Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for An Adaptive, Open-Label Study to Evaluate the Biodistribution of 89Zirconium-labelled GSK2398852 in the Heart and Other Organs of Patients with Transthyretin Cardiomyopathy (ATTR-CM) using Positron Emission Tomography (PET) Imaging
Compound Number	:	GSK2315698 + GSK2398852+ Radiolabelled 89Zr-GSK2398852
Effective Date	:	19-Feb-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204512.
- This RAP will be provided to the study team members to convey the content of the Interim and Final Statistical Analysis Complete (SAC) deliverable.

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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:

Revision Chronology:		
2016N308062_00	04-OCT-2017	Original

2. SUMMARY OF KEY PROTOCOL INFORMATION

The principal aim of this PET imaging study is to investigate the cardiac uptake of ^{89}Zr-GSK2398852 in patients with transthyretin amyloidosis restrictive cardiomyopathy (ATTR-CM), and its biodistribution to other organs.

This is an open-label non-randomised ^{89}Zr-GSK2398852 PET imaging study in clinically stable patients with either wild type or inherited ATTR-CM. Subjects will participate in up to two dosing sessions.

This study will be divided into two parts: Part A and an optional Part B.

All subjects will participate in a screening period of up to 35 days. Part A subjects (N=3) will participate in up to two dosing sessions approximately 26 days in duration (each). Part B subjects (N=3) will participate in one dosing session of approximately 26 days in duration. Total duration in the study will be approximately 3-4 months for Part A subjects, and approximately 2 months for Part B subjects.

2.1. Nomenclature

In this document:

- GSK2315698 is referred to as CPHPC (carboxy pyrrolidine hexanoyl pyrrolidine carboxylate).
- GSK2398852 is referred to as unlabelled anti SAP mAb.
- ^{89}Zirconium-desferrioxamine (Df) labelled anti-SAP mAb is referred to as ^{89}Zr-GSK2398852.
- The administration of CPHPC and anti-SAP mAb is referred to as Anti SAP treatment.
- Total Mass Dose (TMD) of anti-SAP mAb = unlabelled anti-SAP mAb + ^{89}Zr-GSK2398852.
- Throughout this document, the usage of Total mAb (or Total anti-SAP mAb) refers to both unlabelled and labelled mAb.

2.2. Changes to the Protocol Defined Statistical Analysis Plan

For analyzing the secondary objectives of characterization of the plasma pharmacokinetics of total mAb (unlabelled GSK2398852 and 89Zr-GSK2398852) and characterization of the plasma pharmacokinetics of radioactivity (89Zr-GSK2398852

radio-PK), the descriptive pharmacokinetic parameter of clearance is not analyzed as it is deemed not useful from the CPMS perspective.

The two PET scans with the administration of Oxygen-15 labelled water (WAT) for the characterization of the regional blood flow in the heart were not done due to logistical difficulties.

The PiB PET scan for the characterization of the regional amyloid burden in the heart is not being done due to logistical difficulties.

Descriptive statistics are not being presented for any of the generated PET imaging endpoints due to a small sample size.

The summaries for the generated PET imaging parameters will not be grouped by common total mass dose due to a small sample size.

Correlation of regional pattern of 89Zr-GSK2398852 uptake in the heart with the pattern of blood flow by MRI signal will be assessed informally using a scatter plot. Formal correlations will not be produced because of the small sample size.

The CMR/ECHO analysis will not be performed as this was a baseline safety measurement only, therefore the data were not databased.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
Assessment of ^{89}Zr-GSK2398852 cardiac uptake as evaluated by PET imaging at different mass doses	Standardized Uptake Values (SUV) [i.e. Radioactivity concentrations] in focal anatomical locations within the heart, as well as SUV of the whole heart at different time points after ^{89}Zr-GSK2398852 administration and at different anti-SAP mAb TMDs.
Secondary Objectives	**Secondary Endpoints**
Assessment of ^{89}Zr-GSK2398852 biodistribution in non-cardiac tissues and organs	Focal and total radioactivity uptake (including, but not limited to SUV) in different tissues (including potentially at those peripheral tissue sites where TTR amyloid deposition can be clinically occult) at different time points and after different TMDs.
Characterisation of the plasma pharmacokinetics of total mAb (unlabelled GSK2398852 and ^{89}Zr-GSK2398852)	Descriptive pharmacokinetic (PK) parameters, including the maximum concentration in plasma (Cmax), the time associated with Cmax (Tmax), clearance, terminal half-life (T½) and the area under the concentration-time profile (AUC).
Characterisation of the plasma pharmacokinetics of radioactivity (^{89}Zr-GSK2398852 radio-PK)	Descriptive PK parameters including Cmax, Tmax, clearance, T½ and AUC based on scintillation counter.
Safety & tolerability of Anti-SAP treatment including administration of ^{89}Zr-GSK2398852	All adverse events (AEs) including the incidence and grading of skin rashes, cardiac adverse events and infusion-related reactions, as well as other AEs utilizing standard pharmacovigilance practices.

Objectives	Endpoints
	Absolute changes in safety lab parameters, including cardiac troponin and N-terminal prohormone of brain natriuretic peptide (NT-ProBNP). Other safety information, including electrocardiogram (ECG), inpatient and outpatient cardiac telemetry, vital signs, and physical exam data.
Exploratory Objectives	**Exploratory Endpoints**
Correlation of regional pattern of ^{89}Zr-GSK2398852 uptake in the heart with the pattern of amyloid load by PiB scan and blood flow by WAT scan or MRI signal pattern	Maps of regional PET signals or MRI signals over the myocardium will be visually compared and scored. Regional derived PET and MRI parameters correlated within and across ATTR-CM patients.
Assess feasibility of patients to operate remote data collection equipment. This may include ECGs, vital signs, and streaming video device.	Number of "virtual visits" and number of additional remote assessments collected.

2.4. Study Design

Overview of Study Design and Key Features

Figure 1 Study Schematic – Part A

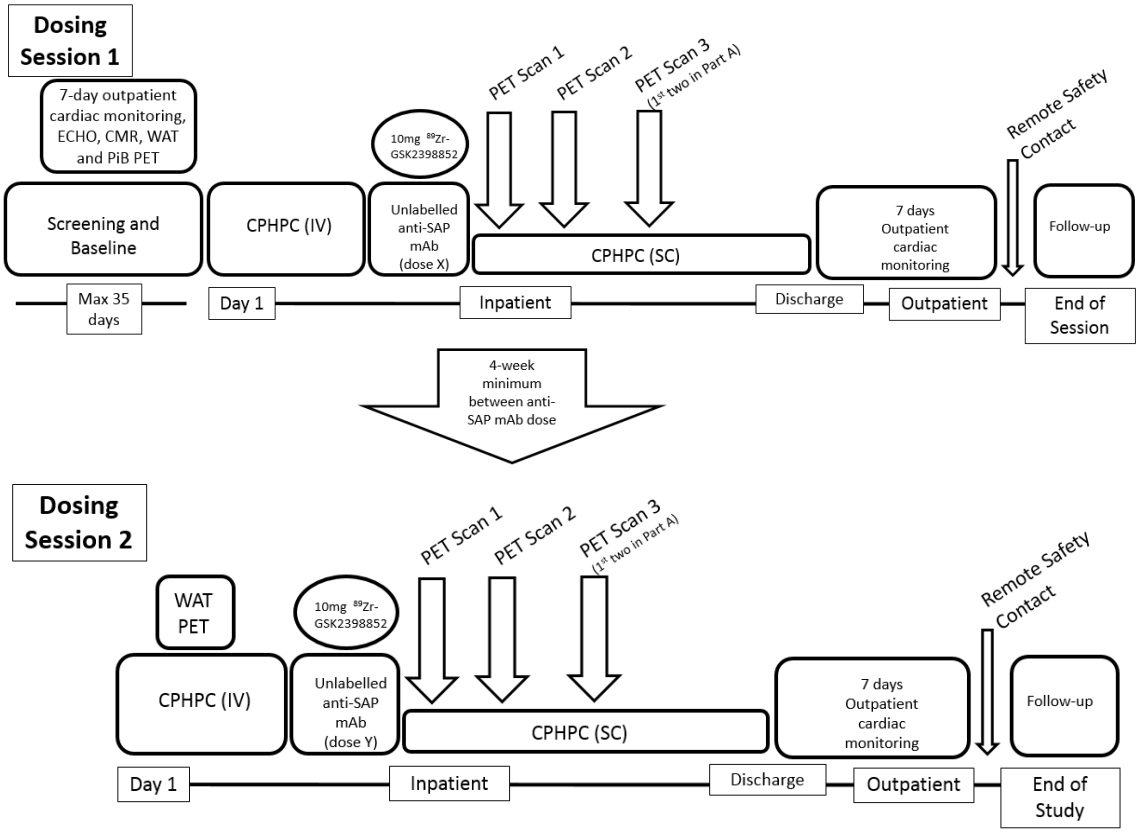
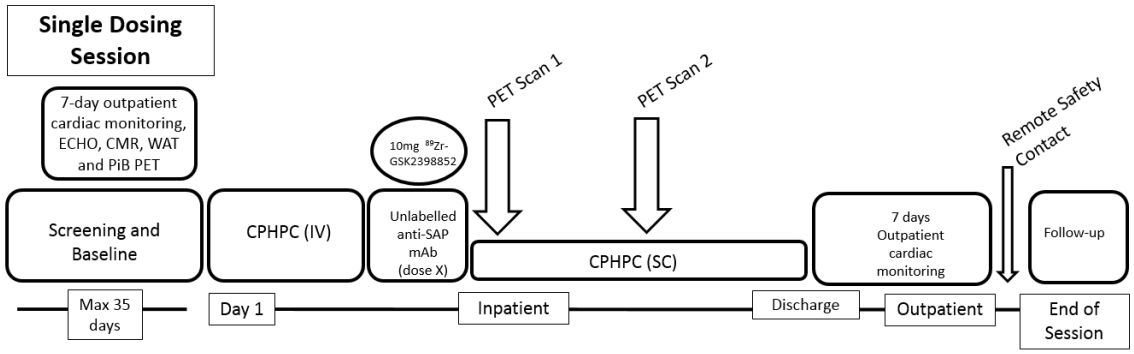


Figure 2 Study Schematic – Part B



Design Features	• This is an open-label, non-randomised ^{89}Zr-GSK2398852 PET imaging study in clinically stable patients with cardiac dysfunction caused by ATTR-CM. • The study will be divided into two parts, Part A and an optional Part B. ○ Part A will complete up to 3 subjects who participate in up to two anti-SAP dosing

Overview of Study Design and Key Features	
	sessions (Figure 1). The first two subjects in Part A will have up to three ^{89}Zr PET scans, while the remaining subject will undergo up to two ^{89}Zr PET scans. o Part B will complete up to three subjects who participate in only one anti-SAP dosing session (Figure 2). Subjects will undergo up to two ^{89}Zr PET scans. Part B will be triggered by the sponsor in consultation with the Principal Investigator. This will be based on data obtained in Part A, which includes but is not restricted to equivocal myocardial uptake of ^{89}Zr-GSK2398852 in all subjects treated in Part A. This decision will also be contingent based on emerging data from the concurrent Phase 2 trial (Study Number 201464). Should Part B not be triggered, then the study will conclude with Part A.
Dosing	• Details of the administration of CPHPC is provided in the protocol Section 5.4 • Details of the administration and dosing or Anti-SAP Treatment and ^{89}Zr-GSK2398852 is provided in the protocol Section 5.6 & Section 5.13
Time & Events	• Details of the Schedule of Activities can be found in Appendix 2, Section 12.2
Treatment Assignment	This is an open-label, non-randomised, adaptive, dose-ranging study.
Interim Analysis	There are two types of interim analysis planned in this study: • **In-stream data reviews:** Data will be reviewed on an ongoing basis throughout the study (including, but not limited to: safety, imaging (PET), PK data) to make decisions on: (i) intra (i.e. subsequent dose administered within a given subject) and inter (i.e. dose administered in a separate subject) mass dose levels; and (ii) the timing of PET scan. • **Interim analysis at the end of Part A:** once the last subject in Part A has completed their final dosing session, a formal review of all available safety data (including AEs, clinical laboratory data, vital signs, ECGs), PK, PET imaging data will be conducted before deciding whether to trigger Part B.

2.5. Statistical Analyses

This is an exploratory study where the primary objective is to assess cardiac uptake of ^{89}Zr-GSK2398852 evaluated by PET imaging at different mass doses. No formal hypotheses will be tested as part of this study.

All generated PET imaging endpoints (e.g., SUVpeak, SUVmean, SUVtotal_organ etc.) over time will be listed to identify the potential for cardiac uptake of ^{89}Zr-GSK2398852 in ATTR-CM patients.

2.6. Sample Size Considerations

At the time of writing no empirical data was available to offer a suitable estimate for the expected between subject variability; therefore, the sample size has been determined primarily by feasibility.

A total of 6 subjects are expected to complete up to two dosing sessions. The study is split into two parts:

- in Part A up to 3 subjects will participate in up to two anti-SAP dosing sessions
- in Part B up to 3 subjects will participate in one anti-SAP dosing session.

Data will be reviewed in-stream with a view to inform subsequent unlabelled anti-SAP mAb mass dose levels.

No sample size re-estimation is planned for this study; however, at the interim (i.e. at completion of Part A) the team may decide to stop the study early and not recruit any subjects into Part B.

3. PLANNED ANALYSES

3.1. Interim Analyses

Decision making for the development programme is time critical and therefore there are two types of interim analysis planned in this study:

- **In-stream data review(s):** Data will be reviewed on an ongoing basis throughout the study (including, but not limited to: safety, imaging (PET), PK data). Any emergent PET imaging data from the current study will be complementary to the ongoing phase II study (Study Number 201464) and its associated interim(s), as well as the broader Anti-SAP program. In addition, during the current study, team review of listings of accruing uncleaned study data (provided directly by Data Management or obtained from site) may trigger changes being made to a number of design parameters, including: (i) subsequent dose levels for the same or future subjects; and (ii) the timing of PET scan, all based on the emerging data. The foreseen primary parameters for this in-stream review is anticipated to be cardiac SUV values plus plasma radio-PK in relation to administered mass dose.
- **Interim analysis at the end of Part A:** once the last subject in Part A has completed their final dosing session, a formal review of all available safety data (including AEs, clinical laboratory data, vital signs, ECGs), PK, PET imaging data will be conducted before deciding whether to trigger Part B. Study data included as part of this interim will be cleaned prior to analysis.

Details for end of Part A interim include

- Plots of individual profiles, listings and tabulated descriptive statistics where appropriate for: blood pressure, heart rate, AEs, clinical chemistry, hematology, urinalysis, cardiac monitoring, NT-ProBNP, Troponin T, serum Creatinine, eGFR
- Listings of PET imaging parameters
- Plots of plasma concentration of GSK2398852, for radioactive assays, versus time.

3.2. Final Analyses

The final planned primary analyses (which will comprise both Part A and the optional Part B together) will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol (which may or may not include participants from Part B following the decision as to whether to trigger Part B based on the interim analysis at the end of Part A).
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. The study has a non-randomised open label design, however, for internal study reporting, subjects will be assigned randomisation numbers. Therefore, the formal process for unblinding the randomization codes will need to be also met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	Comprises of subjects who sign the Informed Consent	Screen failures
Enrolled	Comprises of subjects who ultimately pass screening, even if rescreened. The following subjects are included in the Enrolled population: Subjects who have been assigned a randomisation code. Screen failures are excluded from the enrolled population.	Study Population (Selected Outputs)
All Treated	All subjects who receive at least one Anti-SAP treatment including ^{89}Zr-GSK2398852	PET
Safety[1]	All subjects who receive at least one dose of GSK2315698, GSK2398852, or ^{89}Zr-GSK2398852. As all patients who receive GSK2398852, or ^{89}Zr-GSK2398852 will also have received GSK2315698 (as mandated by the protocol), this definition is equivalent to all subjects who received at least one dose of GSK2315698	Study Population Safety PD/Biomarkers
Pharmacokinetic (PK)	All subjects from the All Treated Population for whom a PK sample is obtained and analysed	PK

Refer to Appendix 9: List of Data Displays which details the population used for each display.
Notes
[1] Population identified separate from "All Treated" as described in protocol. Here exposure to any administered GSK compound warrants belonging to the "Safety" population

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to the DBF (database freeze) milestone for each study part (Part A and Part B) to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the listings of protocol deviations.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Other Considerations for Data Analyses and Data Handling Conventions

The table below provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions:

Section	Component
12.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
12.4	Appendix 4: Data Display Standards & Handling Conventions
12.5	Appendix 5: Derived and Transformed Data
12.6	Appendix 6: Reporting Standards for Missing Data
12.7	Appendix 7: 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 "Safety" population, unless otherwise specified. Screen failures will be summarised or listed based on the "Screened" population.

Table 1 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 1 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated	
	Table	Listing
Subject Disposition		
Subject Disposition	Y	
Reasons for Screening Failures	Y	Y
Reasons for Discontinuation of Study Treatment	Y	Y
Number of Participant	Y	
Reasons for Withdrawals		Y
Study Population		
Study Populations	Y	
Participants Excluded from any Population		Y
Protocol Deviations		
Important Protocol Deviations	Y	Y
Inclusion and Exclusion Criteria Deviations		Y
Demography		
Demography Characteristics	Y	Y
Age Ranges	Y	
Race and Racial Combinations	Y	Y
Concomitant Medications		
Concomitant Medication	Y	Y
Past Medical Conditions	Y	Y
Current Medical Conditions	Y	Y
Exposure		
Exposure to Total anti-SAP mAb*	Y	Y
Exposure to GSK2315698	Y	Y

NOTES :
Y = Yes display generated.
*Total Mass Dose (TMD) of anti-SAP mAb = unlabelled anti-SAP mAb + ^{89}Zr-GSK2398852.

7. PRIMARY STATISTICIAL ANALYSES

7.1. Primary Analyses

7.1.1. Endpoint / Variables

- Standardized Uptake Values (SUV) [i.e. Radioactivity concentrations] in focal anatomical locations within the heart, as well as SUV of the whole heart at different time points after ^{89}Zr-GSK2398852 administration and at different anti-SAP mAb TMDs.

7.1.2. Summary Measure

Data will be listed according to the GSK reporting standards, where applicable. All PET imaging parameters will be listed. Individual subject plots for the PET imaging parameters will also be produced.

Note that, in any one subject in Part A, where the radiolabel PK and cardiac SUV profile of ^{89}Zr-GSK2398852 is consistent with myocardial uptake during either the 1st or 2nd dosing session (i.e. cardiac / plasma SUV ratio ≥0.5), the reproducibility of this specific unlabelled anti-SAP mAb dose in enabling myocardial uptake of ^{89}Zr-GSK2398852 may be evaluated by treating further subjects with the same unlabelled anti-SAP mAb mass dose.

7.1.3. Population of Interest

The analyses in this section will be based on the "All Treated" population, unless otherwise specified.

7.1.4. Statistical Analyses / Methods

Table 2 provides an overview of the planned primary analyses, with full details of data displays being presented in Appendix 9: List of Data Displays which will be based on GSK data standards and statistical principles.

Table 2 Overview of Planned Primary Analyses

Endpoint / Parameter / Display Type	Absolute			
	Summary		Individual	
	T	F	F	L
PET (cardiac images)				
For the whole heart: SUVmean and volume For each cardiac focal anatomical location: SUVpeak over the entire 20-minute scan period, and volume			Y[1]	Y

NOTES :

[1] Figures will be restricted to SUVmean values and SUVpeak values over the entire 20-minute scan period.

T = Table, F = Figure, L = Listing, Y = Yes display generated.

7.2. Secondary Analyses

7.2.1. Endpoint / Variables

Focal and total radioactivity uptake (including, but not limited to SUV) in different tissues (including potentially at those peripheral tissue sites where transthyretin amyloidosis (TTR) amyloid deposition can be clinically occult) at different time points and after different TMDs.

7.2.2. Summary Measure

Data will be listed according to the GSK reporting standards, where applicable. All PET imaging parameters will be listed

7.2.3. Population of Interest

The analyses in this section will be based on the "All Treated" population, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Table 3 provides an overview of the planned secondary analyses, with full details of data displays being presented in Appendix 9: List of Data Displays which will be based on GSK data standards and statistical principles.

Table 3 Overview of Planned Secondary Analyses

Endpoint / Parameter / Display Type	Absolute			
	Summary		Individual	
	T	F	F	L
PET (non-cardiac images)				
For each organ/ tissue: SUVmean and volume			Y[1]	Y

NOTES :
[1] Figure will be restricted to SUVmean values.
T = Table, F = Figure, L = Listing, Y = Yes display generated.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified. Analyses detailed in this section will be performed on data from each study part separately.

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

Table 4 Overview of Planned Adverse Events Analyses

Endpoint / Parameter / Display Type	Absolute	
	Summary	Individual
	T	L
Adverse Events (AEs)		
All AEs by System Organ Class (SOC) and Preferred Term (PT)	Y	Y
Common (≥5%) Adverse Events by Overall Frequency	Y	
Common (≥5%) Grade 2-4 Adverse Events by Overall Frequency	Y	
Drug-Related AEs by SOC and PT	Y	
Common (≥5%) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y	
Common (≥5%) Drug Related Grade 2-4 Adverse Events by SOC and PT	Y	
Subject Numbers for Individual AEs		Y
Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		Y
Serious and Other Significant AEs		
Fatal Serious AEs		Y
Non-Fatal Serious AEs		Y
Reasons for Considering as a Serious AE		Y
Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y	
AEs Related to Treatments other than the Study Drug		Y
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT	Y	Y
Temporally-Associated, Potential mAb-Related Infusion Events[1]		Y
Anti-SAP mAb Infusion Related Reactions[1]		Y

NOTES:

- T = Table, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents Tables related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents Listings related to any displays of individual subject observed raw data.
- [1] Further details provided in Section 8.2

8.1. 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 9: List of Data Displays. Tables will present AEs in the treatment phase. Listings will present all AEs

8.2. Adverse Events of Special Interest (AESI) Analyses

The following categories of AESIs associated with GSK2398852 have been identified to date:

- Rash, Rash AESI will be identified based on the eCRF rash question and flagged in the general AE listing.

- Anti-SAP mAb Infusion-related reaction (IRR).

The identification of anti-SAP mAb IRR will follow a two-step process.

Step 1

A listing of temporally-associated, potential mAb-related infusion events (TPMI) will be produced.

TPMIs will only include AEs that correspond to the following list of preferred terms:

- "Headache", "Flushing", "Feeling hot", "Feeling cold", "Chest discomfort", "Chills", "Face oedema", "Oedema peripheral", "Orbital oedema", "Nausea", "Vomiting", "Diarrhoea", "Fatigue", "Tachycardia", "Presyncope", "Infusion related reaction".

In addition, TPMIs will be restricted to AEs that occurred during the mAb infusion or within 24 hours of the end of the mAb infusion. If the AE start time is missing, the AE will be included as TPMI if the AE start date is the same as the mAb infusion start date or end date (either dates if not the same), or if the AE start date is the next day after the end of the mAb infusion.

Step 2

This initial selection of AEs will be manually reviewed by the clinical team to identify the subset of TPMI events that qualify as IRR.

As a result, a listing of IRR (only including AEs flagged by this clinical review) will be displayed. If there is no AE identified as IRR as part of the clinical review, this listing will not be produced.

The details of the planned displays are provided in Appendix 9: List of Data Displays.

8.3. 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.

Table 5 provides an overview of the planned clinical laboratory analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 5 Overview of Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary	Individual	
	T	F	L
Chemistry			
Chemistry Changes from Baseline	Y		
Chemistry Shifts from Baseline Relative to Normal Range	Y		
Hematology			
Hematology Changes from Baseline	Y		
Clinically-Relevant Changes in Haemoglobin	Y		
Hematology Shifts from Baseline Relative to Normal Range	Y		
Urinalysis			
Urinalysis Changes from Baseline	Y		
Urinalysis Parameters Shifts from Baseline Relative to Normal Range	Y		
All Laboratory			
All Laboratory Data for Subjects with any Value of PCI			Y
Laboratory Values of PCI			Y
Laboratory Data with Character Results			Y
Liver Monitoring/Stopping Event Reporting	Y		
Medical Conditions for Participants with Liver Stopping Events			Y
Substance Use for Participants with Liver Stopping Events			Y
Hepatobiliary Laboratory Abnormalities	Y		

NOTES:

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

8.4. 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.

Table 6 provides an overview of the planned other safety analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 6 Overview of Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary	Individual	
	T	F[1]	L
ECG			
ECG Findings	Y		
All ECG Values for Subjects with any Value of PCI			Y
ECG Values of PCI			Y
Abnormal ECG Findings			Y
Maximum QTc Values Post-Baseline Relative to Baseline by Category	Y		
Change from Baseline in ECG Values by Visit	Y		
Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	Y		
Echocardiogram and Cardiac Monitoring [2]			
Cardiac Telemetry			Y
Vital Signs			
Change from Baseline in Vital Signs	Y	Y	
All Vital Signs for Subjects with any Value of PCI			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents Tables 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] Individual figures of absolute values are profile plots by subject identifiers.
- [2] Cardiac monitoring comments will be listed from the clinical database. Individual subject narratives will be provided separately by investigator.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

The analyses in this section will be based on the "Pharmacokinetic (PK)" population, unless otherwise specified. Data will be listed and summarized according to the GSK reporting standards, where applicable. Table 7 provides an overview of the planned PK analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 7 Overview of Planned Pharmocokinetic Analyses

Endpoints	Absolute			
	Summary		Individual	
	T	F	F	L
PK				
Total mAb	Y	Y	Y	Y
^{89}Zr-GSK2398852	Y	Y	Y	Y

NOTES :
T = Table, F = Figure, L = Listing, Y = Yes display generated.

9.1.1. Endpoint / Variables

Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions

Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data of both GSK2398852 and ^{89}Zr-GSK2398852, as data permits.

Parameter	Parameter Description
Cmax	Maximum observed concentration
Tmax	Time of first observation of maximum concentration
AUCt	Area under the concentration time course till last observation
T1/2	Terminal phase half life
AUCinf	Area under the concentration time course till time infinity

NOTES:

- Additional parameters may be included as required.

9.1.2. Population of Interest

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

9.1.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. No formal statistical models will be fit as part of the PK analysis.

Plasma concentrations of Total mAb, which is the total of both ^{89}Zr-labelled and unlabelled mAb, will be analysed using non-compartmental methods. PK parameters will be summarised by TMD.

Plasma radioactive concentration - measured by scintillation counter, corrected by radioactivity decay and expressed in molar concentration of the mAb - will be analysed by non-compartmental methods. This radioactive concentration will reflect the total of both labelled-mAb and its metabolites. PK parameters will be summarised by TMD, with/without stratification by treatment period.

For each anatomical region defined in the heart, the PET scans will generate up to 3 values on tissue radioactivity concentration (SUV), and the plasma radio-PK values will function as a marker of plasma clearance. The mechanistic model will probe the combination of tissue SUV and radio-PK as compatible with contributions by a vascular component, a free distribution to interstitium and a component related to tracer bound to amyloid-SAP complexes. The extracted parameters will be summarised for each subject and each mass dose.

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

The analyses in this section will be based on the "Safety" population, unless otherwise specified. Data will be listed and summarized according to the GSK reporting standards, where applicable. Table 8 provides an overview of the planned PD analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 8 Overview of Planned Pharmacodynamic Analyses

Endpoints	Absolute			
	Summary		Individual	
	T	F	F	L
Cardiac biomarker				
Troponin T, NT-ProBNP				Y
Plasma SAP Concentration				Y

NOTES :
T = Table, F = Figure, L = Listing, Y = Yes display generated.

11. REFERENCES

Not Applicable

12. APPENDICES

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

12.1.1. Exclusions from Per Protocol Population

There is no per protocol population defined for this study.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Table 9 Part A and Part B Overview

	Dosing Session 1	Dosing Session 2
Part A	X	X
Part B	X	

Table 10 Overview All Groups

			Dosing Sessions 1 and 2																
	Screening[1]	Baseline[2]	Day 1: pre- dose	Day 1	Day 2	Day 3: pre-dose mAb	Day 3: anti-SAP mAb dosing	Day 3: end of mAb infusion[18]	Day 3: 4 hours post end mAb infusion[18]	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 11-18	Day 20[18]	Day 26[16, 18]
Inpatient stay at unit			---------- X ----------																	
Discharge from inpatient																	X			
Outpatient visit	X	X																		X
Remote Contact for Safety Assessment																			X	
Informed consent	X																			
Medical history/risk factors/demographics	X																			
Inclusion/exclusion criteria	X																			
Safety Assessments																				
Physical examination[3]	X		X			X		X			X			X			X			
Adverse event (AE)/ serious adverse event (SAE) Assessment		---------- X ----------																		
Concomitant Medications			---------- X ----------																	
12-lead electrocardiogram (ECG)	X[13]		X[13]		X	X		X	X	X	X	X	X	X	X		X		X[21]	X
Continuous Lead II Telemetry[20]			---------- X ----------																	

			Dosing Sessions 1 and 2																	
	Screening[1]	Baseline[2]	Day 1: pre- dose	Day 1	Day 2	Day 3: pre-dose mAb	Day 3: anti-SAP mAb dosing	Day 3: end of mAb infusion[18]	Day 3: 4 hours post end mAb infusion[18]	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 11-18	Day 20[18]	Day 26[16, 18]
Remote Continuous Cardiac Monitoring[4]		X															X	X		
Vital signs	X[13]		X		X	X		X	X	X	X	X	X	X	X	X	X		X[21]	X
Screening Laboratory Assessments[5]	X																			
Haem/clin chem/ urinalysis	X		X			X					X		X			X				X
Troponin T/ N-terminal prohormone of brain natriuretic peptide (NT-ProBNP)	X		X		X	X				X	X	X	X	X	X	X				X
Pregnancy Test	X[15]		X[15]																	
Investigational medicinal product (IMP) Administration																				
Carboxy pyrrolidine hexanoyl pyrrolidine carboxylate (CPHPC) IV				--- X[10] ---																
CPHPC SC[12]								X[11]		X	X	X	X	X	X	X	X			
Premedication (hydrocortisone/anti-histamine)						X														
Unlabelled anti-SAP mAb							X[7]													
^{89}Zr-GSK2398852							X[7]													
Pharmacokinetics (PK)/SAP[9]																				
Blood sampling for plasma SAP			X		X[6]															
Anti-SAP mAb PK[17]							X	X	X	X	X	X	X							
^{89}Zr-GSK2398852 radio-PK (for scintillation)[14]							X	X	X	X	X	X								

			Dosing Sessions 1 and 2																
	Screening[1]	Baseline[2]	Day 1: pre- dose	Day 1	Day 2	Day 3: pre-dose mAb	Day 3: anti-SAP mAb dosing	Day 3: end of mAb infusion[18]	Day 3: 4 hours post end mAb infusion[18]	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 11-18	Day 20[18]	Day 26[16, 18]
Imaging Procedures																				
Cardiac Magnetic Resonance Imaging (MRI) with contrast		X																		
Echocardiogram (ECHO)		X																		
Pittsburgh Compound B (PIB) Positron Emission Tomography (PET)		X																		
15-Oxygen labelled water (WAT PET)		X			X [8]															
^{89}Zr-GSK2398852 PET / Computerised Tomography (CT)									X [9]	X [9]		X [9, 19]								

Note: If anti-SAP mAb dosing is delayed by one day, then Day 2 assessments should be repeated, and all subsequent assessments should be delayed by one day.

Footnotes:

1. Screening to take place within 35 days of start of Anti-SAP treatment.
2. Baseline will be any time after eligibility confirmed and before Anti-SAP treatment starts. Procedures may be done on different days.
3. Full examination at screening only, brief examination at all other time-points.
4. Out-patient cardiac recording (see Protocol Section 3.4.1.3): Baseline for approximately 1 week, and from Day 11 for approximately 1 week after discharge.
5. See Other Screening Tests in Protocol Appendix 2
6. Requires rapid turnaround. See Protocol Section 5.5
7. See Protocol Section 5.6 for timing of administration of unlabelled anti-SAP mAb and ^{89}Zr-GSK2398852.
8. Dosing Session 2 only, if logistically feasible. Can be done any day/time prior to anti-SAP mAb.
9. Exact timing in relation to end of ^{89}Zr-GSK2398852 infusion will change based on emerging data. See Protocol Section 5.3.1
10. CPHPC IV infusion for a minimum of approximately 48 hours. To be stopped prior to mAb infusion.
11. First SC dose to be administered approximately 5 hours after end of IV CPHPC infusion.
12. Administered three times daily. See Protocol Section 7.1 and Section 7.2
13. In triplicate.
14. See Protocol Table 5
15. Female Subjects Only.
16. The last visit of the final study session will be considered the final follow-up visit. This may be conducted in-person, or by “virtual visit”.
17. See Protocol Table 4for sampling times and windows.

18. See Protocol Table 3for allowable time/visit windows.
19. Third ^{89}Zr PET-CT to be done in first two subjects who complete Part A, only. Subsequent subjects to undergo only two ^{89}Zr PET-CT scans.
20. From Day 6 onward, at investigator discretion, inpatient cardiac monitoring can be performed via remote cardiac telemetry device (e.g. BodyGuardian® device)
21. If logistically possible.

Table 11 Allowable Assessment/Visit Windows

	Day 3: End mAb Infusion	Day 3: 4 hours post end-mAb infusion	Day 20	Day 26
Window	+10 minutes	±10 minutes	±1 day	±2 days

Table 12 Unlabelled anti-SAP mAb PK Sampling (Dosing Sessions 1 and 2)

	Pre anti-SAP mAb infusion	Halfway through infusion	End of unlabelled anti-SAP mAb infusion	7 hours post end of anti-SAP mAb infusion	24 hours after end of infusion (Day 4)	48 hours after end of infusion (Day 5)	72 hours after end of infusion (Day 6)	96 hours after end of infusion (Day 7)
Anti-SAP mAb PK	X	X	X	X	X	X	X	X
Time window		±10 minutes	+10 minutes	±30 minutes	±1 hour	±2 hours	±2 hours	±2 hours

Note: Up to three additional samples may be collected and sampling times may be modified based on emerging data.

Table 13 ^{89}Zr-GSK2398852 Radio-PK Sampling (Dosing Sessions 1 and 2)

	Time after ^{89}Zr-GSK2398852 infusion end						
	10 minutes	60 minutes	4 hours	7 hours	24 hours (Day 4)	48 hours (Day 5)	72 hours (Day 6)
^{89}Zr-GSK2398852 radio-PK (for scintillation)	X	X	X	X	X	X	X
Time Window	± 5 minutes	± 10 minutes	± 1 hour	± 2 hours	± 4 hours	± 4 hours	± 4 hours

Note: Up to three additional samples may be collected and sampling times may be modified based on emerging data. Time windows are for guidance; non-adherence to these times will not constitute a protocol deviation.

12.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

12.3.1. Treatment Phases

Treatment phases are defined for the purpose of AE summaries and listings.

AEs will be assigned to pre-treatment, on-treatment, and post-treatment phases according to the date/time of occurrence relative to Dates/Times of First and Last Doses of Study Drug.

Treatment Phase	Definition
Pre-Treatment	Date/Time of AE < First Dose Date/Time of Study Drug[1]
On-Treatment	First Dose Date/Time of Study Drug[1] ≤ Date/Time of AE ≤ Last Dose Date/Time of Study Drug[2] + 56 Days
Post-Treatment	Date/Time of AE> Last Dose Date/Time of Study Drug[2] + 56 Days

[1]Earliest dose of GSK2315698 or GSK2398852 or 89Zr-GSK2398852 in the study
[2]Latest dose of GSK2315698 or GSK2398852 or 89Zr-GSK2398852 in the study

Unless stated otherwise, AE summaries will only include AEs assigned to the on-treatment phase. All AE listings will include treatment phase assignment.

12.3.2. Treatment Sessions

Treatment sessions are defined for the purpose of AE listings.

AEs will be assigned to treatment sessions according to the time of occurrence relative to Dates/Times of First and Last Doses of Study Drug for each treatment session.

Treatment Sessions	Definition
Treatment Session 1	Session 1 First Dose Date/Time of Study Drug[1] ≤ Date/Time < Session 2 First Dose Date/Time of Study Drug[1] or ≤ Session 1 Last Dose Date/Time of Study Drug[2] + 56 Days (if Session 2 is not applicable).
Treatment Session 2	Session 2 First Dose Date/Time of Study Drug[1] ≤ Date/Time ≤ Session 2 Last Dose Date/Time of Study Drug[2] + 56 Days

[1]Earliest treatment session dose of GSK2315698 or GSK2398852 or ^{89} Zr-GSK2398852
[2]Latest treatment session dose of GSK2315698 or GSK2398852 or ^{89}Zr-GSK2398852

12.3.3. AE Onset Time and Duration

The following AE onset times and duration will be included in all AE listings.

	Definition
AE Onset Day Since First Dose of Study Drug[1] (Days)	If First Dose Date/Time of study drug[1] > AE Onset Date/Time, Onset Day = AE Onset Date - First Dose Date If First Dose Date/Time of study drug[1] ≤ AE Onset Date/Time, Onset Day = AE Onset Date - First Dose Date +1 Day Missing if subject is not exposed to any study drug
AE Onset Day Since Treatment Session First Dose of CPHPC (Days)	If Session CPHPC First Dose Date/Time of study drug > AE Onset Date/Time, Onset Day = AE Onset Date – Session CPHPC First Dose Date If Session CPHPC First Dose Date/Time of study drug ≤ AE Onset Date/Time, Onset Day = AE Onset Date – Session CPHPC First Dose Date +1 Day Missing if AE not assigned to treatment session
AE Onset Day Since Treatment Session First Dose of mAb (Days)	If Session mAb First Dose Date/Time of study drug > AE Onset Date/Time, Onset Day = AE Onset Date – Session mAb (labelled or unlabelled) First Dose Date If Session mAb First Dose Date/Time of study drug ≤ AE Onset Date/Time, Onset Day = AE Onset Date – Session mAb (labelled or unlabelled) First Dose Date +1 Day Missing if AE not assigned to treatment session
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on Inform/CRF OR value is missing.

[1]Earliest dose of GSK2315698 or GSK2398852 or 89Zr-GSK2398852 in the study

12.4. Appendix 4: Data Display Standards & Handling Conventions

12.4.1. Baseline Definitions

For all endpoints, the baseline value used for descriptive summaries and listings will be the latest assessment prior to first administration of anti-SAP treatment.

The first administration of anti-SAP treatment will be defined as the first administration of either study drug, i.e. CPHPC or anti-SAP mAb (labelled or unlabelled).

Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint after baseline (over treatment sessions and follow up period) and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 12.4.1 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.

12.4.2. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: \arprod\gsk2398852\mid204512\final
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards.	
Generation of RTF Files	
• RTF files will be generated for all the tables	

12.4.3. Reporting Standards

General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): • 4.03 to 4.23: General Principles • 5.01 to 5.08: Principles Related to Data Listings • 6.01 to 6.11: Principles Related to Summary Tables • 7.01 to 7.13: Principles Related to Graphics	
Formats	
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.	
Planned and Actual Time	
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in summary figures, summaries, statistical analyses and calculation of any derived parameters. • 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. • Actual times relative to the first study dose of anti-SAP treatment (CPHPC or labelled mAb or unlabelled mAb) will be used in individual subject plots • Reporting for Data Listings: • Planned and actual time relative to study drug dosing (first dose of either GSK2315698 or anti-SAP mAb (labelled and unlabelled)) will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).	
Unscheduled Visits	
• Unscheduled visits will be used for baseline derivations in summary tables. Post-baseline unscheduled visits will not be included in summary tables, with the exception of the following summaries: Summary of Hematology/Chemistry/ Urinalysis Shifts from Baseline Relative to normal range (worst case post baseline). Summary of Haemoglobin Change from Baseline Relative to Clinical Importance Range, Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category, Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category, Summary of hepatobiliary laboratory abnormalities, Summary of ECG findings. • All unscheduled visits will be included in individual subject plots. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

12.4.4. Appendix 4A: Additional Endpoint Information

All the PET imaging variables are derived by the PET imaging centre and not the responsibility of S&P.

12.4.5. Evaluation of PET Images

The acquired PET information is reconstructed into PET images with due corrections for attenuation, scattered radiation, etc.

The PET images are visually reviewed to identify the general features of body distribution and especially anatomical localization in the heart.

Regions of Interest (RoI) are outlined in the images to define radioactivity distribution.

All organ and blood analyses are expressed as SUV (Measured radioactivity concentration corrected for radioactive decay and normalized for administered amount of radioactivity per body weight).

Depending on organ and selection of tissue components, SUV may have different definitions.

Local tissue radioactivity concentration in organs in Regions of Interest (RoI)

SUVpeak:

A small sphere of 10-12 mm diameter placed in a representative location as seen in the image or transferred from the CT scan. Average of voxel (picture element) values within this volume is calculated.

SUVmean:

A larger outline of the whole organ or representative area or volume as seen in the image or transferred from the CT scan. Average voxel values (picture elements) within this volume is calculated.

Total organ radioactivity amount in Regions of Interest (RoI)

SUVtotal_organ:

An outline of the whole volume of the organ attempting to capture the total amount of radioactivity in that organ, as defined in the PET images or transferred from CT scan. Average of voxel (picture element) values within this volume is calculated.

VOLUMEtotal_organ:

Corresponding total volume of the organs above.

The SUVtotal_organ and VOLUMEtotal_organ are used for calculation of fraction of administered dose in that organ.

The organs/tissues of interest for analysis include:

Local tissue radioactivity concentration in organs in Regions of Interest (RoI)

Where relevant and depending on radioactivity uptake pattern:

- A minimum of 5 anatomical positions within the heart (only in the specific heart scans)
- Up to 3 focal and 1 larger location in each of the lungs
- Up to 3 focal and 1 larger location in the liver
- One focal and one large area in spleen
- One focal and one large area in pancreas
- One cortex and one medulla focal area in each of the kidneys
- One large area in one thigh muscle
- Up to 5 small areas of the skin

Other focal or larger areas may be included depending on features in the images.

For the regions in the 4*5 scans focused over the heart, separate and average values will be generated for each of the RoIs.

Total organ radioactivity amount in Regions of Interest (RoI)

- Heart
- Liver
- Spleen
- One lung
- Each kidney

Other organs may be included depending on features in the images.

Analysis of PET Data

The tissue SUV and plasma radio-PK values generated will constitute the primary information from the studies. Since plasma radio-PK will be dependent upon time after administration plus mass dose, it will be necessary to relate the tissue SUV to the instant and possibly also to the AUC of the plasma radio-PK.

It is expected that the tissue-to-plasma ratio of the mAb in the heart will be approximately 0.1-0.2 after equilibration between plasma and tissue interstitium. This is guided by an expected plasma

space plus interstitium relative space of 0.1-0.2. Within the blood pool of the heart chambers the ratio is expected to be 0.5 (hematocrit about 0.5).

We have placed a limit by which the tissue-to-plasma ratio in the cardiac muscle is indicative of entry to the interstitium and binding to amyloid-SAP complexes at 0.5 in balance between a sufficient increase as compared to passive distribution and avoidance of "spill-over" from cardiac blood pools.

More complex models of distribution between plasma and tissue may be explored.

Storage and potential further analyses of images

The primary PET and CT images in digital form will be anonymized and stored in an image repository under the control of GSK and may be used for further analyses.

12.5. Appendix 5: Derived and Transformed Data

12.5.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from the first study dose of aSAP treatment (GSK2315698 or labelled mAb or unlabelled mAb):
  • Ref Date or Study Dose Date = Missing → Study Day = Missing
  • Ref Date < aSAP treatment first study Dose Date → Study Day = Ref Date – aSAP treatment First Study Dose Date
  • Ref Data ≥ aSAP treatment first study dose date Dose Date → Study Day = Ref Date – (aSAP treatment First Study Dose Date) + 1

12.5.2. Study Population

Demographics
Age

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

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

Extent of Exposure

- Number of days of exposure to CPHPC will be calculated based on the following formula in each Treatment Session:

  Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1
- The cumulative dose of CPHPC will be calculated from the sum of the individual doses administered in each dosing session and over the study as a whole.
- Number of days of exposure to total anti-SAP mAb will be calculated as the number of doses administered.
- The cumulative dose of total aSAP mAb will be calculated from the sum of the individual doses administered (over all dosing sessions).

12.5.3. 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:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

Corrected QT Intervals

- IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as :

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Non-Quantifiable Laboratory an Biomarker Values

- 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.

12.5.4. Triplicate ECG and Vital Sign measurements

ECG measurements are performed in triplicate at Screening and at the Day 1 Pre-dose timepoint of each dosing session. Vital signs are performed in triplicate at screening. The average of the triplicate measurements will be used for all summary tables, whereas individual measurements will be displayed in figures and listings. As a consequence, the average of the 3 Session 1 Day 1 Pre-dose measurements will be used as the baseline value for ECG summary tables. In case of missing Session 1 Day 1 Pre-dose ECG measurement, the average of the 3 Screening values will be used as the baseline value instead.

12.6. Appendix 6: Reporting Standards for Missing Data

12.6.1. 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.

12.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

Handling of Missing and Partial Dates

Element	Reporting Detail
General	Missing or 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 date of study drug first dose (earliest dose of GSK2315698 or anti-SAP mAb (labelled or unlabelled)); in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Treatment States and Phases. ○ Missing Start Time: 00:00 will be used unless the (possibly imputed) date is the date of study drug first dose for any treatment session; in this case the study treatment start time will be used and hence the event is considered On-treatment as per Appendix 3: Treatment States and Phases. ○ Missing Stop Day: The last day of the month will be used (i.e. a '28', '29', '30' or '31' will be used for the day dependent on the month and year) or day of last follow-up assessment if earlier. ○ Missing Stop Time: There will be no imputation of missing stop times. • Completely missing start or end dates/times will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. However, AEs will completely missing start dates/times will be assigned to the On-treatment phase and to the subject first treatment session, unless an on-treatment start can be ruled out from the end date/time (i.e. if the

Element	Reporting Detail
	AE ended prior to study treatment start date/time)
Concomitant Medications/ Medical History	• 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. o If the entire date is missing it is assumed that the concomitant medication occurred in all phases. • The recorded partial date will be displayed in listings.

12.7. Appendix 7: Values of Potential Clinical Importance

12.7.1. Haematology Values of Potential Clinical Importance

Haematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count		0.60	2.2
Neutrophil Count		0.60	2.2
Haemoglobin	Male	0.70	1.2
	Female	0.75	1.2
Platelet Count		0.70	2.50
Lymphocytes		0.60	

12.7.2. Chemistry Values of Potential Clinical Importance

Chemistry Analyte	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
Albumin (mmol/L)	0.75	
Calcium (mmol/L)	0.80	1.20
Glucose (mmol/L)	0.60	2.00
Magnesium (mmol/L)	0.50	1.20
Potassium (mmol/L)	0.77	1.17
Sodium (mmol/L)	0.92	1.07
Creatinine (mmol/L)		1.6

12.7.3. Liver Function Test Values of Potential Clinical Importance

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

12.7.4. ECG Values and QTc Change of Potential Clinical Importance

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

12.7.5. Vital Sign Values and Changes of Potential Clinical Importance

VS Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	<90 and > 180	mmHg
Diastolic Blood Pressure	<30 and > 110	mmHg
Heart Rate	<35 and > 140	Bpm
Systolic Blood Pressure (Change from Baseline)	Increase >50	mmHg
	Decrease < 50	mmHg
Diastolic Blood Pressure (Change from Baseline)	Increase > 30	mmHg
	Decrease < 30	mmHg
Heart Rate (Change from Baseline)	Increase > 50	bpm
	Decrease < 50	bpm

12.8. Appendix 8: Abbreviations & Trade Marks

12.8.1. Abbreviations

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

Abbreviation	Description
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

12.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
[WinNonlin]
[SAS]

12.9. Appendix 9: List of Data Displays

12.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.14	NA
PD	NA	2.1 to 2.2
Safety	3.1 to 3.22	3.1 to 3.1
Pharmacokinetic	4.1 to 4.5	4.1 to 4.6
Section	**Listings**	
ICH Listings	1 to 31	
Other Listings	32 to 41	

12.9.2. Data Display Format

For all summaries PART A, Part B and Part A+B will be summarised as separate column headers. If Part B does not occur, then only PART A will be summarised, and the column header will be "Anti-SAP".
For listings and figures the Part will be displayed only if PART A and PART B occur.

12.9.3. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 10: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
PD	PD_Fn	PD_Tn	PD_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

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

12.9.4. Deliverables

Delivery [Priority] [1]	Description
IA SAC	Interim Analysis Statistical Analysis Complete
SAC	Final Statistical Analysis Complete

NOTES:

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

12.9.5. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Summary of Participant Disposition for the Participant Conclusion Record		IA, SAC
1.2.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		IA, SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		IA, SAC
1.4.	Enrolled	NS1	Summary of Number of Participant		IA, SAC
Protocol Deviation					
1.5.	Safety	DV1	Summary of Important Protocol Deviations		SAC
Population Analysed					
1.6.	Screened	SP1	Summary of Study Populations		SAC
Demographic and Baseline Characteristics					
1.7.	Safety	DM1	Summary of Demographic Characteristics	Please include BMI in this table.	SAC
1.8.	Enrolled	DM11	Summary of Age Ranges		SAC
1.9.	Safety	DM5	Summary of Race and Racial Combinations		SAC
Prior and Concomitant Medications and Medical Conditions					
1.10.	Safety	CM1	Summary of Concomitant Medications	All medications that are collected will be included in this table.	SAC
1.11.	Safety	MH1	Summary of Past Medical Conditions		SAC
1.12.	Safety	MH1	Summary of Current Medical Conditions		SAC
Exposure and Treatment Compliance					

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.13	Safety	POP_T1	Summary of Exposure to Study Treatment (CPHPC)	Display overall and by treatment session	SAC
1.14	Safety	POP_T1	Summary of Exposure to Study Treatment (anti-SAP mAb (unlabelled and labelled))	Display overall and by treatment session	SAC

12.9.6. PD Figures

PET Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1.	All Treated	PD_F1	Individual Subject Plot: SUVpeak Over Time for Cardiac Focal Anatomical Locations	Display by page for different cardiac focal anatomical locations Panel by subject and dosing session X axis: Actual time (days) Y axis: SUVpeak	IA, SAC
2.2.	All Treated	PD_F1	Individual Subject Plot: SUVmean Over Time for Each Organ/ Tissue	Display by page for different organs/ tissues Panel by subject and dosing session X axis: Actual time (days) Y axis: SUVmean	IA, SAC

12.9.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term - On-treatment		IA, SAC
3.2.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency – On-treatment		IA, SAC
3.3.	Safety	AE3	Summary of Common (>=5%) Grade 2-4 Adverse Events by Overall Frequency – On-treatment		IA, SAC
3.4.	Safety	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term/by Overall Frequency – On-treatment		IA, SAC
3.5.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences) – On-treatment		IA, SAC
3.6.	Safety	AE3	Summary of Common (>=5%) Drug-Related Grade 2-4 Adverse Events by Overall Frequency – On-treatment		IA, SAC
Serious and Other Significant Adverse Events					
3.7.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences) – On-treatment		IA, SAC
3.8.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term – On-treatment		IA, SAC
Laboratory: Chemistry					
3.9.	Safety	LB1	Summary of Chemistry Changes from Baseline		IA, SAC
3.10.	Safety	LB4	Summary of Chemistry Shifts from Baseline Relative to Normal Range		IA, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hematology					
3.11.	Safety	LB1	Summary of Hematology Changes from Baseline		IA, SAC
3.12.	Safety	LB4	Summary of Hematology Shifts from Baseline Relative to Normal Range		IA, SAC
3.13.	Safety	LB15	Summary of Haemoglobin Change from Baseline Relative to Clinical Importance Ranges		IA, SAC
Laboratory: Urinalysis					
3.14.	Safety	LB1	Summary of Urinalysis Changes from Baseline		IA, SAC
3.15.	Safety	LB4	Summary of Urinalysis Parameters Shifts from Baseline Relative to Normal Range		IA, SAC
Laboratory: Hepatobiliary (Liver)					
3.16.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		IA, SAC
3.17.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		IA, SAC
ECG					
3.18.	Safety	EG1	Summary of ECG Findings		IA, SAC
3.19.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		IA, SAC
3.20.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit		IA, SAC
3.21.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		IA, SAC
Vital Signs					
3.22.	Safety	VS1	Summary of Change from Baseline in Vital Signs		IA, SAC

12.9.8. Safety Figures

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.1	Safety	PD_F1	Profile Plot of Vital Signs Parameters Over Time by Subject	Panel by subject and dosing session X axis: Study day Y axis: Value of vitals parameter.	IA, SAC

12.9.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma Concentration					
4.1.	PK	PK01	Summary of Plasma concentration of 89Zr-GSK2398852 Pharmacokinetic Concentration-Time Data by TMD	Please rename the “Treatment” column as “Dose”.	IA, SAC
4.2.	PK	PK01	Summary of Plasma Concentration of Total mAb Pharmacokinetic Concentration-Time Data by TMD	Please rename the “Treatment” column as “Dose”.	IA, SAC
4.3.	PK	PK01	Summary of ^{89}Zr-GSK2398852 PK parameters by TMD, with/without period stratification		IA, SAC
4.4.	PK	PK01	Summary of Total mAb PK parameters by TMD, with/without period stratification		IA, SAC
4.5.	PK	PK_T1	Summary of Plasma concentration of 89Zr-GSK2398852 Pharmacokinetic Concentration-Time Data by focal anatomical region		IA, SAC

12.9.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK16a	Individual Plasma Concentration-Time Plots of 89Zr-GSK2398852 (Linear and Semi-log)		IA, SAC
4.2.	PK	PK16a	Individual Plasma Concentration-Time Plots of Total mAb (Linear and Semi-log)		IA, SAC
4.3.	PK	PK17	Mean Plasma Concentration-Time Plots of 89Zr-GSK2398852 (Linear and Semi-log) by TMD		IA, SAC
4.4.	PK	PK17	Mean Plasma Concentration-Time Plots of Total mAb (Linear and Semi-log) by TMD		IA, SAC
4.5.	PK	PK18	Median Plasma Concentration-Time Plots of 89Zr-GSK2398852 (Linear and Semi-log) by TMD		IA, SAC
4.6.	PK	PK18	Median Plasma Concentration-Time Plots of Total mAb (Linear and Semi-log) by TMD		IA, SAC

12.9.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure		IA, SAC
2.	Safety	ES2	Listing of Reasons for Study Withdrawal		IA, SAC
3.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation		IA, SAC
Protocol Deviations					
4.	Safety	DV2	Listing of Important Protocol Deviations		IA, SAC
5.	Safety	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations		IA, SAC
Populations Analysed					
6.	Enrolled	SP3	Listing of Participants Excluded from Any Population		IA, SAC
Demographic and Baseline Characteristics					
7.	Safety	DM2	Listing of Demographic Characteristics	Please include BMI.	IA, SAC
8.	Safety	DM9	Listing of Race		IA, SAC
Prior and Concomitant Medications and Medical Conditions					
9.	Safety	CP_CM3	Listing of Concomitant Medications		IA, SAC
10.	Safety	MH2	Listing of Medical Conditions		IA, SAC
Exposure and Treatment Compliance					
11.	Safety	EX3	Listing of Exposure to CPHPC		IA, SAC
12.	Safety	EX3	Listing of Exposure to anti-SAP mAb	Please present the cumulative dose as labelled+unlabelled. Add a footnote explaining the same: " The cumulative doses presented comprises both labelled and unlabelled mAb".	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
13.	Safety	AE8CP	Listing of All Adverse Events	The AE listing should include a column for rash and a column for the grade	IA, SAC
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		IA, SAC
15.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		IA, SAC
Serious and Other Significant Adverse Events					
16.	Safety	AE8CP	Listing of Fatal Serious Adverse Events		IA, SAC
17.	Safety	AE8CP	Listing of Non-Fatal Serious Adverse Events		IA, SAC
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		IA, SAC
19.	Safety	AE8CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		IA, SAC
20.	Safety	AE8CP	Listing of Temporally-Associated, Potential mAb-Related Infusion Events	See RAP Section 8.2 for further details on AE selection process	IA, SAC
21.	Safety	AE8CP	Listing of Anti-SAP mAb Infusion Related Reactions	See RAP Section 8.2 for further details on AE selection process	
22.	Safety	AE8CP	Listing of Adverse Events Related to Treatments other than Study Drug		IA, SAC
Hepatobiliary (Liver)					
23.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events		IA, SAC
24.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events		IA, SAC
All Laboratory					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
25.	Safety	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Concern/Potential Clinical Importance		IA, SAC
26.	Safety	LB5	Listing of Laboratory Values of Potential Clinical Importance		IA, SAC
27.	Safety	LB14	Listing of Laboratory Data with Character Results		IA, SAC
ECG					
28.	Safety	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance		IA, SAC
29.	Safety	EG3	Listing of ECG Values of Potential Clinical Importance		IA, SAC
30.	Safety	EG5	Listing of Abnormal ECG Findings		IA, SAC
Vital Signs					
31.	Safety	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance		IA, SAC
32.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance		IA, SAC

12.9.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic and Biomarkers					
33.	All Treated	PD_L1	Listing of Quantitative Derived Parameters of Cardiac PET Images of Focal Anatomical Locations		IA, SAC
34.	All Treated	PD_L2	Listing of Quantitative Derived Parameters of PET Images of Different Organs/ Tissues		IA, SAC
35.	Safety	PD_L3	Listing of Troponin T and NT-ProBNP		IA, SAC
36.	Safety	PK07	Listing Plasma SAP concentrations		IA, SAC
Safety					
37.	Safety	SAFE_L1	Listing of Cardiac Telemetry		IA, SAC
PK					
38.	PK	PK07	Listing of Plasma Concentration Time Data of 89Zr-GSK2398852		IA, SAC
39.	PK	PK07	Listing of Whole Blood Concentration Time Data of 89Zr-GSK2398852		IA, SAC
40.	PK	PK07	Listing of Plasma Concentration Time Data of Total mAb		IA, SAC
41.	PK	PK13	Listing of Derived Pharmacokinetic Parameters for Plasma Concentration of 89Zr-GSK2398852		IA, SAC
42.	PK	PK13	Listing of Derived Pharmacokinetic Parameters for Plasma Concentration of Total mAb		IA, SAC

12.10. Appendix 10: Example Mock Shells for Data Displays

Example POP_T1
Protocol: 204512 Page 1 of x
Population: Safety

Table 1.12
Summary of Exposure to Study Treatment (CPHPC)

Planned Period			Anti-SAP (N=xx)
SESSION 1	Duration of Exposure (days)	n	xx
		Mean	xx.x
		SD	xx.xx
		Median	xx.x
		Min.	xx
		Max.	xx
	Cumulative Dose (mg)	n	xx
		Mean	xxxx.x
		SD	xxxx.xx
		Median	xxxx.x
		Min.	xxxx
		Max.	xxxx
SESSION 2	Duration of Exposure (days)	n	xx
		Mean	xx.x
		SD	xx.xx
		Median	xx.x
		Min.	xx
		Max.	xx
	Cumulative Dose (mg)	n	xx
		Mean	xxxx.x
		SD	xxxx.xx

		Median	xxxx.x
		Min.	xxxx
		Max.	xxxx
Overall	Duration of Exposure (days)	n	xx
		Mean	xx.x
		SD	xx.xx
		Median	xx.x
		Min.	xx
		Max.	xx
	Cumulative Dose (mg)	n	xx
		Mean	xxxx.x
		SD	xxxx.xx
		Median	xxxx.x
		Min.	xxxx
		Max.	xxxx
	Time on study treatment[1]	n	xx
		Mean	xxxx.x
		SD	xxxx.xx
		Median	xxxx.x
		Min.	xxxx
		Max.	xxxx

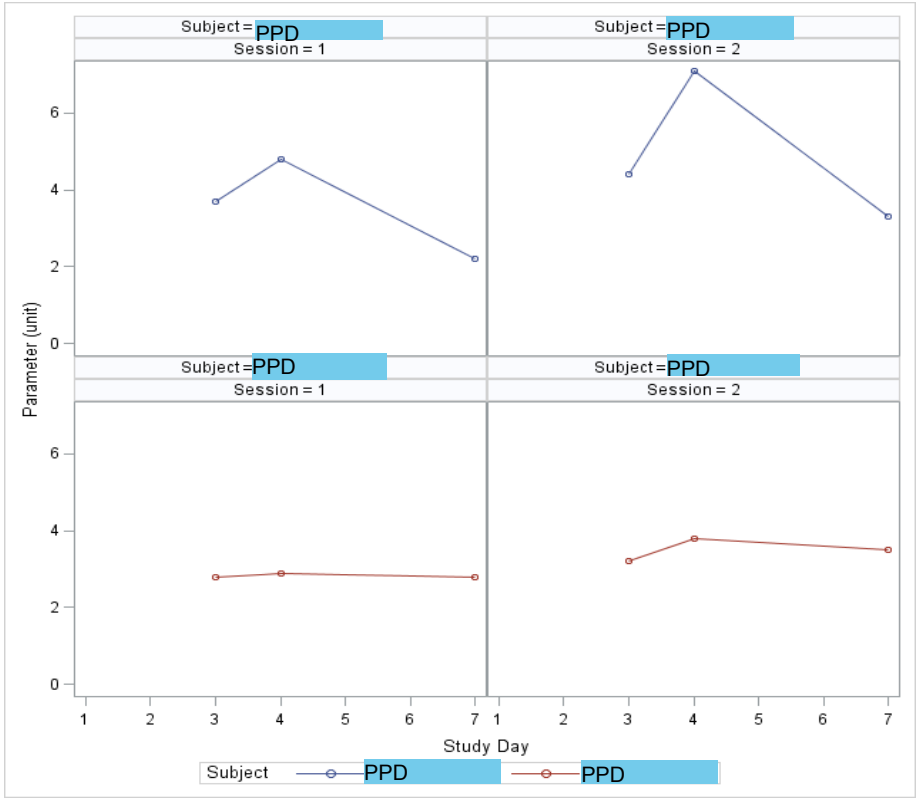
[1] The time on study drug does not exclude dose interruptions. In other words, it is the total time span of exposure to treatment. It is calculated as the total number of days between first dosing date of GSK2315698 and last dosing date of GSK2315698 (both days inclusive).

PPD

Example PD_F1
Protocol: 201452
Population: All Treated

Figure x.x
Individual Subject Plot: <SUVpeak/SUVmean> Over Time <for Cardiac Focal Anatomical Regions / for Each Organ/ Tissue>

Location: <Location>



Example PK_T1
Protocol: AAA111111
Population: PK

Table x.x
Summary of [Analyte] [Matrix] Pharmacokinetic Concentration-Time Data [units]
{by Group}

Focal Anatomical Region of the heart	Dose	N	{Add. time var.}	Planned Relative Time	n	No. Imputed [1]	Mean	{95% CI (Lower,Upper)}	SD	Median	Min.	Max.
Region 1	50mg	24		Pre-dose	24	20	xxxx.x	(xxxx.x,xxxx.x)		xxxx.x	xxxx	xxxx
				30 min	24	1	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				1 hr	23	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				2 hr	24	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
	100mg	24		Pre-dose	24	3	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				30 min	21	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				1 hr	21	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				2 hr	21	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
	200mg	24		Pre-dose	24	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				30 min	23	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				1 hr	24	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
				2 hr	24	0	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xxxx.x	xxxx	xxxx
Region 2												

.....

"[1] Original result values which are NQ have been imputed as per IDSL Standards and counts are displayed in No.Imputed column

PPD

Example : PD_L1
Protocol : 204512
Population : All Treated

Listing x
Listing of Quantitative Derived Parameters of Cardiac PET Images of focal anatomical locations

Site Id./ Unique Subject Id.	Planned Period/ Planned Visit	Date/ Study Day	Parameter (unit)	LA Blood	LV Blood	LVW High	LVW Low	MS High	MS Low	RV Blood
PPD	Session 1/ Day 3	DDMMMYY/ 3	Volume (mm3)	xxx	xxx	xxx	xxx	xxx	xxx	xxx
			SUVpeak (<unit>)	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Session 1/ Day 4	DDMMMYY/ 4	Etc.							

Note: SUVpeak is averaged over the entire 20-minute scan period. LA Blood = blood pool left atrium; LV Blood = Blood pool left ventricle; LVW High = Left ventricle wall, high intake; LVW Low = Left ventricle wall, low intake; MS High = Mid septum, high intake; MS Low = Mid septum, low intake; RV Blood = Blood pool right ventricle.

Example : PD_L2
Protocol : 204512
Population : All Treated

Listing x
Listing of Quantitative Derived Parameters of PET Images of Different Organs/ Tissues

Site Id./ Unique Subject Id.	Planned Period/ Planned Visit	Date/ Study Day	Organ / Tissue	SUVmean (<unit>)	Volume (mm3)
PPD	Session 1/ Day 3	DDMMMYY/ 3	Adrenal sinister	x.xx	xxxx
			Aorta	x.xx	xxxx
			Bone marrow	x.xx	xxxx
			Brain	x.xx	xxxx
			Gut	x.xx	xxxx
			Heart	x.xx	xxxx
			Etc.		

Example : PD_L3
Protocol : 204512
Population : Safety

Listing x.x
Listing of <Endpoint or Endpoint Type>

				<Variable 1 (unit)>		<Variable 2 (unit)>		<Variable 3 (unit)>		Etc.
Site Id./ Unique Subject Id.	Planned Period/ Planned Visit	Date/ Study Day	<Planned Time / Time>	Value	Change from baseline	Value	Change from baseline	Value	Change from baseline	
PPD	Baseline/ Day – 2	DDMMMYY/ -2	xx:xx/ xx:xx	xxx		xxx	xxx	xxx	xxx	
	Trt Session 1/ Day X	DDMMMYY/ X	xx:xx/ xx:xx	xxx	xxx	xxx	xxx	xxx	xxx	
	Etc.	DDMMMYY/ X	xx:xx/ xx:xx	xxx	xxx	xxx	xxx	xxx	xxx	

Programming notes: Time column to be removed if not applicable.

SAFE_L1
Protocol: MID204512

Population: Safety

Listing X

Listing of Cardiac Telemetry

Site Id./ Unique Subject Id.	Age(y)/ Sex/ Race	Planned Period/ Planned Visit	Start Date/ Start Time/ Study Day	Stop Date/ Stop Time/ Study Day	Result	Holter monitoring method	Other - description
PPD	57/ Male/ WHITE	/ Baseline	PPD 09:00/ 1	20:00/ 1	ABNORMAL - NOT CLINICALLY SIGNIFICANT	TELEMETRY	
		Session 1/ Day 11	PPD 09:00/ 30	20:00/ 30	NORMAL	OTHER	BODYGUARDIAN TELEMETRY
		Session 2/ Day 11	PPD 09:00/ 60	20:00/ 60	ABNORMAL - CLINICALLY SIGNIFICANT	TELEMETRY	