Heart Rate	<35 and > 140	Bpm
Systolic Blood Pressure (Change from Baseline)	Increase >30	mmHg
	Decrease < 30	mmHg
Diastolic Blood Pressure (Change from Baseline)	Increase > 30	mmHg
	Decrease < 30	mmHg
Heart Rate (Change from Baseline)	Increase > 50	bpm
	Decrease < 50	bpm

10.7. Appendix 7: Pharmacokinetic / Pharmacodynamic Analyses

10.7.1. Systems

All non-linear mixed effects modelling will be performed using NONMEM (ICON Solutions) and PsN (Perl Speaks NONMEM). R (The R Foundation for Statistical Computing) will be used for exploratory graphical analysis, graphical model diagnostics and, if needed, modifications of the dataset. The analysis will be performed by, or under the direct auspices of, CPMS, GlaxoSmithKline in the GSK modelling environment PME (Predictive Modelling Environment) using the currently supported versions of all software packages.

10.7.2. Data Assembly

The merge of PK, PD, regimen and CRF data together with the creation of the NONMEM-specific dataset will be performed by, or under the direct auspices of, Clinical Statistics (Programmer), GlaxoSmithKline. This dataset programming will be conducted in the GSK Harmonisation for Analysis and Reporting Program (HARP) environment using the currently supported version of SAS. The dataset will be consistent with the specifications summarised in Section 10.7.5.

10.7.3. PK/PD Modelling of GSK2315698 and SAP Concentrations

An exploratory graphical analysis of the data will be performed by generating the plots as presented in Appendix 9: List of Data Displays.

A PK/PD model for GSK2315698 and its effect on plasma SAP levels was developed previously [Sahota, 2015]. Covariates in this model are creatinine clearance (affecting GSK2315698 clearance), subject gender (affecting SAP baseline), and baseline amyloid load (affecting SAP distribution). Because of the target mediated drug disposition (TMDD) of GSK2315698, PK and PD will be analysed simultaneously, or parameters of either PK or PD will be fixed to reported estimates while exploring PD or PK, respectively.

As a first step the oral absorption of GSK3039294 and conversion into GSK2315968 will be added to the model. To that end, all available plasma GSK2315968 data will be analysed using the PK/PD model, extended with first order absorption and oral bioavailability. Based on preclinical data it is expected that the conversion of GSK3039294 to GSK2315698 is very fast. Therefore, it will be assumed that this conversion will occur mainly during the absorption phase, and that the distribution and elimination of GSK2315698 are not altered. GSK3039294 and the intermediate molecule GSK3037412 do not affect plasma SAP levels, and therefore it will be assumed that the PK/PD relationship between GSK2315698 and SAP is not changed.

Summarising, this means that for the first step all distribution and elimination parameters and all PD parameters will be fixed to the reported parameter estimates, and only bioavailability (F) and absorption related parameters (e.g. Ka) will be estimated. If a simple first order process for oral absorption and conversion is not sufficient to describe

the data (e.g. in case the conversion does not occur very fast), the part of the PK/PD model describing the absorption and conversion into GSK2315698 will be developed in a data driven fashion.

Subsequently, using the PK/PD model updated for oral absorption of GSK3039294 and conversion into GSK2315698, visual predictive checks (VPCs) will be conducted to assess graphically whether simulations from the PK/PD model are able to reproduce both the central trend and variability in the observed SAP concentrations from the current study as a function of time.

This VPC will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, time of SAP sampling and individual values of model covariates). The median and the 5th and 95th percentiles (or 10th and 90th, dependent on the size of the final dataset) will be compared to the observed data. Applicable stratification, such as dose level of GSK3039294 and baseline amyloid load, will be used.

If the VPC shows a difference between the simulated and observed PK, it will be investigated if the population PK/PD model can be adjusted with the current PK and SAP data. This process will be data driven.

10.7.4. Diagnostics

Model acceptability will be judged by convergence, covariance estimation and standard goodness-of-fit plots that may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time.

For the final PK/PD model, visual predictive checks (VPCs) will be conducted as described in Section 10.7.3.

10.7.5. Specifications for NONMEM-specific Dataset

The concentration dataset will be a comma delimited text file, named "NM_GSK2315698_201664_PKPD_v1.csv". The version number will be updated each time a new version is created and issued.

This file will include events of dosing, GSK3039294, GSK2315698 or SAP concentration as rows, with the variables in the table below as columns. Rows will be in increasing order of unique subject identification number; and all events in the same subject must be consecutive and in chronological order, ending with the last GSK3039294 / GSK2315698 / SAP concentration event (i.e. dosing events that occur after the last quantifiable concentration in a subject will not be included in the data file).

Non-numerical concentration values (such as missing samples, not assayed samples, non-quantifiable samples or non-reportable samples) will not be included. Subjects with no quantifiable concentration values will not be included.

Name	Implicit Unit	Description	Programming Notes	Format
ID	-	Unique subject identification number		numeric
TRFD	h	Event time from start of first dose of GSK3039294 for each subject		numeric
DV	mg/L	For concentration events: plasma concentration of GSK3039294 or GSK2315698 or SAP For dosing events: 0		numeric
AMT	mg	For dosing events: dose of GSK3039294 For concentration events: 0		numeric
MDV	-	For concentration events: 0 For dosing events: 1		Numeric
CMT	-	Compartment: For dosing events: 1 For GSK3039294 concentration events: 2 For GSK2315698 concentration events: 3 For SAP concentration events: 5		Numeric
NOMT	h	Planned sample time for GSK3039294/GSK2315698/SAP For dosing events: 0 For pre-dose concentration events: 0		Numeric
TRLD	h	Event time from most recent dose of GSK3039294 For dosing events: 0		Numeric
PERD	-	Study period (part): PART A COHORT 1 DOSE 1 =1 PART A COHORT 1 DOSE 2=2 PART A COHORT 2 DOSE 1=3 PART A COHORT 2 DOSE 2=4 PART B COHORT 3=5 PART B COHORT 4=6 PARTB COHORT 4 ALT=7 PART C COHORT 5=8		Numeric
DOSE	mg	Total daily dose of GSK3009294 in mg (for all events)		Numeric

Name	Implicit Unit	Description	Programming Notes	Format
STUD	-	Numeric part of study identifier (i.e. 201664)		Numeric
FED	-	Fed/fasted status: Part A and Week 1 of Part B (except for Day 5): 0 All other: 1		Numeric
POP	-	Study population: Healthy volunteers (Parts A&B): 0 Patients (Part C): 1		Numeric
AGE	Years	Age at study baseline		Numeric
WT	Kg	Weight at event date, or nearest available previous value in same subject		Numeric
BMI	kg/m^2	Body mass index at event date, or nearest available previous value in same subject		Numeric
SEX	-	Subject gender: Male=0 Female=1		Numeric
CRCL	mL/min	Creatinine clearance at session baseline (from MDRD measurement at screening visit)		Numeric
AMLOAD	-	Overall amyloid load at session baseline: None=0 Small=1 Moderate=2 Large=3		Numeric

Name	Implicit Unit	Description	Programming Notes	Format
AMLOC	-	Liver involvement =1 No liver involvement =0		Numeric

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
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 subject across all treatments
AUC(0-6)	Area under the concentration-time curve from time zero (pre-dose) to 6 hours
AUC(0-24)	Area under the concentration-time curve from time zero (pre-dose) to 24 hours
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence Interval
Cmax	Maximum observed concentration
CminSAP	The first occurrence of the minimum observed plasma SAP concentration determined directly from the raw SAP concentration-time data
CPHPC	R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid
CPMS	Clinical Pharmacology Modelling and Simulation
CPSSO	Clinical Pharmacology Science and Study Operations
CV	Coefficient of variance
DEC	Dose Escalation Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
HARP	Harmonisation of Analysis & Reporting Program
hrs	Hours
IDSL	Integrated Data Standards Library
PD	Pharmacodynamic
PK	Pharmacokinetic
PCI	Potentially Clinically Important
PIMS	Patient Information Management System
QSI	Quantitative Sciences India
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event(s)
SAP	Serum Amyloid P component
SAS	Statistical Analysis Software
SD	Standard Deviation

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
SAS/STAT
WinNonlin

10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays. Each display will be repeated for each part (where applicable) with part information included in the title and will be identified in the numbering by the prefix x:

- x=1: Part A Healthy Volunteers, Single Dose
- x=2: Part B Healthy Volunteers, Repeat Dose
- x=3: Part C Systemic Amyloidosis Patients, Repeat Dose

Section	Tables	Figures
Study Population	1.x01 to 1.x08	N/A
Safety	2.x01 to 2.x16	2.x01
Pharmacokinetic	3.x01 to 3.x04	3.x01 to 3.x06
Pharmacodynamic	4.x01 to 4.x02	4.301 to 4.302
PK/PD	5.x01 to 5.x05	5.x01 to 5.x10
Section	**Listings**	
ICH Listings	1 to 27	
Other Listings	28 to 34	

10.9.2. Mock Example Referencing

Non IDSL specifications will be referenced as indicated, as applicable.

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 and Biomarker	PD_Fn	PD_Tn	PD_Ln

10.9.3. Deliverables

Deliverables	Description
IA	Renal safety interim analysis at end of Part B
SAC	Final SAC analysis at end of Part C

10.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.x01	Safety	CP_ES1 (XO)	Summary of Subject Disposition	Add part information in the title, repeat for all parts.	SAC
1.x02	Screened	ES6	Summary of Reasons for Screen Failures	Add part information in the title, repeat for all parts	SAC
Protocol Deviation					
1.x03	Safety	DV1	Summary of Important Protocol Deviations	Add part information in the title, repeat for all parts.	SAC
Demographics and Baseline Characteristics					
1.x04	Safety	DM3 (XO)	Summary of Demographic characteristics	Include BMI Add part information in the title, repeat for all parts.	SAC
1.x05	Safety	DM5	Summary of Race and Racial Combinations	Add part information in the title, repeat for all parts.	SAC
1.x06	Safety	DM6	Summary of Race and Racial Combinations Details	Add part information in the title, repeat for all parts.	SAC
1.x07	Enrolled	DM11	Summary of Age Ranges	Add part information in the title, repeat for all parts.	SAC
Prior and Concomitant Medications					
1.x08	Safety	MH1	Summary of Current/Past Medical Conditions	Add part information in the title, repeat for all parts.	SAC

10.9.5. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
2.x01	Safety	EX1	Summary of Exposure to Study Treatment	Add part information in the title, repeat for all parts	SAC
Adverse Events					
2.x02	Safety	CP_AE1x (xo)	Summary of All Adverse Events by System Organ Class and Preferred Term	Add part information in the title, repeat for all parts.	SAC
2.x03	Safety	CP_AE1x (xo)	Summary of Drug-Related Adverse Events	Add part information in the title, repeat for all parts.	SAC
2.x04	Safety	AE15	Summary of Common (>=X%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Add part information in the title, repeat for all parts.	SAC
Labs					
2.x05	Safety	LB1	Summary of Chemistry Changes from Baseline	Add part information in the title, repeat for all parts.	SAC
2.x06	Safety	LB17	Summary of Emergent Laboratory Results by Potential Clinical Importance (PCI) Criteria	Add part information in the title, repeat for all parts.	SAC
2.x07	Safety	LB15	Summary of Emergent Laboratory Results Relative to Normal Range	Add part information in the title, repeat for all parts.	SAC
2.x08	Safety	LB1	Summary of Haematology Changes From Baseline	Add part information in the title, repeat for all parts.	SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.x09	Safety	LB17	Summary of Emergent Hematology Results by Potential Clinical Importance (PCI) Criteria	Add part information in the title, repeat for all parts.	SAC
2.x10	Safety	LB15	Summary of Emergent Hematology Results Relative to Normal Range	Add part information in the title, repeat for all parts.	SAC
2.x11	Safety	UR3	Summary of Urinalysis Dipstick Results	Add part information in the title, repeat for all parts.	SAC
2.x12	Safety	LB1	Summary of Urine Concentration Changes from Baseline	Add part information in the title, repeat for all parts.	SAC
Vital Signs					
2.x13	Safety	VS1	Summary of Vital Signs	Add part information in the title, repeat for all parts.	SAC
2.x14	Safety	VS1	Summary of Change From Baseline for Vital Signs	Add part information in the title, repeat for all parts.	SAC
Telemetry					
2.x15	Safety	HM1	Summary of Telemetry Interpretations	Part B Cohort 3 and Part C patients with known cardiac amyloid involvement only	SAC
2.x16	Safety	HM2	Summary of Telemetry Abnormalities	Part B Cohort 3 and Part C patients with known cardiac amyloid involvement only	SAC

10.9.6. Safety Figures

Safety Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.x01	Safety	pkcf1x	Individual Profiles Over Time for Renal Parameters by Parameter	IA at the end of Part B - Add part information in the title, repeat for Part A and B. SAC – Part C only.	IA/SAC

10.9.7. Pharmacokinetic Tables

These tables are the responsibility of Clinical Statistics.

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK Concentration Data					
3.x01	PK	PKCT1	Summary of Plasma GSK2315698 Pharmacokinetic Concentration-Time Data by Dose Level	Add part information in the title, repeat for all parts.	SAC
3.x02	PK	PKCT1	Summary of Plasma GSK3039294 Pharmacokinetic Concentration-Time Data by Dose Level	Add part information in the title, repeat for all parts.	SAC
PK Parameters					
3.103	PK	PKPT1	Summary of Plasma GSK2315698 Pharmacokinetic Parameters by Dose Level - Part A Healthy Volunteers, Single Dose		SAC

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.203	PK	PKPT1	Summary of Plasma GSK2315698 Pharmacokinetic Parameters - Part B Healthy Volunteers, Repeat Dose, Cohort 3 Day 4 and 5 (Food Effect Exploration)	Page by Day	SAC
3.104	PK	PKPT1	Summary of Plasma GSK3039294 Pharmacokinetic Parameters by Dose Level - Part A Healthy Volunteers, Single Dose		SAC
3.204	PK	PKPT1	Summary of Plasma GSK3039294 Pharmacokinetic Parameters - Part B Healthy Volunteers, Repeat Dose, Cohort 3 Day 4 and 5 only (Food Effect Exploration)	Page by Day	SAC

10.9.8. Pharmacokinetic Figures

. **Pharmacokinetic : Figures -** These figures are the responsibility of Clinical Statistics					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK					
3.101	PK	pkcf6	Individual Plasma GSK2315698 Concentration-Time Plot by Dose (Linear and Semi-Log) Part A Healthy Volunteers, Single Dose	**Page By:** NA **Panel By:** Dose level **X-Axis:** Time Post Dose (h) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish subject IDs	SAC

. **Pharmacokinetic : Figures -** These figures are the responsibility of Clinical Statistics					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.202	PK	pkcf1x	Individual Plasma GSK2315698 Concentration-Time Plot by Subject (Linear and Semi-Log) Part B Healthy Volunteers, Single Dose, Cohort 3 Days 4 and 5 only (Food Effect Exploration)	**Page By:** Scale – linear and semi-log **Panel By:** Subject ID **X-Axis:** Time Post Most Recent Dose (h) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish Day 4 (fasted) vs Day 5 (fed)	SAC
3.203	PK	pkcf6	Individual Plasma GSK2315698 Concentration-Time Plot by Day (Linear and Semi-Log) Part B Healthy Volunteers, Single Dose, Cohort 3 Days 4 and 5 only (Food Effect Exploration)	**Page By:** NA **Panel By:** Fed / Fasted **X-Axis:** Time Post Most Recent Dose (h) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish subject IDs **Note:** Fed is Day5, Fasted is Day 4	SAC
3.201	PK	pkcf6	Individual Plasma GSK2315698 Concentration-Time Plot of Pre-Dose Samples (Semi-Log) Part B Healthy Volunteers, Single Dose	**Page By:** NA **Panel By:** Cohort **X-Axis:** Time Post First Dose (day) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish dose levels See protocol Section 7.4.1 for days on which pre-dose samples are planned	SAC

. **Pharmacokinetic : Figures -** These figures are the responsibility of Clinical Statistics					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.301	PK	pkcf6	Individual Plasma GSK2315698 Concentration-Time Plot of Pre-Dose Samples (Semi-Log) Part C Systemic Amyloidosis Patients, Repeat Dose	**Page By:** NA **Panel By:** NA **X-Axis:** Time Post First Dose (day) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish dose levels See protocol Section 7.4.1 for days on which pre-dose samples are planned	SAC
Median Concentration-Time Plots					
3.102	PK	Pkcf5	Median Plasma GSK2315698 Concentration-Time Plot (Linear and Semi-Log) Part A Healthy Volunteers, Single Dose	**Page By:** NA **Panel By:** Scale – linear and semi-log **X-Axis:** Time Post Dose (day) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish dose level	SAC
3.205	PK	Pkcf5	Median Plasma GSK2315698 Concentration-Time Plot (Linear and Semi-Log) Part B Healthy Volunteers, Single Dose Cohort 3 Days 4 and 5 only	**Page By:** NA **Panel By:** Scale – linear and semi-log **X-Axis:** Time Post Most Recent Dose (h) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish Day 4 (fasted) vs Day 5 (fed)	SAC

. **Pharmacokinetic : Figures -** These figures are the responsibility of Clinical Statistics					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.204	PK	Pkcf5	Median Plasma GSK2315698 Concentration-Time Plot of Pre-Dose Samples (Semi-Log) Part B Healthy Volunteers, Single Dose	**Page By:** NA **Panel By:** NA **X-Axis:** Time Post First Dose (day) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish dose levels See protocol Section 7.4.1 for days on which pre-dose samples are planned	SAC
3.302	PK	Pkcf5	Median Plasma GSK2315698 Concentration-Time Plot of Pre-Dose Samples (Semi-Log) Part C Systemic Amyloidosis Patients, Repeat Dose	**Page By:** NA **Panel By:** NA **X-Axis:** Time Post First Dose (day) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish dose levels See protocol Section 7.4.1 for days on which pre-dose samples are planned	SAC

. **Pharmacokinetic : Figures -** These figures are the responsibility of Clinical Statistics					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK Parameters					
3.103	PK		Dose-normalised GSK2315698 PK Parameters versus Dose Level Part A Healthy Volunteers, Single Dose	**Page By:** Parameter **Panel By:** NA **X-Axis:** Dose level (mg) **Y-Axis:** PK parameter (unit) **Legend:** NA **Note:** Only plot AUC(0-inf)/D, AUC(0-t)/D and Cmax/D	SAC
3.206	PK		GSK2315698 PK Parameters versus Fed/Fasted Status Part B Healthy Volunteers, Single Dose Cohort 3 Days 4 and 5 only	**Page By:** Parameter **Panel By:** NA **X-Axis:** Fed / Fasted **Y-Axis:** PK parameter (unit) **Legend:** NA **Note:** Only plot AUC(0-6) and Cmax; Fed is Day5, Fasted is Day 4	SAC

10.9.9. Pharmacodynamic Tables

These tables are the responsibility of Clinical Statistics.

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma SAP Concentrations					
4.x01	PD	PD1/PD2	Summary of Absolute Plasma SAP Concentration Data	Add part information in the title, repeat for parts B and C. Part B by dosing regimen. Data transformation as required. Include 95% CI	SAC
4.x02	PD	PD4	Summary of Plasma SAP parameters	Add part information in the title, repeat for parts B and C. $Cmin_{SAP}$ (Part B & C). Part B by dosing regimen. Part C by baseline total body amyloid load (large/non-large) and overall. $tmin_{SAP}$, $Trep_{SAP\_80\%}$, $Trep_{SAP\_90\%}$, $Trep_{SAP\_100\%}$. Part C only. By baseline total body amyloid load (large/non-large) and overall.	SAC

10.9.10. Pharmacodynamic Figures

These figures are the responsibility of Clinical Statistics.

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Individual Plasma SAP Concentrations					
4.301.	PD	pkcf6?	Individual Plasma SAP Concentration-Time Plot of Pre-Dose Samples by Amyloid Load (Linear and Semi-Log) Part C Systemic Amyloidosis Patients, Repeat Dose	**Page By:** Scale – linear and semi-log **Panel By:** Amyloid load category (HV=none; patients=low/moderate/high) **X-Axis:** Time Post First Dose (day) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish dose levels	SAC
4.302.	PD	pkcf6?	Individual Plasma SAP Concentration-Time Plot At Day 21 by Amyloid Load (Semi-Log) Part C Systemic Amyloidosis Patients, Repeat Dose	**Page By:** NA **Panel By:** Amyloid load category (HV=none; patients=low/moderate/high) **X-Axis:** Time Post Most Recent Dose (h) **Y-Axis:** Result **Legend:** Symbols/ lines distinguish subject IDs	SAC

10.9.11. Pharmacokinetic / Pharmacodynamic Tables

These tables are the responsibility of Clinical Pharmacology Modelling and Simulation.

Pharmacokinetic / Pharmacodynamic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Population PK/PD Analysis					
5.1.	PK/PD		Summary Table of Parameter Estimates of Base Model		SAC
5.2.	PK/PD		Summary Table of Parameter Estimates of Final Model		SAC
5.3.	PK/PD		Summary Table of Models Tested		SAC
5.4.	PK/PD		NONMEM Output File of Base Model (with Control File)		SAC
5.5.	PK/PD		NONMEM Output File of Final Model (with Control File)		SAC

10.9.12. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures - Figures 5.01 to 5.06 are the responsibility of CPMS; Figures 5.07 to 5.10 are the responsibility of CS					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable]**
Population PK/PD Analysis					
5.01	PK/PD		Goodness of Fit Plots of Base Model (GSK2315698 Concentration Data)		SAC
5.02	PK/PD		Goodness of Fit Plots of Final Model (GSK2315698 Concentration Data)		SAC
5.03	PK/PD		Goodness of Fit Plots of Base Model (SAP Concentration Data)		SAC
5.04	PK/PD		Goodness of Fit Plots of Final Model (SAP Concentration Data)		SAC

Pharmacokinetic / Pharmacodynamic: Figures - Figures 5.01 to 5.06 are the responsibility of CPMS; Figures 5.07 to 5.10 are the responsibility of CS					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable]**
5.05	PK/PD		Visual Predictive Check of Final Model (GSK2315698 Concentration Data)		SAC
5.06	PK/PD		Visual Predictive Check of Final Model (SAP Concentration Data)		SAC
5.07/ 5.08	PK/PD		Scatter Plot of $Cmin_{SAP}$ versus GSK2315698 (CPHPC) AUC[0-24]	Add part information in the title, repeat for parts B and C. **X-Axis:** GSK2315698 AUC[0-24] **Y-Axis:** $Cmin_{SAP}$ For both parts B and C. Panel by dosing regimen for Part B. Use a different plotting character for large and non-large amyloid load patients for Part C. Include a legend to highlight this	SAC
5.09/ 5.10	PK/PD		Scatter Plot of $Cmin_{SAP}$ versus GSK3039294 (pro-drug) dose	Add part information in the title, repeat for parts B and C. **X-Axis:** GSK3039294 dosage **Y-Axis:** $Cmin_{SAP}$ For both parts B and C. Panel by dosing regimen for Part B. Use a different plotting character for large and non-large amyloid load patients for Part C. Include a legend to highlight this	SAC

10.9.13. ICH Listings

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Randomisation					
1	Safety	CP_TA1	Listing of Randomised and Actual Treatments	Page by study part	SAC
Subject Disposition					
2	Safety	ES2	Listing of Reasons for Study Withdrawal	Page by study part	SAC
3	Screened	ES7	Listing of Reasons for Screening Failure	Page by study part	SAC
Populations Analysed					
4	Screened	SA3a	Listing of Subjects Excluded from Any Populations	Page by study part	SAC
Protocol Deviations					
5	Safety	DV2	Listing of Important Protocol Deviations	Page by study part	SAC
6	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	Page by study part	SAC
Demographics					
7	Safety	DM2	Listing of Demographic Characteristics	Page by study part	SAC
8	Safety	DM9	Listing of Race	Page by study part	SAC
Concomitant Medications					
9	Safety	CP_CM3	Listing of Concomitant Medications	Page by study part	SAC

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
10	Safety	EX3	Listing of Exposure	Page by study part	SAC
Adverse Events					
11	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	Page by study part	SAC
12	Safety	CP_AE9	Listing of All Adverse Events	Page by study part	SAC
13	Safety	CP_AE9	Listing of Serious Adverse Events (Fatal and Non-Fatal)	Page by study part. Include column to flag if event is drug related	SAC
14	Safety	CP_AE9	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Page by study part	SAC
15	Safety	AE2	Listing of Relationship between System Organ Class and Verbatim Text	Page by study part	SAC
LABS					
16	Safety	CP_LB6	Listing of Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	Page by study part	SAC
17	Safety	CP_LB6	Listing of Haematology Laboratory Data of Potential Clinical Importance	Page by study part	SAC
18	Safety	CP_LB6	Listing of Clinical Chemistry Laboratory Data for Subjects With Abnormalities of Potential Clinical Importance	Page by study part	SAC

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
19	Safety	CP_LB6	Listing of Clinical Chemistry Laboratory Data of Potential Clinical Importance	Page by study part	SAC
20	Safety	UR2b	Listing of Urinalysis Data	Include Microscopy and dipsticks Page by study part	SAC
21	Safety	UR2b	Listing of Urinalysis Data for Subjects with Abnormalities of Potential Clinical Importance	Include Microscopy and dipsticks Page by study part	SAC
22	Safety	UR2b	Listing of Urinalysis Data of Potential Clinical Importance	Include Microscopy and dipsticks Page by study part	SAC
ECGs					
23	Safety	CP_EG4	Listing of All ECG Values for Subjects with Abnormalities of Potential Clinical Importance	Page by study part	SAC
24	Safety	CP_EG4	Listing of ECG Values of Potential Clinical Importance	Page by study part	SAC
25	Safety	CP_EG6	Listing of Abnormal ECG Findings	Page by study part	SAC
Vital Signs					
26	Safety	CP_VS4	Listing of Vital Signs for Subjects with Abnormalities of Potential Clinical Importance	Page by study part	SAC
27	Safety	CP_VS4	Listing of Vital Signs of Potential Clinical Importance	Page by study part, flag high/low increase/decrease as per PCI	SAC

10.9.14. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK					
28	PK	pkcl1x	Listing of GSK3039294 Plasma Concentration-time Data	Page by study part	SAC
29	PK	pkpl1x	Listing of GSK3039294 Plasma Pharmacokinetic Parameters	Page by study part (Part A and Part B Cohort 3 Days 4 and 5)	SAC
30	PK	pkcl1x	Listing of GSK2315698 Plasma Concentration-time Data	Page by study part	SAC
31	PK	pkpl1x	Listing of GSK2315698 Plasma Pharmacokinetic Parameters	Page by study part (Part A and Part B Cohort 3 Days 4 and 5)	SAC
SAP					
32	PD		Listing of Plasma SAP concentrations	Page by study part (Part B & C only)	SAC
33	PD		Listing of Plasma SAP parameters	$Cmin_{SAP}$ (Part B & C). Part B by dosing regimen. $tmin_{SAP}$, $Trep_{SAP\_80\%}$, $Trep_{SAP\_90\%}$, $Trep_{SAP\_100\%}$. (Part C only). Page by study part (Part B & C only)	SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Other					
34	Safety	CP_ML1p	Listing of Dosing Times, Meal Start and End Times on Fed Treatment Days	Part B Cohort 3 Day (4 and) 5 only	SAC