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

Title	:	Reporting and analysis plan for a multiple treatment session, open label phase 2 clinical study of GSK2398852 administered following and together with GSK2315698 in cohorts of patients with cardiac amyloidosis
Compound Number	:	GSK2398852+GSK2315698
Effective Date	:	01-MAY-2018

Description:

- The purpose of this RAP is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 201464.
- This RAP is intended to describe the efficacy, safety, pharmacokinetic, pharmacodynamic and biomarker analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Interim and Final Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

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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:		
2015N249732_00	09-MAY-2016	Original
2015N249732_01	20-APR-2017	Changes made to reflect regulatory input from the FDA. Other changes made to correct minor errors included in the original version.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Pharmacokinetic (PK) parameters for GSK2398852 will be derived based on a population PK model rather than descriptively summarized. The sparse sampling schedule is unlikely to allow reliable estimation of the parameters by descriptive summary.

There are no other changes or deviations to the originally planned statistical analysis specified in study protocol amendment 1 (Dated: 20-APR-2016).

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

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
Assessment of reduction in cardiac amyloid load after repeated administrations of Anti-SAP treatment as evaluated by CMR in all study groups	Change in left ventricular (LV) mass over time from baseline to 8-week post-treatment follow-up
Assessment of safety & tolerability of repeated administration of Anti-SAP treatment, including compatibility with chemotherapy treatment in Group 3	Clinical safety data from adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), cardiac monitoring and ECHO to 8-week post-treatment follow-up Incidence and grading of skin rashes classified using the Common Terminology Criteria for Adverse Events (CTCAE)

Objectives	Endpoints
Secondary Objectives	**Secondary Endpoints**
Investigation of rash associated with Anti-SAP treatment	Histopathological & immunohistochemical examination of skin biopsies + blood biomarkers (as data permit)
Characterisation of the pharmacokinetics of anti-SAP mAb	PK parameters including the maximum concentration (Cmax), the time associated with Cmax (tmax), and the area under the concentration-time profile (AUC).
Assessment of changes in circulating markers associated with pharmacodynamic effect during repeated administrations	Circulating biomarkers including but not limited to complement pathway components, acute phase proteins (e.g. CRP, SAA) and cytokines (e.g. IL6, IL8, IL10, TNFα).
Evaluation of changes in imaging markers of cardiac dysfunction monitored by serial CMR and / or ECHO.	Change in cardiac functional measures, including, but not limited to strain (e.g. global longitudinal strain [GLS]), LV twist, stroke volume (SV), ejection fraction (EF), end diastolic volume (EDV) & E/e' ratio over time from baseline to 8 week post-treatment follow-up
Exploratory Objectives	**Exploratory Endpoints**
To assess the reduction in cardiac amyloid load after repeated administrations of Anti-SAP treatment as evaluated by CMR in all study groups	Change in cardiac ECV over time from baseline to 8-week post-treatment follow-up
Assessment of effects of Anti-SAP treatment on individual subject quality of life	Change in individual subject quality of life as measured by the MOS SF-36, KCCQ, DLQI and EORTC QLQ 30 questionnaires over time from baseline to 8-week post-treatment follow-up
Assessment of clinical cardiac functional improvement	Change in 6 minute walk test (6MWT) distance (Groups 1 and 2) from baseline to 8-week post-treatment follow-up Change in N-terminal pro b-type Natriuretic Peptide (NT-proBNP) from baseline to 8-week post-treatment follow-up
Assessment of reduction in cardiac uptake of radioisotope bone tracers (Group 1 only)	Change in 99mTc-DPD or 99mTc-PYP uptake from baseline to 8-week post-treatment follow-up.

Objectives	Endpoints
Assessment of change in amyloid load on SAP scan (Groups 2 & 3 only and where SAP scan available)	Change in overall body load and in affected organs (excluding cardiac load) on SAP scan assessment from baseline to 8-week post-treatment follow-up
Assess the correlation between circulating biomarkers and structural and functional CMR measures	Circulating biomarkers (e.g. cardiac – NT proBNP and high-sensitivity (hs) Troponin-T, cytokines) over time Structural, Functional, and Tissue Characterization CMR measures over time, as data permit
Evaluate changes in imaging markers of cardiac structure as monitored by serial CMR and / or ECHO imaging	Change in cardiac structural measures, including, but not limited to LV wall thickness (CMR and/or, ECHO), and LV mass (ECHO) over time from baseline to 8-week post-treatment follow-up
Evaluate changes in imaging markers of cardiac tissue characterization as monitored by serial CMR	Change in cardiac tissue characterization measures, including, but not limited to late gadolinium enhancement (LGE), native T1 and ECV, over time from baseline to 8-week post-treatment follow-up
Assess the correlation between myocardial perfusion using CMR and cardiac structural, functional, and tissue characterization as measured by CMR and/or ECHO	Dynamic contrast enhanced (DCE)-CMR measuring myocardial vascular perfusion and structural, functional, and tissue characterization measures (CMR and/or ECHO), as data permit
Assessment of the immunogenicity of anti-SAP mAb when co-administered with CPHPC.	Measurement of anti-drug antibodies before and after treatment with anti-SAP mAb (baseline and 8-week post-treatment follow-up)
To characterise the subject experience of Anti-SAP Treatment regimen	Subject Exit Interviews completed over the telephone after the 8 week follow-up or Early Withdrawal Visit

Objectives	Endpoints
Long term follow-up Objectives	**Long term follow-up Endpoints**
Assessment of long term safety at 6 and 12 months post last anti-SAP mAb dose	Clinical safety data from adverse events (AEs), clinical laboratory tests, vital signs,12-lead ECG, cardiac monitoring and ECHO
Assessment of Anti-SAP Treatment outcomes at 6 and 12 months post last anti-SAP mAb dose	Long term changes in LV mass over time up to 12-month post-treatment follow-up Long term changes in imaging markers from CMR and / or ECHO over time up to 12-month post-treatment follow-up (as per 8-week follow-up) Long term changes in NT-proBNP over time up to 12 month post-treatment follow-up Long term changes in 6MWT distance over time up to 12-month post-treatment follow-up (Groups 1 and 2). Measurement of anti-drug antibodies (6 and 12 month post-treatment follow-up)

2.3. Study Design

Overview of Study Design and Key Features	

Design Features	• Open label, non-randomised, three-group, monthly repeat Anti-SAP treatment study in systemic amyloidosis subjects with cardiac dysfunction caused by cardiac amyloidosis.
	• The three groups are:
	  ○ Group 1: Cardiac TTR subjects
	  ○ Group 2: Post-chemotherapy AL amyloidosis subjects
	  ○ Group 3: Newly diagnosed Mayo stage II or IIIa AL amyloidosis subjects with cardiac dysfunction
	• Group 1 and Group 2 will begin recruitment in parallel. Recruitment into Group 3 will only be initiated after data has been reviewed and an acceptable cardiac and systemic safety profile for Anti-SAP treatment has been demonstrated and following review by regulatory agencies.
	• A minimum of 10 subjects per group will be recruited initially. Additional subjects may be enrolled in each of the 3 groups based on emerging data.
	• Subjects will be required to participate in up to six Anti-SAP treatment sessions receiving anti-SAP mAb at monthly intervals. Anti-SAP treatment consists of CPHPC followed by anti-SAP mAb.

Overview of Study Design and Key Features	
	• Within a given treatment session, anti-SAP mAb will be given as two 6-8 hour infusions, on Day 1 and Day 3. CPHPC administration will consist of intravenous (IV) infusion for 48 to 72 hours prior to anti-SAP mAb administration, followed by CPHPC sub-cutaneous (SC) injections for 11 days after the start of anti-SAP mAb administration.
Dosing	• Details of dosing regimens and considerations for dosing adjustments are described in Section 4.5 of the protocol.
Treatment Assignment	• Repeated administrations of Anti SAP treatment on a monthly schedule for up to 6 courses for subjects in all 3 groups.
Interim Analysis	• Interim analyses will take place according to the triggering rules described in Table 1 and their content will follow the analysis selections given in Table 2. • Further details can be found in Section 3.1

2.4. Statistical Hypotheses

No formal hypothesis will be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

Data will be reviewed on an ongoing basis throughout the study, including but not limited to, safety, imaging, PK, PD, clinical, biomarker data.

Study specific decisions will be supported by the periodic review of study data, as described in Section 10.8.2 of the protocol.

Interim analyses will take place as described in Table 1. In the event that an interim analysis is not required anymore, this will be documented by the study team prior to the interim analysis.

A selection of RAP analyses will be provided at each interim analysis, depending on the number of subjects available and the number of cohorts concerned, as per Table 2. Study data included as part of the interim selection will be cleaned prior to analysis.

Table 1 Interim Analysis Trigger and Analysis Selection

Interim Analysis Trigger	Interim Analysis Selection [1]
Group 1, 5 subjects with at least 3 courses of Anti-SAP treatment	Selection #1 for Group 1
Group 1, 10 subjects with at least 3 courses of Anti-SAP treatment	Selection #1 for Group 1
Group 1, 10 subjects completing 8-week post-treatment follow-up visit	Selection #2 for Group 1
Group 2, 3 subjects with at least 3 courses of Anti-SAP treatment	Selection #1 for Group 2
Group 2, 5-7 subjects with at least 3 courses of Anti-SAP treatment	Selection #1 for Group 2
Group 2, 10 subjects with at least 3 courses of Anti-SAP treatment	Selection #1 for Group 2
Group 2, 10 subjects completing 8-week post-treatment follow-up visit	Selection #2 for Group 2
Group 3, 5-7 subjects with at least 3 courses of Anti-SAP treatment	Selection #1 for Group 3
Group 3, 10 subjects with at least 3 courses of Anti-SAP treatment	Selection #1 for Group 3
Group 3, 10 subjects completing 8-week post-treatment follow-up visit	Full RAP deliverables for All 3 Groups

[1] Selection details in Table 2

Table 2 Details of Interim Analysis Selection

Analysis	Interim Analysis Selection #1	Interim Analysis Selection #2
Primary pharmacodynamic endpoint (LV mass by CMR)		
• Tabulated descriptive statistics, Plots of individual profiles	Y	Y
• Statistical Inference Summaries and Figures[1], Listings		Y
Imaging markers monitored by serial CMR and / or ECHO[2]: GLS (CMR & ECHO), LV twist (CMR), SV (CMR & ECHO), EF (CMR & ECHO), EDV (CMR & ECHO) E/e' ratio (ECHO), E/A ratio (ECHO), E-wave deceleration time on the mitral flow (ECHO), LA volume index (ECHO), RV FAC (ECHO), global and segmental T1 (CMR), global and segmental ECV (CMR), other global and segmental strain measurements (CMR), global and segmental myocardial perfusion (CMR)		
• Tabulated descriptive statistics, Plots of individual profiles	Y	Y
• Statistical Inference Summaries and Figures[1] , Listings		Y
Exploratory assessment of clinical cardiac functional improvement (6MWT, Groups 1 and 2 only)		
• Tabulated descriptive statistics, Plots of individual profiles	Y	Y
• Listings		Y
Exploratory assessment of reduction in cardiac uptake of radioisotope bone tracers (^{99m}Tc-DPD or ^{99m}Tc-PYP, Group 1 only)		
• Listings	Y	Y
Exploratory assessment of amyloid load on SAP scan (Groups 2 & 3 where SAP scan available)		
• Listings	Y	Y

Analysis	Interim Analysis Selection #1	Interim Analysis Selection #2
Safety and Tolerability		
• AE listings • AE posterior probabilities [3] • Skin rash listing • Laboratory individual profile plots for NT pro BNP, hs-Troponin T, serum Creatinine, eGFR and C3 • Profile plots for blood pressure and heart rate • Listings of ECG abnormalities • Listing of clinical chemistry, hematology and urinalysis • Cardiac monitoring investigator narratives (not available from clinical database)	Y	Y
• Other laboratory individual profile plots and listings (incl. circulating markers associated with PD effect and safety lab parameters)		Y
Pharmacokinetics (mAb and CPHPC)		
• Individual plasma CPHPC plots vs sample occasion (by group and treatment cycle) • Individual plasma mAb plots vs sample occasion (by group and treatment cycle)	Y	Y
Pharmacodynamics		
• Plasma SAP plot vs sample occasion (stratified by group and treatment cycle)	Y	Y

NOTES:
Y = Yes: Analysis selected at interim.
[1] Statistical inferential analyses (see Section 8.1 for details) may be triggered earlier than for Selection #2 based on initial results and phase III planning requirements. Analyses involving multiple imputation of missing data will not be performed at the interim.
[2] The CMR / ECHO parameters of interest will be selected prior to analysis, possibly revised for each interim as necessary and captured as a note to file.
[3] AE posterior probabilities may be provided after 10 subjects complete at least 3 courses of Anti-SAP treatment in a given cohort

Please refer to Appendix 11: List of Data Displays which details the interim and/or final analysis selection for each display being generated.

The population of interest for selected interim analyses will be the Safety population. Analyses on the Standard of Care population will be performed, at the earliest, when all subjects from a given study group complete their 12-month post-treatment follow-up visit.

Outcomes from the periodic data reviews may include:

- Regulatory interactions and initiation of recruitment into Group 3
- Triggering of Phase III planning and related regulatory interactions
- Sample size re-estimation/adjustment

- Adjustment of the schedule and timing of the assessments
- Confirmed continuation of the study.

3.2. Final Analyses

The final planned analyses (including full RAP deliverables for all 3 groups) will be performed after the completion of the following sequential steps:

1. All subjects have completed their 12-month post-treatment follow-up visit.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for releasing the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

Even though this is an open-label non-randomised study, randomisation codes will be produced per GSK processes and assigned to all subjects who pass screening.

The final analyses may also be performed after all subjects from a single study group have completed their 12-month post-treatment follow-up visit. The same sequential steps would apply, as for the completion of all 3 study groups.

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)
Safety	• Comprises of all subjects who receive at least one dose of study treatment (any dose of GSK2315698 or GSK2398852)	• Study Population • Safety • Efficacy • PD/Biomarkers • PK
Standard of Care	• Comprises of subjects providing standard of care data from the observational database, as described in Section 4.2	• Study Population • PD

NOTES :

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, subject management or subject 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 freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the 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.

4.2. Standard of Care Population and Database

The Standard of Care population will consist of a selection of subjects followed at the National Amyloidosis Centre (NAC) and part of an observational database providing demographic and pharmacodynamic (imaging) data.

This selection will consist of subjects with available imaging assessment of cardiac parameters by serial CMR and / or ECHO. AL subjects will be further restricted to those meeting key inclusion/exclusion criteria for this study. Subjects enrolled in this study will be excluded from the Standard of Care data in order to ensure independent data sets. The final Standard of Care subject selection will be documented prior to database freeze.

The Standard of Care data will be transmitted electronically from the NAC or from the Central Imaging Core Laboratory. It will be stored with the study data in a validated data system (HARP study reporting area).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 3 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 3 Overview of Appendices

Section	Component
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
Section 10.4	Appendix 4: Derived and Transformed Data
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
Section 10.6	Appendix 6: Values of Potential Clinical Importance
Section 10.7	Appendix 7: Model Checking and Diagnostics for Statistical Analyses
Section 10.8	Appendix 8: Population Pharmacokinetic Analyses
Section 10.9	Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned 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.

Analyses detailed in this section will be performed on data from each study group separately. Data displays will be paginated by study groups.

Table 4 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 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 Withdrawals		Y
Subjects Enrolled by Country and Site ID	Y	
Planned and Actual Treatments		Y
Treatment Status and Reason for Discontinuation of Study Treatment	Y	Y
Protocol Deviations		
Important Protocol Deviations	Y	Y
Inclusion and Exclusion Criteria Deviations		Y
Populations Analysed		
Study Populations	Y	
Subjects Excluded from Analysis Populations		Y
Demography[1]		
Demography Characteristics	Y	Y
Age Ranges	Y	
Race and Racial Combinations	Y	Y
Concomitant Medications		
Concomitant Medication	Y	Y
Medical Conditions	Y	Y
Exposure		
Exposure to CPHPC Treatment	Y	Y
Exposure to mAb Treatment	Y	Y

NOTES :

- Y = Yes display generated.
- [1] If data allows, tables and listings for demography will be provided for the Standard of Care Population (in addition to the Safety Population)

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacodynamic Analyses (LV Mass Measured by CMR)

7.1.1. Overview of Planned Pharmacodynamic Analyses (LV Mass Measured by CMR)

The primary pharmacodynamic analyses (summary statistics and statistical analysis) will be based on the "Safety" population unless otherwise specified.

Analyses detailed in this section will be performed on data from each study group separately. Data displays will be paginated by study groups.

Table 5 provides an overview of the planned primary pharmacodynamic analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Pharmacodynamic Analyses

Endpoint	Absolute					
	Stats Analysis			Summary	Individual	
	T	F	L	T	F	L
Primary endpoint (key efficacy endpoint)						
Change from baseline in LV mass				Y		Y
LV mass (absolute values) [1]	Y	Y	Y	Y	Y [2]	Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- 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] Statistical analyses will be performed on the absolute values, but mean changes from first dose of anti-SAP mAb will be estimated from the model.
- [2] Individual figures of absolute values are profile plots by subject identifiers

7.1.2. Planned Pharmacodynamic Statistical Analyses (LV Mass Measured by CMR)

Primary Statistical Analyses

Endpoint

The primary endpoint is change from baseline in LV mass (g) measured by CMR at 8-week post-treatment follow-up.

Descriptive summaries, listings and plots will be provided for LV mass (g) measured by CMR.

The primary inferential analysis will model absolute values of LV mass and mean changes from first dose of anti-SAP mAb will be estimated from the statistical model over time at each protocol planned timepoint, i.e. at 2, 3, 4, 5, 8, 11 and 17 months. Note that the 8, 11 and 17-month timepoints correspond to the planned 8-week, 6-month and 12-month follow-up visits for a subject completing all 6 treatment sessions. Please refer to Appendix 11: List of Data Displays which details the population to be used for each display being generated.

Planned MRI scans are scheduled at screening, throughout treatment, with additional follow-up scans planned once a subject completes treatment or discontinues. Historical MRI scans (prior to trial start) will also be retrieved for some subjects. Measurements will therefore be available pre-treatment (i.e. pre-trial and screening), on-treatment and post-treatment.

Model Specification

Model 1

The primary analysis models LV mass values over time using two linear components (i.e. two slopes) corresponding to the on-treatment and post-treatment parts of the data. As such it makes use of all available study data (i.e. both on- and post-treatment data). It allows for the derivation of

changes from first dose of anti-SAP mAb at planned timepoints with posterior probabilities of interest. The primary analysis is performed without any missing data imputation. Multiple imputation of missing data will also be considered as sensitivity analyses, as described in the "Handling of Missing Data for Analysis" Section.

A Bayesian two-piece linear mixed model (LMM) will be fitted to all study data collected after informed consent, i.e. pre-treatment (screening), on-treatment, and post-treatment visits. The primary analysis model will exclude pre-trial data from the observational database. This Bayesian two-piece LMM will incorporate information regarding when treatment was stopped by including an intercept and two different slope parameters for (i) on-treatment and (ii) post-treatment data, as described in Leuchs *et al* (2014).

The change in slope from on-treatment to post-treatment will be assumed to take place 56 days (8 weeks) after last dose of anti-SAP mAb, which is the planned visit day of the 8-week follow-up MRI scan.

LV mass is the dependent variable. Time will be defined as a number of days with respect to first dose of anti-SAP mAb, and derived as the assessment date – date of first dose of anti-SAP mAb. For screening scans, time will be set to 0.

All LV mass measurements will be included as absolute values in the model. The mean change from first dose of anti-SAP mAb at any given time point will be estimated as the resulting population average over all subjects' posterior draws.

The likelihood is given by $Y_{ij} \sim N(\mu_{ij}, \sigma_e^2)$, with $\mu_{ij} = \alpha_{0i} + \alpha_{1i} X_{1ij} + \alpha_{2i} X_{2ij}$

Where, for the *i*th subject and jth observation, Y_{ij} is the LV mass, and X_{1ij} and X_{2ij} are transformations of the number of days relative to first dose of anti-SAP mAb, X_{ij}, such that:

- $X_{1ij} = \begin{cases} X_{ij} & \text{when } X_{ij} < t_i \\ t_i & \text{when } X_{ij} \geq t_i \end{cases}$ with t_i 56 days after last dose of anti-SAP mAb
- $X_{2ij} = \begin{cases} 0 & \text{when } X_{ij} < t_i \\ X_{ij} - t_i & \text{when } X_{ij} \geq t_i \end{cases}$ with t_i 56 days after last dose of anti-SAP mAb

Terms fitted in the model include:

- Continuous Covariates: Number of days relative to first dose of anti-SAP mAb (denoted by X_{ij} with transformed X_{1ij} and X_{2ij} in the way described above)

Non-informative prior distributions are defined for all parameters of the Bayesian model, with:

$\alpha_{0i} \sim N(\beta_0, \sigma_0)$

$\alpha_{1i} \sim N(\beta_1, \sigma_1)$

$\alpha_{2i} \sim N(\beta_2, \sigma_2)$

$\sigma_e \sim InvGam\ (0.01, 0.01)$

$\sigma_0 \sim InvGam\ (0.01,0.01)$

$\sigma_1 \sim InvGam\ (0.01,0.01)$

$\sigma_2 \sim InvGam\ (0.01,0.01)$

with hyperparameters:

$\beta_0 \sim N(0,10000)$

$\beta_1 \sim N(0,10000)$

$\beta_2 \sim N(0,10000)$

Example of primary SAS code:

```
proc mcmc data = ADDATA outpost=OUTPOST nmc=50000 thin=5 NBI=1000
seed=7893;
  PARMS beta0 beta1 beta2 sigmae sigma0 sigma1 sigma2;
  PRIOR sigma: ~ IGAMMA(0.01, SCALE=0.01);
  PRIOR beta: ~ NORMAL(0, var=10000);
  RANDOM alpha0 ~ NORMAL(beta0, var=sigma0) SUBJECT=SUBJID;
  RANDOM alpha1 ~ NORMAL(beta1, var=sigma1) SUBJECT=SUBJID;
  RANDOM alpha2 ~ NORMAL(beta2, var=sigma2) SUBJECT=SUBJID;
  mu = alpha0 + alpha1 * X1 + alpha2 * X2;
  MODEL Y ~ NORMAL(mu, var=sigmae);
run;
```

Correlation between regression parameters:

If data and model convergence allow, the correlation between regression parameters may be taken into account by use of a multivariate normal (MN) distribution. The joint prior distribution for intercept and slope parameters will be as follows:

$$\begin{pmatrix} \alpha_{0i} \\ \alpha_{1i} \\ \alpha_{2i} \end{pmatrix} \sim MN\left(\begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \end{pmatrix} , \ \Sigma_{3\times3} \right)$$

where $\Sigma_{3\times3} \sim Inv.Wish(k,\Omega)$, i.e. the covariance matrix $\Sigma_{3\times3}$ follows an Inverse Wishart distribution with *k* degrees of freedom and inverse-scale matrix Ω. The least informative Inverse Wishart distribution will be chosen by setting *k* to 3, and Ω to some prior guess at the value of the covariance matrix multiplied by *k* (Lunn et al, 2012).with hyperparameters:

$$\begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \end{pmatrix} \sim \left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} , \ \begin{pmatrix} 10000 & 0 & 0 \\ 0 & 10000 & 0 \\ 0 & 0 & 10000 \end{pmatrix} \right)$$

Example of SAS code with correlation between regression parameters:

```
proc mcmc data = ADDATA outpost=OUTPOST nmc=50000 thin=5 NBI=1000
seed=7893;
  ARRAY alpha[3];
  ARRAY beta[3];
  ARRAY siga[3,3];
  ARRAY omega[3,3] (1000 0 0 0 1 0 0 0 1);
  ARRAY mub[3] (0 0 0);
```

```
  ARRAY sigb[3,3] (10000 0 0 0 10000 0 0 0 10000);
  PARMS beta sigma ve;
  PRIOR beta ~ MVN(mub, sigb);
  PRIOR siga ~ IWISH(3, omega);
  PRIOR sige ~ IGAMMA(0.01, SCALE=0.01);
  RANDOM alpha ~ MVN(beta, siga) SUBJECT=SUBJID;
  mu = alpha[1] + alpha[2] * ADY1 + alpha[3] * ADY2;
  MODEL AVAL ~ NORMAL(mu, var=sige);
run;
```

Model 2

A Bayesian LMM will be fitted ignoring the change in slope from on-treatment to post-treatment data, i.e. including only one slope parameter from first dose of anti-SAP mAb. Other model assumptions will remain the same.

Model 3

If the observational database provides sufficient pre-trial data, a Bayesian three-piece LMM will be fitted. This Bayesian three-piece LMM will incorporate information regarding when treatment was started/stopped by including an intercept and three different slope parameters for (i) pre-treatment, (ii) on-treatment and (iii) post-treatment data. The slope parameter will be assumed to change after the first dose of anti-SAP mAb, and 56-days after the last dose of anti-SAP mAb.

In this model, screening scans will be assigned to the actual day of scan measurement (unlike Model 1 and Model 2 where screening scans are assigned to Day 0).

Standard of Care Data Analysis

In order to support study data interpretation and missing data imputation for Model 1 (see "Handling of Missing Data for Analysis", Option 3), a Bayesian LMM will be fitted to reference standard of care data. The LMM will include a subject effect, an intercept and a continuous linear effect of time (slope).

All available post-diagnosis data from subjects in the Standard of Care population will be used for this Bayesian LMM analysis of Standard of Care data.

Further details on Standard of Care data are provided in Section 4.2.

Handling of Missing Data for Analysis

Model 1 will be repeated with several options for the handling of missing post-treatment data, corresponding to different assumptions.

Option 1 "No imputation"

Model 1 will first be performed without any missing data imputation. The Bayesian two piece LMM makes use of post-treatment information through the inclusion of on- and post-treatment slopes. As a consequence, post- discontinuation data contribute to the estimation of population mean changes over time. Without data imputation, missing post-treatment values are assumed to follow the same pattern as observed post-treatment values (i.e. 'Missing at Random' [MAR] assumption).

As such, subjects who drop out and only have partial or absolutely no on-treatment or post-treatment data will still contribute to the analysis model estimates using their available on-treatment and/or post-treatment data. Unobserved on-/post-treatment data will be assumed to follow a similar pattern as on-/post-treatment data observed in other subjects.

Option 2 "Internal study data as reference"

Missing 8-week, 6-month and 12-month follow-up visit values may however follow a separate pattern from respectively observed 8-week, 6-month and 12-month follow-up visit values, in which case there could be a 'Missing Not at Random' (MNAR) mechanism.

A Pattern Mixture Model (PMM) framework makes it possible to impute follow-up visit values under the MNAR assumption. The imputation process will be performed for missing follow-up visits, i.e. for 8-week, 6-month and 12-month follow-up visits. Treatment session missing LV mass measurements will be assumed to be MAR, and will therefore not follow any imputation process.

Two patterns of subjects are considered at each follow-up visit:

- Pattern of subjects with an observed assessment at follow-up visits
- Pattern of subjects with a missing assessment at follow-up visits

The MNAR assumption with Option 2 is that missing values only depend on prior visit values, i.e. they do not depend on any future measurements (for any subjects). Therefore, missing follow visit values will be imputed using the available data with a non-future dependence restriction. The imputation will be as follows:

1. Identify study subjects with a missing follow-up visit (either 8-week, 6-month or 12-month follow-up). These are the values to impute.
2. Fit a linear regression model to the observed study follow-up visit data (follow-up visit i), regressing upon each of the i – 1 preceding follow-up visits as well as the last treatment session assessment (included as continuous effects in the model). This is the imputation model.
3. Impute missing values identified in Step 1 *m* times using the model described in Step 2:
    a. Draw *m* values for the effect parameters for the imputation model from the posterior distribution given the observed study data
    b. Under each of the *m* models, and for each missing visit, impute the corresponding

predicted value, thus generating m imputed datasets.

Imputed values will be assigned to the planned follow-up study day, i.e. 8 weeks (56 days), 6 months (183 days) or 12 months (365 days) after the subject last mAb dose.

Option 3 "Standard of care data as reference"

Option 3 will follow the same PMM approach as Option 2, with a different reference method for the imputation of missing follow-up visit values. Missing follow-up visit values will be assumed to follow the same pattern as the Standard of Care reference data. The imputation will be as follows:

1. Identify study subjects with a missing follow-up visit (either 8-week, 6-month or 12-month follow-up). These are the values to impute.
2. Fit a linear mixed model to the reference standard of care data as defined in the "Model Specifications" section. This is the imputation model.
3. Impute missing values identified in Step 1 m times using the model described in Step 2:
    a. Draw m values for the effect parameters for the imputation model from the posterior distribution given the standard of care data
    b. Under each of the m models, and for each missing follow-up visit, impute the corresponding predicted value, thus generating m imputed datasets. Missing follow-up visit LV mass measurements will be imputed assuming LV mass follows the standard of care predicted slope from the last non-missing LV mass assessment date.

Imputed values will be assigned to the planned follow-up study day, i.e. 8 weeks (56 days), 6 months (183 days) or 12 months (365 days) after the subject last mAb dose.

Irrespective of the reference base used, once the multiple imputed datasets have been generated, the analysis model is fitted to each imputed dataset. Draws from the posterior distributions of each imputed dataset will then be mixed to summarize the posterior distribution, as described by Zhou and Reiter (2010).

Prior distributions for all parameters in the model will be similar to those specified for the primary analysis, i.e. non-informative normal distributions ($N(0,10000)$) for regression parameters and non-informative inverse gamma distributions ($InvGam\ (0.01,0.01)$) for variance parameters. Posterior distributions will follow the primary analysis presentation.

Model Checking & Diagnostics

- Refer to Appendix 7: Model Checking and Diagnostics for Statistical Analyses.

Results Presentation

- Study subjects
    - Summaries of the posterior distribution, including the mean, median, SD and 95% credible interval (CrInt) will be tabulated for the following parameters:
        - Intercept, on-treatment slope and post-treatment slope
    - Summaries of the posterior distribution, including the mean, median, SD and 95% CrInt will be produced for the change from first dose of anti-SAP mAb at each planned protocol time

point, i.e. at 2, 3, 4, 5, 8, 11 and 17 months.
- The posterior probability of a reduction in LV mass from first dose of anti-SAP mAb of >0g, >50g, 70g will be provided for each of the above contrasts. Reduction thresholds of interest may be revised based on emerging data.
- Posterior distribution plots will be produced for slope parameters and changes from first dose of anti-SAP mAb to 2, 3, 4, 5, 8, 11 and 17 months
- The posterior mean change from baseline will be plotted over time together with 95% credible intervals
- Absolute values and changes from baseline will also be descriptively summarized over time.
- Individual subject profile plots of LV mass over time will be produced

- Standard of care subjects
  - Summaries of the posterior distribution, including the mean, median, SD and 95% CrInt will be tabulated for the following parameters:
    - Intercept, slope
  - Summaries of the posterior distribution, including the mean, median, SD and 95% CrInt will be produced for the change from first scan at the same time points as for study subjects, i.e. at 2, 3, 4, 5, 8, 11 and 17 months.
  - Posterior distribution plots will be produced for the slope parameter and changes from first scan to 2, 3, 4, 5, 8, 11 and 17 months
  - Absolute values and changes from first scan will also be descriptively summarized over time.
  - Individual subject profile plots of LV mass over time will be performed

Sensitivity and Supportive Statistical Analyses

The models described above all assume that the relationship between time and LV mass is linear. This assumption will be investigated within the same two-piece Bayesian Linear Mixed Model by exploring other functions of time including:

- Restricted Cubic Splines
- Polynomial
- Negative exponential

There will be no missing data imputation for these sensitivity analyses.

Prior distributions for all parameters in the model will be similar to those specified for the primary analysis, i.e. non-informative normal distributions ($N(0,10000)$) for regression parameters and non-informative inverse gamma distributions ($InvGam\ (0.01,0.01)$) for variance parameters. Posterior distributions will follow the primary analysis presentation.

7.2. Safety Analyses

7.2.1. Overview of Planned Adverse Events Analyses

The safety analyses will be based on the "Safety" population.

Analyses detailed in this section will be performed on data from each study group separately. Data displays will be paginated by study groups.

Unless stated otherwise, summaries will only include AEs assigned to the on-treatment phase. The only exceptions will be the summaries of pre-treatment and post-treatment AEs by System Organ Class (SOC) and Preferred Term (PT).

Unless stated otherwise, summaries of on-treatment AEs will display AE frequencies over the full duration of the on-treatment phase. Two summaries will display AE frequencies by individual treatment session instead: All AEs by SOC, PT and Treatment Session; Rashes by SOC, PT, Maximum CTCAE Grade and Treatment Session. See Appendix 2: Treatment States and Phases for more details on AE assignment to treatment phases and treatment sessions.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 6 Overview of Planned Adverse Events Analyses

Endpoint / Parameter/ Display Type	Absolute	
	Summary	Individual
	T	L
Adverse Events (AEs)		
All AEs by SOC and PT	Y	Y
Pre-Treatment AEs by SOC and PT	Y	
Post-Treatment AEs by SOC and PT	Y	
All AEs by SOC, PT and Treatment Session	Y	
Most Frequent [1] Adverse Events by Overall Frequency	Y	
Drug-Related AEs by SOC and PT	Y	
Subject Numbers for Individual AEs		Y
Relationship Between AE SOCs, PT and Verbatim Text		Y
Posterior Probabilities for Specific AEs	Y	
Summary of Common (≥5%) Non-Serious Adverse Events	Y	
Serious and Other Significant AEs		
Fatal Serious AEs	Y	Y
Drug-Related Fatal Serious AEs	Y	
Non-Fatal Serious AEs	Y	Y
Serious AEs	Y	
Reasons for Considering as a Serious AE		Y
Drug-Related Non-Fatal Serious AEs	Y	
Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y	
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study	Y	Y

Endpoint / Parameter/ Display Type	Absolute	
	Summary	Individual
	T	L
Treatment by SOC and PT		
Anti-SAP mAb infusion related reactions[2]		Y
AEs related to treatments other than study drug		Y
Rashes		
Rashes by SOC, PT and Maximum CTCAE Grade	Y	Y
Rashes by SOC, PT, Maximum CTCAE Grade and Treatment Session	Y	
Rash Details		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] AEs occurring in more than one subject in a given cohort
- [2] AEs selected based on the following list of PTs: “Headache”, “Flushing”, “Feeling hot”, “Feeling cold”, “Chest discomfort”, “Chills”, “Face oedema”, “Oedema peripheral”, “Orbital oedema”, “Nausea”, “Vomiting”, “Diarrhoea”, “Fatigue”, “Tachycardia”, “Presyncope”, “Infusion related reaction”. This list will be reviewed and finalised prior to database freeze.

Posterior distributions of the true proportion of subjects with AEs will be derived within a Bayesian framework for a selection of specific drug-related AEs. This selection of AEs will be periodically reviewed during the study interims triggered by at least 10 subjects completing at least 3 courses of anti-SAP treatment in a given cohort. A final list will be agreed and documented prior to database freeze.

Posterior 95% CrInt for the true proportion of subjects with a specified AE will be provided together with the posterior probabilities that the true proportion of subjects with that AE is >10%, >30% and >50%.

Prior distributions will be neutral non-informative conjugate Beta(1/3,1/3) prior distributions.

7.2.2. Overview of Planned Clinical Laboratory Analyses

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

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 7 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL
	Summary	Individual		Summary
	T	F	L	T
Chemistry				
Clinical Chemistry		Y[1]	Y	Y
Hematology				
Hematology		Y[2]	Y	Y
Clinically-Relevant Changes in Haemoglobin			Y	Y
Urinalysis				
Urinalysis			Y	Y
Hepatobiliary (Liver)				
Liver Monitoring/Stopping Event Reporting	Y			
Hepatobiliary Laboratory Abnormalities	Y			
Medical Conditions for Subjects with Liver Stopping Events			Y	
Substance Use for Subjects with Liver Stopping Events			Y	
Scatter Plot of Maximum vs. Baseline for ALT		Y		
Scatter Plot of Maximum ALT vs Maximum Total Bilirubin		Y		
All Laboratory				
All Laboratory Data for Subjects with any Value of PCI			Y	
Laboratory Values 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] Liver Function and Renal function parameters. Individual figures of absolute values are profile plots by subject identifiers.
- [2] Haemoglobin only. Individual figures of absolute values are profile plots by subject identifiers.

The number and percentage of subjects with clinically-relevant changes in haemoglobin between Day -2 and timepoints up to Day 24 will be summarised for each study group and by treatment session. Two thresholds of clinical relevance will be defined as reductions from Day -2 of at least 10g/L and 20 g/L.

7.2.3. Overview of Planned Other Safety Analyses

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

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 8 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL
	Summary	Individual		Summary
	T	F[1]	L	T
ECG				
ECG Findings	Y		Y	
Maximum Emergent QTc Values by Category	Y			
ECG Values			Y	Y
Maximum Change from Baseline in QTc Values by Category				Y
All ECG Values for Subjects with any Value of PCI			Y	
ECG Values of PCI			Y	
Abnormal ECG Findings			Y	
Echocardiogram and Cardiac Monitoring				
Cardiac monitoring [2]			Y	
All echocardiogram results for subjects requiring unscheduled assessment [3]			Y	
Vital Signs				
Vital Signs		Y	Y	Y
All Vital Signs for Subjects with any Value of PCI			Y	
Vital Signs 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.
- [3] Subset of echocardiogram results for subjects with any unscheduled echocardiogram triggered for safety reasons. All echocardiogram data to be included for these subjects by treatment session.

8. SECONDARY STATISTICAL ANALYSES

8.1. Pharmacodynamic and biomarker analyses

8.1.1. Overview of Planned Pharmacodynamic and Biomarker Analyses

The secondary and exploratory pharmacodynamic and biomarker analyses (summary statistics and statistical analysis) will be based on the "Safety" population unless otherwise specified.

Analyses detailed in this section will be performed on data from each study group separately. Data displays will be paginated by study groups.

Table 9 provides an overview of the planned secondary and exploratory pharmacodynamic and biomarker analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 9 Overview of Planned Secondary Pharmacodynamic and Biomarker Analyses

Endpoint	Absolute						Change from Baseline
	Stats Analysis			Summary	Individual		Summary
	T	F	L	T	F[2]	L	T
Secondary Pharmacodynamic and Biomarker Endpoints							
Imaging markers of cardiac dysfunction monitored by serial CMR and / or ECHO							
GLS, LV twist, SV, EF, EDV measured by CMR and E/e' ratio measured by ECHO	Y[1]	Y[1]	Y[1]	Y	Y	Y	Y
GLS, SV, EF, EDV measured by ECHO				Y	Y	Y	Y
Circulating markers associated with pharmacodynamic effect during repeated administrations							
Fluid Phase complement markers : C3, C4, CH50				Y	Y	Y	Y
Inflammatory biomarkers : hsCRP, SAA				Y	Y	Y	Y
Plasma Cytokines: TNFα, IL-8, IL-6, IL-10, IL-13, IL-2, IL-4, IL-12p70, IL 1β, IFNγ				Y	Y	Y	Y
Exploratory Pharmacodynamic and Biomarker Endpoints							
Cardiac amyloid load as evaluated by CMR							
Cardiac ECV	Y[1]	Y[1]	Y[1]	Y	Y	Y	Y
Cardiac biomarkers							
hs-Troponin T, NT-Pro-BNP				Y	Y	Y	Y
Cardiac uptake of radioisotope bone tracers (Group 1 only)							
^{99m}Tc-DPD, ^{99m}Tc-PYP uptake				Y		Y	
Amyloid load on SAP scan (Groups 2 & 3 only and where SAP scan available)							
Overall body load and in affected organs (excluding cardiac load)				Y	Y	Y	Y
Imaging markers of cardiac structure as monitored by serial CMR and / or ECHO imaging							
LV mass (ECHO)	Y[1]	Y[1]	Y[1]	Y	Y	Y	Y
LV wall thickness (CMR and/or ECHO)				Y	Y	Y	Y
Evaluate changes in imaging markers of cardiac tissue characterization as monitored by serial CMR							
Native T1 and ECV	Y[1]	Y[1]	Y[1]	Y	Y	Y	Y
Native T2, LGE				Y	Y	Y	Y

Endpoint	Absolute						Change from Baseline
	Stats Analysis			Summary	Individual		Summary
	T	F	L	T	F[2]	L	T
Other imaging markers of cardiac dysfunction monitored by serial CMR and / or ECHO							
Longitudinal, Radial and Circumferential Strain (CMR and/or ECHO)				Y	Y	Y	Y
E/A ratio, E-wave deceleration time, LA volume index, RV FAC (ECHO)				Y	Y	Y	Y
Myocardial perfusion							
DCE-CMR measure of myocardial perfusion				Y	Y	Y	Y
Plasma SAP concentration							
SAP concentration				Y	Y	Y	Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- [1] Statistical analyses will be performed on the absolute values, but mean changes from first dose of anti-SAP mAb will be estimated from the model..
- [2] Individual figures of absolute values are profile plots by subject identifier
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents Tables related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data

8.1.2. Planned Pharmacodynamic and Biomarker Statistical Analyses

Secondary Statistical Analyses for Imaging Markers of Cardiac Dysfunction

Endpoints

Imaging markers of cardiac dysfunction monitored by serial CMR and / or ECHO include:

- Global Longitudinal Strain (GLS) measured by CMR and ECHO. GLS includes 3 separate measurements: feature tracking and tagging (CMR) and speckle tracking (ECHO)
- LV twist measured by CMR
- Stroke Volume (SV) measured by CMR and ECHO
- Ejection Fraction (EF) measured by CMR and ECHO
- End Diastolic Volume (EDV) measured by CMR and ECHO
- E/e' ratio measured by ECHO, with 2 separate measurements: lateral, septal

The following endpoints are listed as exploratory endpoints in the protocol, however analyses will follow those of secondary endpoints markers:

- LV Mass measured by ECHO
- ECV (Global) measured by serial CMR
- Native T1 (Global) measured by serial CMR

Descriptive summaries, listings and plots will be provided for each of these.

Statistical analyses will be performed for a selection of imaging markers. This selection of markers will include all markers measured by serial CMR as well as LV Mass and E/e' ratio measured by

Secondary Statistical Analyses for Imaging Markers of Cardiac Dysfunction
ECHO. Other markers measured by ECHO will be summarised using descriptive statistics only. Inferential analyses will model absolute values, and mean changes from first dose of anti-SAP mAb will be estimated from the statistical model over time at the planned protocol time points: • at 2, 3, 4, 5, 8, 11 and 17-month time points for CMR endpoints • at 1, 2, 3, 4, 5, 6, 8, 11, 17 month time points for ECHO endpoints Note that the 8, 11 and 17-month timepoints correspond to the planned 8-week, 6-month and 12-month follow-up visits for a subject completing all 6 treatment sessions. Planned MRI and/or ECHO scans are scheduled at screening or baseline, throughout treatment, with additional follow-up scans planned once a subject completes treatment or discontinues. Historical MRI and/or ECHO scans (prior to trial start) will also be retrieved for some subjects. Measurements will therefore be available pre-treatment (i.e. pre-trial and screening), on-treatment and post-treatment.
Model Specification
Model 1 described for the primary endpoint of LV mass in Section 7.1.2 will be performed for the selection of secondary imaging markers of cardiac dysfunction for which statistical analyses are planned (all markers measured by serial CMR, and LV Mass and E/e' ratio measured by ECHO). Model 1 goodness-of-fit will be assessed by visual investigation of residual plots. If the two-piece LMM is found to be an inappropriate fit for the data, models 2, 3 and other sensitivity analyses exploring different functions of time may also be performed as described for the primary endpoint of LV mass in Section 7.1.2. There will be no missing data imputation for these sensitivity analyses. If data permits, the standard of care data analysis described for the primary endpoint of LV mass in Section 7.1.2 will also be performed for secondary imaging markers of cardiac dysfunction.
Handling of Missing Data for Analysis
The handling of missing post-treatment data will be handled with Option 1 described in Section 7.1.2 (i.e. no imputation). Options 2 and 3 may be additionally considered after an initial review of analysis results.
Model Checking & Diagnostics
• Refer to Appendix 7: Model Checking and Diagnostics for Statistical Analyses.

Secondary Statistical Analyses for Imaging Markers of Cardiac Dysfunction

Results Presentation

- Study subjects
  - Model results and descriptive summaries will follow the same presentation as described for the primary endpoint of LV mass in Section 7.1.2
  - As for the primary endpoint, posterior probabilities for changes from first dose of anti-SAP mAb above or below specific thresholds may be considered. Thresholds of interest will be defined based on emerging data.

- Standard of care subjects
  - Model results and descriptive summaries will follow the same presentation as described for the primary endpoint of LV mass in Section 7.1.2. Some endpoints may not be available for Standard of Care subjects, and outputs will be produced where applicable.

Secondary Analyses for Circulating markers

Endpoints

Circulating markers associated with pharmacodynamic effect during repeated administrations:

- Complement markers : C3, C4, CH50
- Inflammatory biomarkers : hsCRP, SAA
- Plasma cytokines : TNFα, IL-8, IL-6, IL-10, IL-13, IL-2, IL-4, IL-12p70, IL 1β, IFNγ

Model Specification

These continuous endpoints will be summarized using descriptive statistics only. Refer to Section 10.3.9 for reporting standards.

Handling of Missing Data for Analysis

Missing data will not be imputed for these descriptive analyses.

Results Presentation

- Absolute values and changes from baseline will be descriptively summarized over time by visit across all treatment sessions and follow-up periods where applicable.
- Individual subject profiles over time will be plotted.

Exploratory Pharmacodynamic and Biomarker Analyses

Endpoint(s)

Exploratory Pharmacodynamic and Biomarker endpoints are as follows:

- Cardiac amyloid load as evaluated by CMR
  - Cardiac ECV (Global, Segmental)
- Cardiac biomarkers

Exploratory Pharmacodynamic and Biomarker Analyses

  - hs-Troponin T, NT-Pro-BNP
- Cardiac uptake of radioisotope bone tracers
  - ^{99m}Tc-DPD
  - ^{99m}Tc-PYP
- Amyloid load on SAP scan
  - Overall body load in affected organs (excluding cardiac load)
- Imaging markers of cardiac structure as monitored by serial CMR and / or ECHO imaging
  - LV wall thickness (CMR and ECHO)
  - LV mass (ECHO)
- Other imaging markers of cardiac dysfunction as monitored by serial CMR and /or ECHO:
  - E/A ratio (ECHO)
  - E-wave deceleration time on the mitral inflow (ECHO)
  - Left Atrial (LA) volume index (ECHO)
  - Right Ventricle Fractional Area Change (FAC) (ECHO)
  - Longitudinal, Radial and Circumferential Strain (Global and Segmental values by CMR and/or ECHO)
- Evaluate changes in imaging markers of cardiac tissue characterization as monitored by serial CMR
  - LGE
  - Native T1 (Global, Segmental)
  - Native T2 (Global, Segmental)
- DCE-CMR measure of myocardial perfusion (Global, Segmental)
- Plasma SAP concentrations

The derivation of LGE is described in Section 10.3.7. The derivation of the DCE-CMR global measure of myocardial perfusion is described in Section 10.3.8.

Model Specification

These endpoints, whether continuous or categorical, will be summarized using descriptive statistics. Segmental values (where applicable) will not be tabulated. Refer to Section 10.3.9 for reporting standards.

In addition, inferential analyses will be performed for LV mass (ECHO), ECV (Global) and Native T1. These analyses are already described as part of the secondary statistical analyses for imaging markers of cardiac dysfunction.

The association between cardiac MRI markers (structural: LV Mass and ECV; tissue characterization: native T1 and LGE; functional: LV twist, GLS, SV and EF) and a selection of endpoints (biomakers: NT proBNP, hs-Troponin T; PD: DCE-CMR global measure of perfusion; efficacy: 6MWT; QoL: MOS SF-36 Physical and Mental component summary scores and KCCQ overall summary score) will be studied using Spearman correlation coefficients.

These correlations will be calculated at the following time points: baseline, treatment session 3 Day 24 visit, 8-week follow-up visit, 6-month follow-up visit and 12-month follow-up visit.

Exploratory Pharmacodynamic and Biomarker Analyses
Handling of Missing Data for Analysis
Missing data will not be imputed for these descriptive analyses.
Results Presentation
For each exploratory pharmacodynamic and biomarker endpoint: • Absolute values and changes from baseline will be descriptively summarized over time by visit across all treatment sessions and follow-up periods where applicable. • Individual subject profiles over time will be plotted. Imaging marker segmental values will be displayed on the same plot, i.e. plots will include as many curves as segments. The legend will identify all segment categories. For analyses of association between endpoints: • Spearman correlation coefficients will be tabulated by timepoint for all pairs of endpoints to be studied, together with 95% confidence intervals • Scatter plots will be produced to visualize the association for all pairs of endpoints to be studied, by timepoint and across all timepoints

8.2. Immunogenicity Analyses

8.2.1. Overview of Planned Immunogenicity Analyses

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

Analyses detailed in this section will be performed on data from each study group separately. Data displays will be paginated by study groups.

Table 10 provides an overview of the planned immunogenicity analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 10 Overview of Planned Immunogenicity Analyses

Endpoints	Absolute	
	Summary	Individual
	T	L
Anti-drug antibodies	Y	Y
Immune complexes	Y	Y
Auto-antibodies	Y	Y

NOTES :
- T = Summary Tables, L = Individual subject Listings, Y = Yes display generated.
- Summary = Represents Tables related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents Listings related to any displays of individual subject observed raw data

8.3. Pharmacokinetic Analyses

8.3.1. Overview of Planned Pharmacokinetic Analyses

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

Table 11 provides an overview of the planned statistical summary of drug concentrations, with full details being presented in Appendix 11: List of Data Displays and Appendix 8: Population Pharmacokinetic Analyses.

Table 11 Overview of Planned Pharmacokinetic Analyses

Endpoints	Summary		Individual	
	T	F	F	L
GSK2315698 concentration[1]	Y	Y	Y[2]	Y
GSK2398852 concentration	Y	Y	Y[2]	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] Group 3 only
- [2] Linear and Semi-Log plots will be created on the same display

8.3.2. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.9: Reporting Process & Standards).

8.3.2.1. Plasma concentration of GSK2315698

- The data will be listed by subject group, ID, treatment session and sampling occasion.
- The pattern of the data will be explored by plots of concentration vs time. Data will be connected for each subject while stratified by subject group, by treatment session and by both.
- Summary statistics will be generated by sampling occasion, while stratified by subject group, by treatment session, and by both.

8.3.2.2. Plasma concentration of GSK2398852

- The data will be listed by subject group, ID, treatment session and sampling occasion.
- The pattern of the data will be explored by plots of concentration vs time. Data will be connected for each subject while stratified by subject group, by treatment session and by both.
- Summary statistics will be generated by sampling occasion, while stratified by subject group, by treatment session, and by both.

8.3.3. Population Pharmacokinetic (PopPK) Analyses

8.3.3.1. GSK2315698

Concordance in CPHPC pharmacokinetics between this study and previous studies will be assessed by visual predictive check of the concentration data from this study against a model that was developed with data from studies CPH113776 and CPH114527. This assessment will be reported by Clinical Pharmacology Modelling and Simulation (CPMS) and will be included as an appendix to the Clinical Study Report (CSR). Refer to Appendix 8: Population Pharmacokinetic Analyses (Section 10.8.1)

8.3.3.2. GSK2398852

The primary goal of this analysis is to characterize the population pharmacokinetics of GSK2398852 administered intravenously in subjects with cardiac amyloidosis. A summary of the planned population pharmacokinetic analyses is outlined below:

- Drug plasma concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK model.
- The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of GSK2398852 in this population will be investigated.
- The individual subject PK parameters will be estimated and summarised.
- To support this analysis a NONMEM file will be generated.
- The details for the analysis including dataset specifications are provided in Appendix 8: Population Pharmacokinetic Analyses with detailed methodology for the analysis.

8.4. Pharmacokinetic / Pharmacodynamic Analyses

Blood concentration of SAP prior to mAb administration will be assessed with and without stratification of subject groups and treatment course, by visual predictive check using a previously established PKPD model, taking into account for assay difference if applicable. This assessment will be reported by CPMS and will be included as an appendix to the CSR. See Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses for details.

8.5. Efficacy Analyses

8.5.1. Overview of Planned Efficacy Analyses

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

Analyses detailed in this section will be performed on data from each study group separately. Data displays will be paginated by study groups.

Table 12 provides an overview of the planned efficacy analyses, which will consist of 6MWT analyses for Study Groups 1 and 2 only. This analysis of 6MWT corresponds to the protocol objective of cardiac functional assessment. Full details of data displays are presented in Appendix 11: List of Data Displays.

Table 12 Overview of Planned Efficacy Analyses

Endpoints	Absolute			Change from Baseline
	Summary	Individual		Summary
	T	L	F	T
6MWT (Groups 1 and 2 only)	Y	Y	Y	Y

NOTES :

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

8.6. Quality of Life Analyses

8.6.1. Overview of Planned Quality of Life Analyses

The quality of life analyses will be based on the "Safety" population, unless otherwise specified.

Analyses detailed in this section will be performed on data from each study group separately. Data displays will be paginated by study groups.

Table 13 provides an overview of the planned quality of life analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 13 Overview of Planned Quality of Life Analyses

Endpoints	Absolute		Change from Baseline[1]
	Summary	Individual	Summary
	T	L	T
MOS SF-36 domain and overall scores	Y	Y	Y
KCCQ scores	Y	Y	Y
EORTC QLQ-C30 scores	Y	Y	Y
DLQI overall and section scores	Y	Y	Y

NOTES :

- T = Summary Tables, L = Individual subject Listings, Y = Yes display generated.
- Summary = Represents Tables related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents Listings related to any displays of individual subject observed raw data
- [1] Quality of life endpoints are collected at Baseline and 8-week follow-up, therefore changes from baseline will only be derived for the 8-week follow-up timepoint

8.6.2. MOS SF-36 Questionnaire

The Medical Outcomes Survey Short Form 36 (MOS SF-36) has 36 questions evaluating the subjects' quality of life over a 1 week period. Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3) gives details of the derivation steps which will be applied to the MOS SF-36:

- Recoding of MOS SF-36
- Handling Missing MOS SF-36 Items
- Domain Scale Scores
- Standardized Z Scores
- Norm-based Domain Scores (NBS)
- Physical and Mental Component Summaries (PCS and MCS)

All questions are scored using normative-based scoring.

The norm-based scores (NBS) at baseline and 8-week follow-up and changes from baseline at 8-week follow-up for each domain and the overall physical and mental component summaries will be summarized and listed:

- Physical functioning (PF)
- Role-physical (RP)
- Bodily pain (BP)
- General health (GH)
- Vitality (VT)
- Social functioning (SF)
- Role-emotional (RE)
- Mental health (MH)
- Physical component summary (PCS)
- Mental component summary (MCS).

SF-36 items and scales are scored so that a higher score indicates a better health state. The NBS scales would be expected to be distributed around 50 with a standard deviation of 10 for healthy individuals.

8.6.3. KCCQ Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item, self-administered questionnaire. There are 10 summary scores derived from the KCCQ items:

- Physical limitation
- Symptom stability
- Symptom frequency
- Symptom burden
- Total symptom Score
- Self efficacy
- Quality of life

- Social limitation
- Overall summary score
- Clinical summary score

Scores are transformed to a range of 0-100, in which higher scores reflect better health status. Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.4) provides details of the derivation for each of these scores, including instructions as how to handle missing data.

8.6.4. EORTC QLQ C30 Questionnaire

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30) consists of 30 questions. Subjects from groups 2 and 3 only will complete this questionnaire.

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include:

- Global heal status / QoL scale
- Functional scales:
    - Physical functioning
    - Role functioning
    - Emotional functioning
    - Cognitive functioning
    - Social functioning
- Symptom scales /items
    - Fatigue
    - Nausea and vomiting
    - Pain
    - Dyspnoea
    - Insomnia
    - Appetite loss
    - Constipation
    - Diarrhoea
    - Financial difficulties

Scores are transformed to a range of 0-100, in which higher scores reflect higher response levels. Therefore:

- A high score for a functional scale represents a high / healthy level of functioning
- A high score for the global health status / QoL represents a high QoL
- However, a high score for a symptom scale represents a high level of symptomatology / problems

Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.5) provides details of the derivation for each of these scores, including instructions as how to handle missing data.

8.6.5. DLQI questionnaire

The dermatology quality of life index (DLQI) is a 10-item validated questionnaire that has been used to assess the impact of skin disease on subject quality of life. It will be administered to subjects in the study who develop dermatological toxicity.

The DLQI is composed of an overall score, as well as of 6 section scores, as follows:

- Symptoms and feelings
- Daily activities
- Leisure
- Work and school
- Personal relationships
- Treatment

The higher the score, the more quality of life is impaired.

Derivation of the overall score and of the 6 section scores is provided in Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.6). Handling of missing answers is also described.

8.7. Exit Interviews

Exit interviews will be conducted over telephone after the 8-week follow-up (or following the last study visit if a subject withdraws from the study without attending the 8-week follow-up visit) in a subset of subjects only, to explore subjects' experience with study treatment. A qualitative research report will be prepared and provided separately by an external service supplier (Adelphi). As a consequence, there is no corresponding plan for data displays.

9. REFERENCES

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10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Time and Events
Section 10.2	Appendix 2: Treatment States & Phases
Section 10.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.4	Appendix 4: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.6	Appendix 6: Values of Potential Clinical Importance
Section 10.7	Appendix 7: Model Checking and Diagnostics for Statistical Analyses
Section 10.8	Appendix 8: Population Pharmacokinetic Analyses
Section 10.9	Appendix 9: Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses
Other RAP Appendices	
Section 10.10	Appendix 10: Abbreviations & Trade Marks
Section 10.11	Appendix 11: List of Data Displays
Section 10.12	Appendix 12: Example Mock Shells for Data Displays

10.1. Appendix 1: Time & Events

10.1.1. Protocol Defined Time & Events

Table 14 Overview All Groups (for details of inpatient stay see Table 15)

			Session 1			Session 2			Session 3			Session 4			Session 5			Session 6			Follow-up		
	Screening[1]	Baseline[2]	Day -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	8week F/U[3]	6 months[3]	12 months[3]
Inpatient stay at unit[4, 14]			X			X			X			X			X			X					
Outpatient visit at unit	X	X		X	X		X	X		X	X		X	X		X	X		X	X	X	X	X
Informed consent	X																						
Medical history/risk factors/demographics	X																						
Inclusion/exclusion criteria	X																						
Safety Assessments																							
Physical examination[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MOS SF-36, KCCQ, EORTC[6] questionnaires		X																			X		
DLQI questionnaire				X	X		X	X		X	X		X	X		X	X		X	X	X		
12 lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lead II telemetry			X			X			X			X			X			X					
Cardiac monitor[7]		X	X			X			X			X			X			X			X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments																							
FSH/E2 - see Table 6	X																						
Urine βhCG[8]	X		X			X			X			X			X			X				X	X
Haem/clin chem/urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24h Urine collection for protein and creatinine[9]	X	X			X			X			X			X			X			X		X	

			Session 1			Session 2			Session 3			Session 4			Session 5			Session 6			Follow-up		
	Screening[1]	Baseline[2]	Day -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	Days -2 to 11	Day 17	Day 24 ± 1 day	8week F/U[3]	6 months[3]	12 months[3]
HepB/Hep C/HIV	X																						
Blood biomarkers																							
Complement and Inflammatory markers		X	X			X			X			X			X			X					
hs-Troponin T/NT-ProBNP	X	X	X		X	X		X	X		X	X		X	X		X	X		X	X	X	X
Anti-Drug Antibody (anti-SAP mAb)		X																			X	X	X
Auto-antibodies		X																					
mAb/SAP immune complex			X	X																			
Pharmacokinetics/SAP[10]																							
Blood sampling for SAP			X		X	X		X	X		X	X		X	X		X	X					
Blood sampling for CPHPC			X			X			X			X			X			X					
Blood sampling for anti-SAP mAb			X	X		X	X		X	X		X	X		X	X		X	X		X		
Imaging Procedures																							
Cardiac MRI with contrast[13]	X[1]										X										X	X	X
Cardiac MRI without contrast								X						X			X						
ECHO		X			X			X			X			X			X			X	X	X	X
SAP scan - Groups 2/3 UK only		X																			X		
Bone scan (DPD/ PYP) – Group 1 only		X																			X		
Other																							
Skin biopsy / blood sample / urinalysis / EOSI[11]			(X)			(X)			(X)			(X)			(X)			(X)					
6MWT - Groups 1 & 2		X									X										X	X	X
Genetic sample[12](optional)		X																					
Exit Interview																					X		
Ongoing Subject Review																							
Concomitant therapy	X																						
Adverse event review			X																				

Footnotes:

1. Screening to take place within 42 days of start of treatment. CMR at screening will be performed after a subject has passed all other screening assessments
2. Baseline will be anytime after eligibility confirmed from screening and before anti-SAP treatment start
3. Follow-up at timepoint from last anti-SAP mAb dose
4. Refer to Table 15 for details of monthly inpatient visit
5. Full examination at screening only, brief examination at all other time-points
6. EORTC Groups 2 and 3 only
7. Out-patient cardiac recording using suitable device see Protocol Section 7.4.7.2. Recording at baseline, 8wk follow-up and 6 month follow-up for approximately 2 weeks
8. Pregnancy test before commencement of CPHPC infusion
9. 24h collection - 3.5ml serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples
10. Sampling time points in Table 15 and Table 16
11. In the event of rash, assessments to be performed (see Protocol Table 8). The Investigator/Sub-Investigator must perform a twice daily review
12. Informed consent for optional genetics sub-study must be obtained before collecting a sample
13. For subjects with a GFR <40ml/min/1.73m^2, MRI will be performed at the scheduled times but without contrast
14. Subjects are allowed to be admitted on Day -3 to allow for pre-dose assessments to be performed

Table 15 Inpatient stay

Study procedures	Day -2[13] pre-CPHPC dose	Day -2	Day -1	Day 1-3 anti-SAP mAb dose[1]	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Safety Assessments												
Brief physical examination (including skin)	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG	X	X	X	X	X	X	X	X	X	X	X	X
Lead II telemetry			X	X	X	X	X	X	X	X		
Cardiac monitoring[2]						X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration												
Administration of CPHPC (2 days IV infusion)		X	X[3]									
Administration of CPHPC (SC)				X	X	X	X	X	X	X	X	X[12]
Administration of anti-SAP mAb (6h IV infusion on days 1 and 3)				X								
Clinical Laboratory Assessments												
Haem/clin chem/urinalysis	X			X	X	X				X		X
24h Urine collection for protein and creatinine[4]				X			X					X
Urine microscopy[5]	X					X	X					X
Blood biomarkers												
Complement and Inflammatory Markers				X		X	X					
Cytokines	X			X	X	X						
hs-Troponin T/NT-ProBNP	X			X	X	X	X	X	X	X	X	X
Blood sampling for mAb/SAP immune complex [6]	X			X								
Pharmacokinetics/SAP												
Blood sampling for SAP	X		X[7]	X	X			X				
Blood sampling for CPHPC[8]				X[8]								
Blood sampling for anti-SAP mAb				X	X			X				X

Study procedures	Day -2[13] pre-CPHPC dose	Day -2	Day -1	Day 1-3 anti-SAP mAb dose[1]	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Ongoing Subject Review												
Skin biopsy[9]/blood sample/urinalysis/EOSI[10]			X[11]	(X)								
Concomitant therapy	X											
Adverse event review	X											

Footnotes: all timings relative to first anti-SAP mAb dose of session

1. See Table 16 for expanded details of days 1 to 3
2. At PI discretion appropriate alternate telemetry device may be used.during days 5-10. Cardiac monitoring continues to Day 19 and to be performed with suitable device see Protocol Section 7.4.7.2
3. If SAP levels are not below target then the CPHPC will be dosed for a further day and anti-SAP mAb dose deferred 1 day
4. 24h collection - 3.5mL serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples
5. Renal examination of urine i.e. not just dipstick and culture
6. Session 1 only
7. Rapid turnaround to ensure SAP depleted to target prior to dosing anti-SAP mAb
8. Group 3 only
9. Biopsies only on any rash development (i.e. ≥ Grade 1) and will be decided by clinical judgement of the Investigator ± dermatologist (see Protocol Table 8 for full assessments)
10. In the event of a rash the Investigator/Sub-Investigator must perform a twice daily review
11. On confirmation from medical monitor see Protocol Table 8
12. Morning dose only to be administered (see Protocol Table 2)
13. Subjects are allowed to be admitted on Day -3 to allow for pre-dose assessments to be performed

Table 16 Detailed Events - Days 1 to 3 (anti-SAP mAb dosing)

Study procedure	Day 1										Day 2					Day 3									
	Pre-dose	0h	1h	2h	3h	4h	6h	8h	12h	16h	0h	4h	8h	12h	16h	Pre-dose	0h	1h	2h	3h	4h	6h	8h	12h	16h
Safety assessments																									
12 lead ECG	X		X			X		X	X		X					X		X			X		X	X	
Lead II telemetry	X										X					X									
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration																									
Administration of CPHPC (SC)- see Table 2	X										X					X									
Administration of anti-SAP mAb		X									n/a						X								
Clinical lab assessments																									
Haem/clin chem/urinalysis	X										X[8]					X									
24h Urine collection for protein and creatinine[1]	X															X									
Urine microscopy	X			X			X									X			X			X			
Blood sample mAb/SAP immune complex[2]	X						X[3]															X[3]			
Blood biomarkers																									
Complement & Inflammatory markers	X			X		X		X			X					X			X		X		X		
Cytokines	X		X		X		X				X					X		X		X		X			
hs-Troponin T/NT-proBNP	X										X					X									

Study procedure	Day 1										Day 2					Day 3									
	Pre-dose	0h	1h	2h	3h	4h	6h	8h	12h	16h	0h	4h	8h	12h	16h	Pre-dose	0h	1h	2h	3h	4h	6h	8h	12h	16h
Pharmacokinetics																									
Blood sampling - SAP	X						X				X[5]					X						X			
Blood sampling- CPHPC[4]	X										X[5]					X									
Blood sampling - anti-SAP mAb	X						X[6]	X	X		X[5]					X						X[6]			
Ongoing subject review																									
Skin biopsy/blood sample/urinalysis/EOSI[7]		(X)									(X)						(X)								
Concomitant therapy review	X										X					X									
Adverse event review	X										X					X									

Footnotes: all timings relative to first anti-SAP mAb dose of session

1. 24h collection - 3.5mL serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples
2. Session 1 only
3. At end of anti-SAP mAb infusion
4. CPHPC sampling is for Group 3 only
5. Blood sample to be taken immediately prior to first CPHPC SC injection and 2h post CPHPC SC injection of that day
6. Blood Sampling to coincide with the end of infusion of the anti-SAP mAb
7. Biopsies on any rash development will be decided by clinical judgement of the Investigator and dermatologist (see Protocol Table 8 for full assessments) Skin biopsies & paired blood sample / urinalysis should only be performed for each new and / or clinically progressive rash
8. To include clotting tests for Session 1 only (see Protocol Table 6)

10.2. Appendix 2: Treatment States and Phases

The handling of missing or partial AE dates and times and their impact on the assigned treatment phase/session and the calculation of onset time and duration is described in Section 10.5.2.1.

10.2.1. Treatment Phases

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

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

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

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

Unless stated otherwise, AE summaries will only include AEs assigned to the on-treatment phase. The only exceptions will be the summaries of pre-treatment and post-treatment AEs by SOC and PT. All AE listings will include treatment phase assignment.

10.2.2. Treatment Sessions

Treatment sessions are defined for the purpose of specific AE or PK summaries by treatment session. Only two AE summaries will display AE frequencies by treatment session: All AEs by SOC, PT and Treatment Session; Rashes by SOC, PT, Maximum CTCAE Grade and Treatment Session. All AE listings will include treatment session assignment.

AEs and PK samples 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 3 First Dose Date/Time of Study Drug[1] or Session 2 Last Dose Date/Time of Study Drug[2] + 56 Days (if Session 3 is not applicable).
Treatment Session 3	Session 3 First Dose Date/Time of Study Drug[1] ≤ Date/Time < Session 4 First Dose Date/Time of Study Drug[1] or Session 3 Last Dose Date/Time of Study Drug[2] + 56 Days (if Session 4 is not applicable).
Treatment Session 4	Session 4 First Dose Date/Time of Study Drug[1] ≤ Date/Time < Session 5 First Dose Date/Time of Study Drug[1] or Session 4 Last Dose Date/Time of Study Drug[2] + 56 Days (if Session 5 is not applicable).
Treatment Session 5	Session 5 First Dose Date/Time of Study Drug[1] ≤ Date/Time < Session 6 First Dose Date/Time of Study Drug[1] or Session 5 Last Dose Date/Time of Study Drug[2] + 56 Days (if Session 6 is not applicable).
Treatment Session 6	Session 6 First Dose Date/Time of Study Drug[1] ≤ Date/Time < Session 6 Last Dose Date/Time of Study Drug[2] + 56 Days

[1]Earliest treatment session dose of GSK2315698 or GSK2398852
[2]Latest treatment session dose of GSK2315698 or GSK2398852

10.2.3. AE Onset Time and Duration

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

	Definition
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 subjects is not exposed to any study drug
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
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 First Dose Date If Session mAb First Dose Date/Time of study drug ≤ AE Onset Date/Time, Onset Day = AE Onset Date – Session mAb 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 in the study

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions		
RandAll NG		Data Displays for Reporting
Code	Description	Description
A	GSK2315698 + GSK2398852	Anti-SAP

10.3.2. Baseline Definition & Derivations

10.3.2.1. 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.

10.3.2.2. 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 10.3.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.3.3. Derivation of MOS SF-36 Scores

10.3.3.1. Recoding of MOS SF-36

Some of the items in the SF-36 will be re-coded as follows such that higher values represent better functioning:

Physical Functioning (PF): Items 3a-3j: No Recoding Required

Response choices	Pre-coded value	Final value
Yes, limited a lot	1	1
Yes, limited a little	2	2
No, not limited at all	3	3

Role Physical (RP): Items 4a-4d: No Recoding Required

Response choices	Pre-coded value	Final value
All of the time	1	1
Most of the time	2	2
Some of the time	3	3
A little of the time	4	4
None of the time	5	5

Bodily Pain (BP): Item 7:

Response choices	Pre-coded value	Final value
None	1	6.0
Very mild	2	5.4
Mild	3	4.2
Moderate	4	3.1
Severe	5	2.2
Very severe	6	1.0

Bodily Pain (BP): Item 8
Scoring for item 8--if both items 7 and 8 are answered:

Response choices	If item 8 Pre-coded value	and	Item 7 Pre-coded value	then	Item 8 final item value
Not at all	1		1		6
Not at all	1		2 through 6		5
A little bit	2		1 through 6		4
Moderately	3		1 through 6		3
Quite a bit	4		1 through 6		2
Extremely	5		1 through 6		1

Bodily Pain (BP): Item 8
Scoring for item 8--if item 7 is not answered:

Response choices	Pre-coded value	Final value
Not at all	1	6.0
A little bit	2	4.75
Moderately	3	3.5
Quite a bit	4	2.25
Extremely	5	1.0

General Health (GH): Items 1 and 11a-11d:

Item 1	Response choices	Pre-coded value	Final value
	Excellent	1	5.0
	Very good	2	4.4
	Good	3	3.4
	Fair	4	2.0
	Poor	5	1.0

Item 11a & 11c	Response choices	Pre-coded value	No Recoding Required Final value
	Definitely true	1	1

	Mostly true	2	2
	Don't know	3	3
	Mostly false	4	4
	Definitely false	5	5

Item 11b & 11d	Response choices	Pre-coded value	Final value
	Definitely true	1	5
	Mostly true	2	4
	Don't know	3	3
	Mostly false	4	2
	Definitely false	5	1

Vitality (VT): Items 9a, 9e, 9g, & 9i:

Item 9a & 9e	Response choices	Pre-coded value	Final value
	All of the time	1	5
	Most of the time	2	4
	Some of the time	3	3
	A little of the time	4	2
	None of the time	5	1

Item 9g & 9i	Response choices	Pre-coded value	No Recoding Required Final value
	All of the time	1	1
	Most of the time	2	2
	Some of the time	3	3
	A little of the time	4	4
	None of the time	5	5

Social Functioning (SF): Items 6 & 10:

Item 6	Response choices	Pre-coded value	Final value
	Not at all	1	5
	Slightly	2	4
	Moderately	3	3
	Quite a bit	4	2
	Extremely	5	1

Item 10	Response choices	Pre-coded value	No Recoding Required Final value
	All of the time	1	1
	Most of the time	2	2
	Some of the time	3	3
	A little of the time	4	4
	None of the time	5	5

Role Emotional (RE): Items 5a - 5c:

Response choices	Pre-coded value	No Recoding Required Final value
All of the time	1	1
Most of the time	2	2
Some of the time	3	3
A little of the time	4	4
None of the time	5	5

Mental Health (MH): Items 9b, 9c, 9d, 9f, & 9h:

Items 9b,9c, & 9f	Response choices	Pre-coded value	No Recoding Required Final value
	All of the time	1	1
	Most of the time	2	2
	Some of the time	3	3
	A little of the time	4	4
	None of the time	5	5

Item 9d & 9h	Response choices	Pre-coded value	Final value
	All of the time	1	5
	Most of the time	2	4
	Some of the time	3	3
	A little of the time	4	2
	None of the time	5	1

10.3.3.2. Handling Missing MOS SF-36 Items

For each of the eight domain scales (PF, RP, BP, GH, VT, SF, RE and MH), the Half-Scale Rule will be applied for missing data. If any items within a domain scale are missing (but at least half of the items in the domain scale have responses), then the final value for the missing items should be substituted with the average of the final values within the domain (i.e. after recoding if necessary) for the same subject. If any items within a domain scale are missing (but fewer than half of the items in the domain scale have responses), then the domain scale will be set to missing. Each domain score will be considered missing if more than half of the items within the scale have missing values.

10.3.3.3. Domain Scale Scores

After item recoding and imputing of missing values, a raw score will be computed for each domain scale. This score is the simple algebraic sum of responses for all items in that scale as shown in the table below:

Domain	Actual raw score (sum final values after re-coding)	Lowest and highest possible raw scores	Possible raw score range
Physical functioning (PF)	3a+3b+3c+3d+3e+3f+ 3g+3h+3i+3j	10, 30	20
Role-physical (RP)	4a+4b+4c+4d	4, 20	16
Bodily pain (BP)	7+8	2, 12	10
General health (GH)	1+11a+11b+11c+11d	5, 25	20
Vitality (VT)	9a+9e+9g+9i	4,20	16
Social functioning (SF)	6+10	2, 10	8
Role-emotional (RE)	5a+5b+5c	3, 15	12
Mental health (MH)	9b+9c+9d+9f+9h	5, 25	20

After item re-coding, a raw score is computed for each scale and transformed to a 0 to 100 scale as shown below:

$$Transformed\ Scale = \frac{(Actual\ raw\ score - lowest\ possible\ raw\ score)}{Possible\ raw\ score\ range} \times 100$$

Example: A Physical Functioning raw score of 21 would be transformed as follows:

$$\frac{(21-10)}{20} \times 100$$

where the lowest possible score=10 and the possible raw score range=20.

10.3.3.4. Standardized Z Scores

Each transformed domain scale score is standardised using a z-score transformation, subtracting a population mean and dividing the resultant value by a population standard deviation. The population means and standard deviations of the transformed domain scores are based on the 1998 US general population. The formulas for z-score standardization of domain scales are thus:

PF_Z = (Transformed PF – 83.29094) / 23.75883

RP_Z = (Transformed RP – 82.50964) / 25.52028

BP_Z = (Transformed BP – 71.325227) / 23.66224

GH_Z = (Transformed GH – 70.84570) / 20.97821

VT_Z = (Transformed VT – 58.31411) / 20.01923

SF_Z = (Transformed SF – 84.30250) / 22.91921

RE_Z = (Transformed RE – 87.39733) / 21.43778

MH_Z = (Transformed MH – 74.98685) / 17.75604.

10.3.3.5. Norm-based Domain Scores (NBS)

Norm-based scoring (NBS) makes it possible to compare and interpret the SF-36 domain scale scores. The norm-based scores (NBS) for the 8 domains are derived by multiplying each z-score by 10 and adding 50 to the result.

10.3.3.6. Physical and Mental Component Summaries (PCS and MCS)

The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores are derived in two steps. First, aggregate scores are derived using a weighted mean of the z-scores calculated (see Section 10.3.3.4) using the formulae shown below:

AGG_PHYS = (PF_Z * 0.42402) + (RP_Z * 0.35119) + (BP_Z * 0.31754) + (GH_Z *0.24954) + (VT_Z * 0.02877) + (SF_Z * -0.00753) + (RE_Z* -0.19206) + (MH_Z * -0.22069)

AGG_MENT = (PF_Z * -0.22999) + (RP_Z * -0.12329) + (BP_Z * -0.09731) +(GH_Z * -0.01571) + (VT_Z * 0.23534) + (SF_Z * 0.26876) +(RE_Z* 0.43407) + (MH_Z * 0.48581).

Secondly, the aggregate physical and mental summary scores are transformed to PCS and MCS score by multiplying each value by 10 and adding 50 to the result. This NBS standardisation of the PCS and MCS means that results for one summary score can be compared to the other, and their scores have a direct interpretation in relation to the distribution of scores in the general US population.

10.3.4. Derivation of KCCQ Scores

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

- Code responses to each of Questions 1a-f as follows:
  - Extremely limited = 1
  - Quite a bit limited = 2
  - Moderately limited = 3
  - Slightly limited = 4
  - Not at all limited = 5
  - Limited for other reasons or did not do = <missing value>

- If at least three of Questions 1a-f are not missing, then compute

  Physical Limitation Score =
  100*[(mean of Questions 1a-f actually answered) – 1]/4

2. Symptom Stability

- Code the response to Question 2 as follows:
  - Much worse = 1
  - Slightly worse = 2
  - Not changed = 3
  - Slightly better = 4
  - Much better = 5
  - I've had no symptoms over the last 2 weeks = 3

- If Question 2 is not missing, then compute

  Symptom Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

- Code responses to Questions 3, 5, 7 and 9 as follows:

  - Question 3
    - Every morning = 1
    - 3 or more times a week but not every day = 2
    - 1-2 times a week = 3
    - Less than once a week = 4

    - Never over the past 2 weeks = 5

  - Questions 5 and 7
    - All of the time = 1
    - Several times a day = 2
    - At least once a day = 3
    - 3 or more times a week but not every day = 4
    - 1-2 times a week = 5
    - Less than once a week = 6
    - Never over the past 2 weeks = 7

  - Question 9
    - Every night = 1
    - 3 or more times a week but not every day = 2
    - 1-2 times a week = 3
    - Less than once a week = 4
    - Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

  S3 = [(Question 3) – 1]/4
  S5 = [(Question 5) – 1]/6
  S7 = [(Question 7) – 1]/6
  S9 = [(Question 9) – 1]/4

  Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:
  - Extremely bothersome = 1
  - Quite a bit bothersome = 2
  - Moderately bothersome = 3
  - Slightly bothersome = 4
  - Not at all bothersome = 5
  - I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

  Symptom Burden Score =
  100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

  = mean of the following available summary scores:
  - Symptom Frequency Score
  - Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

    - Question 10
        - Not at all sure = 1
        - Not very sure = 2
        - Somewhat sure = 3
        - Mostly sure = 4
        - Completely sure = 5

    - Question 11
        - Do not understand at all = 1
        - Do not understand very well = 2
        - Somewhat understand = 3
        - Mostly understand = 4
        - Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score =
  100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

    - Question 12
        - It has extremely limited my enjoyment of life = 1
        - It has limited my enjoyment of life quite a bit = 2
        - It has moderately limited my enjoyment of life = 3
        - It has slightly limited my enjoyment of life = 4
        - It has not limited my enjoyment of life at all = 5

    - Question 13
        - Not at all satisfied = 1
        - Mostly dissatisfied = 2
        - Somewhat satisfied = 3
        - Mostly satisfied = 4
        - Completely satisfied = 5

    - Question 14
        - I felt that way all of the time = 1
        - I felt that way most of the time = 2
        - I occasionally felt that way = 3
        - I rarely felt that way = 4
        - I never felt that way = 5

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score =
  100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:
  - Severely limited = 1
  - Limited quite a bit = 2
  - Moderately limited = 3
  - Slightly limited = 4
  - Did not limit at all = 5
  - Does not apply or did not do for other reasons = <missing value>

- If at least two of Questions 15a-d are not missing, then compute

  Social Limitation Score =
  100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

  = mean of the following available summary scores:
  - Physical Limitation Score
  - Total Symptom Score
  - Quality of Life Score
  - Social Limitation Score

10. Clinical Summary Score

  = mean of the following available summary scores:
  - Physical Limitation Score
  - Total Symptom Score

"Means of questions actually answered" imply the following:

- If there are n questions in a scale, and the subject must answer m to score the scale, but the subject answers only n-i, where n-i >= m, the mean should be calculated as
  (sum of the responses to those n-i questions) / (n-i)
  not
  (sum of the responses to those n-i questions) / n

10.3.5. Derivation of EORTC QLQ-C30 Scores

10.3.5.1. Scale definition and score derivation

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, 1 global health status / QoL scale, and 6 single items.

The item (question) numbers included in each scale, as well as the item ranges are summarised in Table 14.

Table 17 Scoring the EORTC QLQ-C30 (version 3.0)

	Scale	Number of items	Item range*	Item numbers	Function scales
Global Health Status / QoL					
Global Health Status / QoL (revised)[a]	QL2	2	6	29, 30	
Functional Scales					
Physical functioning (revised)[a]	PF2	5	3	1 to 5	F
Role functioning (revised)[a]	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.
[a](revised) scales are those that have been changed since EORTC QLQ-C30 version 1.0, and their short names are indicated by a suffix "2" – for example, PF2.

For all scales, the Raw Score (RS) is the mean of the component items:

$$RS = (I_1 + I_2 + \ldots + I_n)/n$$

Then for **Function scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

And for **Symptom scales /items and Global health status / QoL**:

$$Score = \{(RS - 1)/range\} \times 100$$

10.3.5.2. Handling of missing items

For multi-item scales:

- If at least half of the items from a given scale have been answered, then missing items can be ignored and the calculations should be made using available (non-missing) items only. The denominator in the derivation of RS ('*n*') becomes the number of non-missing items.
- If less than half of the items have been answered, then set the score to missing

For single-item scales, a missing measurement will result in a missing score.

10.3.5.3. SAS code examples

SAS code examples are provided in the EORTC QLQ C-30 scoring manual for emotional functioning and dyspnoea scales.

"SAS statements (SAS for Windows, release 6.08) to calculate the score for the EF scale could be written as follows; XNUM is used to count the number of non-missing items, which should be at least half the total NITEMS items in the scale. Thus this code calculates the average of the nonmissing values, and transforms this average to range from 0 to 100 provided that the subject has completed at least half the necessary items.

For emotional functioning (EF) there are 4 items, each with a range of 3:
NITEMS = 4;
XNUM = N(OF Q21,Q22,Q23,Q24);
XMEAN = MEAN(OF Q21,Q22,Q23,Q24);
IF XNUM GE NITEMS / 2 THEN
EF = (1 - (XMEAN-1)/3) * 100;

For dyspnoea (DY), a symptom comprising a single item with a range of 3:
DY = ((Q8-1)/3) * 100;"

10.3.6. Derivation of DLQI Scores

10.3.6.1. Scale definition and score derivation

The scoring of each DLQI question is as follows:

Answer	Score
Very much	3
A lot	2
A little	1
Not at all	0
Not relevant	0
Question unanswered	0
Question 7 “prevented work or studying”	3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Meaning of DLQI Scores:

Score	Meaning
0-1	No effect at all on patient’s life
2-5	Small effect on patient’s life
6-10	Moderate effect on patient’s life
11-20	Very large effect on patient’s life
21-30	Extremely large effect on patient’s life

Detailed analysis of the DLQI:

The DLQI can be analysed under six headings as follows:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

10.3.6.2. Handling of missing items

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
- If two or more questions are left unanswered the questionnaire is not scored.
- If question 7 is answered 'yes' this is scored 3. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If it is answered 'no', but the second half is left incomplete, the score will remain 0.
- If two or more response options are ticked, the response option with the highest score should be recorded.

- If there is a response between two tick boxes, the lower of the two score options should be recorded.
- The DLQI can be analysed by calculating the score for each of its six sub-scales (see above). When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored.

10.3.7. Derivation of LGE variable

The LGE variable will be defined as follows:

- If Transmural value is 'Yes', then LGE will be set to 'Transmural'
- Else of Endocardial value is 'Yes', then LGE will be set to 'Endocardial'
- Else LGE will be set to 'No'

10.3.8. Derivation of DCE-CMR Global Measure of Myocardial Perfusion

The DCE-CMR global measure of myocardial perfusion will be derived as the mean of myocardial blood flow in each segment, weighted by each segment size.

The formula will be as follows: $\frac{\sum_{i=1}^{n} w_i x_i}{\sum_{i=1}^{n} w_i}$, where n is the number of segments, w_i the segment size and x_i the absolute myocardial blood flow for segment i.

10.3.9. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: \ARPROD\gsk2398852\mid201464
QC Spreadsheet	: \ARPROD\gsk2398852\mid201464\Final_02\Documents QC spreadsheets will also be produced and saved for each interim under: : \ARPROD\gsk2398852\mid201464\internal_XX\Documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (ADaM).	
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 4.24: General Principles o 5.01 to 5.08: Principles Related to Data Listings

Reporting Standards	
○ 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. • 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 :
  • Nominal visits will be used for the purpose of descriptive summary tables
  • Actual times relative to the first study dose of anti-SAP mAb will be used in individual subject plots, and for statistical analyses unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing (first dose of either GSK2315698 or GSK2398852) 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 (see Section 10.3.2.1). Post-baseline unscheduled visits will not be included in summary tables, with the exception of the following summaries: summary of subjects meeting emergent hepatobiliary laboratory abnormality criteria, summary of ECG findings, summary of maximum emergent QTc Values by category, summary of maximum change from baseline in QTc values by category • 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, %
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)
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.4. Appendix 4: Derived and Transformed Data

10.4.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • 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 = Day post-first study dose of aSAP mAb

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

Derivation of Time in Months
• Time in months will be used to derive change at 3, 5, 8, 12 and 18 months, and slope parameters (units per month) for primary and secondary statistical analyses. It will also be used for the horizontal axis of Figures PD_F1 and PD_F4 (see Appendix 12: Example Mock Shells for Data Displays) • Time in months will be derived as Time in days / 30.4375, with Time in days defined as the assessment date – date of first dose of anti-SAP mAb.

10.4.2. 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 (BMI)
• 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

Extent of Exposure
administered in each dosing session and over the study as a whole. • Number of days of exposure to anti-SAP mAb will be calculated as the number of doses administered. • The cumulative dose of aSAP mAb will be calculated from the sum of the individual doses administered (over all dosing sessions).

10.4.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$
Corrected QT Intervals
• IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Adverse Events
AE'S OF Special Interest
A selection of AEs of interest for which posterior probabilities will be derived will be periodically reviewed and its finalization will be documented prior to database freeze (see Section 7.2.1).

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.

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	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 GSK2398852); 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 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 2: 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

Element	Reporting Detail
	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 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: ○ 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.

10.5.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Primary statistical model	Several approaches were considered for the handling of missing data in the primary statistical analysis model. Two of them involved the use of multiple imputation of missing post-treatment visits. More details can be found in Section 7.1.2.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. Haematology Values of Potential Clinical Importance

The criteria for values of potential clinical importance will depend on the study group.

10.6.1.1. Study Group 1

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	

10.6.1.2. Study Group 2

Haematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count		0.30	2.2
Neutrophil Count		0.30	2.2
Haemoglobin	Male	0.65	1.2
	Female	0.7	1.2
Platelet Count		0.25	2.50
Lymphocytes		0.30	2.2

10.6.1.3. Study Group 3

Haematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count		0.30	No limit
Neutrophil Count		0.30	No limit
Haemoglobin	Male	0.6	1.2
	Female	0.7	1.2
Platelet Count		0.25	2.50
Lymphocytes		0.30	

10.6.2. 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
Potassium (mmol/L)	0.77	1.17
Sodium (mmol/L)	0.92	1.07
Creatinine (mmol/L)		1.6

10.6.3. 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

10.6.4. 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

10.6.5. 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

10.7. Appendix 7: Model Checking and Diagnostics for Statistical Analyses

10.7.1. Statistical Analysis Assumptions

Endpoint(s)	• LV Mass • Secondary imaging markers of cardiac dysfunction monitored by serial CMR and / or ECHO
Analysis	• Bayesian LMM

- The Bayesian LMM convergence diagnostics available from SAS MCMC procedure will be reviewed, such as the Geweke test, sample autocorrelations, effective sample sizes, and Monte Carlo errors.
- In case of convergence issues, initial values, burn-in and thinning rate parameters may be adapted, or alternative prior distributions considered as appropriate.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

10.8. Appendix 8: Population Pharmacokinetic Analyses

10.8.1. Systems

All non-linear mixed effects modelling will be performed using NONMEM (ICON Solutions), PsN (Perl Speaks NONMEM) and Pirana (Pirana Software & Consulting BV 2016).

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, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline in the GSK modelling environment MAP (Model-based Analyses Platform) using the currently supported versions of all software packages.

10.8.2. Data Assembly

The merge of PK, 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 10.8.6 and Section 10.8.7.

10.8.3. Population Pharmacokinetic Analysis for GSK2315698

A population PK model has been developed for GSK2315698 in both healthy volunteers and subjects with systemic amyloidosis (GSK Document Number 2012N146440_00). Using this model, visual predictive checks (VPCs) will be conducted to assess graphically whether simulations from the developed model are able to reproduce both the central trend and variability in the observed data from the current study as a function of time.

The 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 PK sampling and individual values of model covariates). The median and the 5^{th} and 95^{th} (or 10^{th} and 90^{th}, dependent on the size of the final dataset) will be compared to the observed data. Applicable stratification, such as dose level of GSK2315698, treatment cycle, subject group and relevant covariates will be used.

10.8.4. Population Pharmacokinetic Analysis for GSK2398852

Subsequent model development will be data driven. The initial model of choice may be a hybrid PBPK model with target mediated drug disposition incorporated. Several tissues

may be grouped together in this model, in particular tissues without amyloid deposition. If a hybrid PBPK model cannot describe the data, a compartmental model will be tested.

The influence of the following covariates on the PK of GSK2398852 may be investigated:

- Subject demographics: age, gender and weight or BMI
- Disease state at (treatment cycle) baseline: overall amyloid load (none/small/moderate/large)
- Organ involvement at (treatment cycle) baseline (e.g. liver)

Other covariates such as subject group may be explored as appropriate.

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 models visual predictive checks (VPCs) will be conducted in the same way as described in Section 10.8.3.

10.8.5. Reporting

A PK/PD report, describing the population PK analysis of GSK2315698 and GSK2398852, as well as the PK/PD analysis of the effect of GSK2315698 on plasma SAP (see Section 10.9) will be produced by CPMS, and will be included as an appendix to the CSR.

10.8.6. Specifications for NONMEM-specific Dataset (PK GSK2315698)

The concentration dataset will be a comma separated values (csv) file, named "NM_GSK2315698_SAP201464_PK_v1.csv". The version number will be updated each time a new version of the dataset is created.

This file will include events of dosing or 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 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
IDTC	-	Combination of unique subject identification number and treatment cycle number: e.g. PPD for subj PPD and treatment cycle 1 e.g. for subj and treatment cycle 2 etc		numeric
TRFD	h	Event time from start of first dose of GSK2315698 within a treatment cycle		numeric
DV	ng/mL	For concentration events: plasma concentration of GSK2315698 For dosing events: 0		numeric
AMT	mg	For dosing events: dose of GSK2315698. Note that for the IV dose this should be the total dose given in one IV infusion (i.e. over several days). Interruptions due to changing of syringes are relatively short, and therefore the infusion will be assumed to be continuous. For concentration events: 0		numeric
RATE	mg/hr	For dosing events of SC dosing: 0 For dosing events of IV dosing: rate of dosing (i.e. dose of GSK2315698 in mg divided by infusion duration) For concentration events: 0		numeric
MDV	-	For concentration events: 0 For dosing events: 1		Numeric
CMT	-	Compartment: For dosing events of SC dosing: 1 For dosing events of IV dosing: 2 For concentration events: 2		Numeric
NOMT	h	Planned PK sample time For dosing events: 0 For pre-dose concentration events: 0		Numeric
TRLD	h	Event time from most recent dose of GSK2315698 For dosing events: 0		Numeric
PERD	-	Study period (treatment cycle)		Numeric
DOSEIV	mg/hr	IV dose of GSK2315698 in mg/hr (for all events)		Numeric
DOSESC	mg	SC dose of GSK2315698 in mg (for all events)		Numeric
STUD	-	Numeric part of study identifier (i.e. 201464)		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

Name	Implicit Unit	Description	Programming Notes	Format
PATGRP	-	Patient group number: Group 1 = 1 Group 2 = 2 Group 3 = 3		numeric
AMLOAD	-	Overall amyloid load at treatment cycle baseline: None=0 Small=1 Moderate=2 Large=3		Numeric
AMLOADBL	-	Overall amyloid load at study baseline: None=0 Small=1 Moderate=2 Large=3		Numeric
AMLOC	-	Liver involvement at treatment cycle baseline: Liver involvement=1 No liver involvement =0		Numeric
AMLOCBL	-	Liver involvement at study baseline Liver involvement=1 No liver involvement =0		Numeric

10.8.7. Specifications for NONMEM-specific Dataset (PK GSK2398852)

The concentration dataset will be a comma delimited text file, named "NM_GSK2398852_SAP201464_PK_v1.csv". The version number will be updated each time a new version of the dataset is created.

This file will include events of dosing or 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 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
IDTC	-	Combination of unique subject identification number and treatment cycle: e.g. PPD for subj PPD and treatment cycle 1 e.g. for subj nd treatment cycle 2 etc		numeric
TRFD	h	Event time from start of first dose of GSK2398852 within a treatment cycle		numeric
DV	ng/mL	For concentration events: plasma concentration of GSK2398852 For dosing events: 0		numeric
AMT	mg	For dosing events: dose of GSK2398852. Note that this should be the total dose per IV infusion. For concentration events: 0		numeric
RATE	mg/hr	For dosing events: rate of dosing (i.e. dose of GSK2398852 in mg divided by infusion duration) For concentration events: 0		numeric
MDV	-	For concentration events: 0 For dosing events: 1		Numeric
CMT	-	Compartment: For dosing events of IV dosing: 1 For concentration events: 1		Numeric
NOMT	h	Planned PK sample time For dosing events: 0 For pre-dose concentration events: 0		Numeric
TRLD	h	Event time from most recent dose of GSK2398852 For dosing events: 0		Numeric
PERD	-	Study period (treatment cycle)		Numeric
DOSE	mg	Dose of GSK2398852 in mg (for all events)		Numeric
STUD	-	Numeric part of study identifier (i.e. 201464)		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
PATGRP	-	Patient group number: Group 1 = 1 Group 2 = 2 Group 3 = 3		numeric
AMLOAD	-	Overall amyloid load at treatment cycle baseline: None=0 Small=1 Moderate=2 Large=3		Numeric

Name	Implicit Unit	Description	Programming Notes	Format
AMLOADBL	-	Overall amyloid load at study baseline: None=0 Small=1 Moderate=2 Large=3		Numeric
AMLOC	-	Liver involvement at treatment cycle baseline: Liver involvement=1 No liver involvement =0		Numeric
AMLOCBL	-	Liver involvement at study baseline Liver involvement=1 No liver involvement =0		Numeric

10.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

10.9.1. Systems

All non-linear mixed effects modelling will be performed using NONMEM (ICON Solutions), PsN (Perl Speaks NONMEM) and Pirana (Pirana Software & Consulting BV 2016).

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, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline in the GSK modelling environment MAP (Model-based Analyses Platform) using the currently supported versions of all software packages.

10.9.2. Data Assembly

The merge of plasma SAP, 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 10.9.5.

10.9.3. Pharmacokinetic/Pharmacodynamic Analysis for plasma SAP Concentration

A population PK/PD model has been developed for the effect of GSK2315698 on SAP in plasma in both healthy volunteers and subjects with systemic amyloidosis (GSK Document Number 2012N146440_00). Using this model, adjusted for the difference in assay, visual predictive checks (VPCs) will be conducted to assess graphically whether simulations from the developed model are able to reproduce both the central trend and variability in the observed data from the current study as a function of time.

The 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 5^{th} and 95^{th} (or 10^{th} and 90^{th}, dependent on the size of the final dataset) will be compared to the observed data. Applicable stratification, such as dose level of GSK2315698, treatment cycle, subject group and relevant covariates, will be used.

10.9.4. Reporting

A PK/PD report, describing the population PK analysis of GSK2315698 and GSK2398852 (see Section 10.8), as well as the PK/PD analysis of the effect of

GSK2315698 on plasma SAP will be produced by CPMS, and will be included as an appendix to the CSR.

10.9.5. Specifications for NONMEM-specific Dataset (SAP)

The concentration dataset will be a comma delimited text file, named "NM_GSK2315698_SAP201464_PD_v1.csv". The version number will be updated each time a new version of the dataset is created.

This file will include events of dosing 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 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
IDTC	-	Combination of unique subject identification number and treatment cycle: e.g. PPD for subj PPD and treatment cycle 1 e.g. for subj and treatment cycle 2 etc		numeric
TRFD	h	Event time from start of first dose of GSK2315698 within a treatment cycle		numeric
DV	mg/L	For concentration events: plasma concentration of SAP For dosing events: 0		numeric
AMT	mg	For dosing events: dose of GSK2315698. Note that for the IV dose this should be the total dose given in one IV infusion (i.e. over several days). Interruptions due to changing of syringes are relatively short, and therefore the infusion will be assumed to be continuous. For concentration events: 0		numeric
RATE	mg/hr	For dosing events of SC dosing: 0 For dosing events of IV dosing: rate of dosing (i.e. dose of GSK2315698 in mg divided by infusion duration) For concentration events: 0		numeric
MDV	-	For concentration events: 0 For dosing events: 1		Numeric
CMT	-	Compartment: For dosing events of SC dosing: 1 For dosing events of IV dosing: 2 For concentration events: 2		Numeric
NOMT	h	Planned sample time for SAP For dosing events: 0 For pre-dose concentration events: 0		Numeric
TRLD	h	Event time from most recent dose of GSK2315698 For dosing events: 0		Numeric

Name	Implicit Unit	Description	Programming Notes	Format
PERD	-	Study period (treatment cycle)		Numeric
DOSEIV	mg/hr	IV dose of GSK2315698 in mg/hr (for all events)		Numeric
DOSESC	mg	SC dose of GSK2315698 in mg (for all events)		Numeric
STUD	-	Numeric part of study identifier (i.e. 201464)		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
PATGRP	-	Patient group number: Group 1 = 1 Group 2 = 2 Group 3 = 3		numeric
AMLOAD	-	Overall amyloid load at treatment cycle baseline: None=0 Small=1 Moderate=2 Large=3		Numeric
AMLOADBL	-	Overall amyloid load at study baseline: None=0 Small=1 Moderate=2 Large=3		Numeric
AMLOC	-	Liver involvement at treatment cycle baseline: Liver involvement=1 No liver involvement =0		Numeric
AMLOCBL	-	Liver involvement at study baseline Liver involvement=1 No liver involvement =0		Numeric

10.10. Appendix 10 – Abbreviations & Trade Marks

10.10.1. Abbreviations

Abbreviation	Description
6MWT	6 Minute Walk Test
ADaM	Analysis Data Model
AE	Adverse Event
AL	Immunoglobin Light Chain Amyloidosis
ALT	Alanine Transaminase
AUC	Area Under the Concentration-Time Profile
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
Cmax	Maximum Concentration
CMR	Cardiac MRI
CPHPC	Carboxy Pyrrolidine Hexanoyl Pyrrolidine Carboxylate
CPMS	Clinical Pharmacology Modelling & Simulation
CRF	Case Report Form
CrInt	Credible Interval
CRP	C Reactive Protein
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Dynamic Contrast Enhanced
DLQI	Dermatology Quality of Life Index
DP	Decimal Places
DPD/^{99m}Tc-DPD	^{99m}Technetium-dicarboxypropane diphosphonate
ECG	Electrocardiogram
ECHO	Echocardiography
eCRF	Electronic Case Record Form
ECV	Extracellular Volume
EDV	End Diastolic Volume
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EORTC QLQ C30	The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
FAC	Fractional Area Change
FDA	Food and Drug Administration
GLS	Global Longitudinal Strain
GSK	GlaxoSmithKline
hs	High-sensitivity
hsCRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
HARP	GSK Harmonisation for Analysis and Reporting Program

Abbreviation	Description
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left Atrial
LGE	Late Gadolinium Enhancement
LLN	Lower Limit of Normal
LMM	Linear Mixed Model
LV	Left Ventricular
mAb	Monoclonal Antibody
MAP	Model-based Analyses Platform
MAR	Missing At Random
MCS	Mental Component Summary
MNAR	Missing Not At Random
MOS SF-36	Medical Outcome Study Short Form (36)
MRI	Magnetic Resonance Imaging
NAC	UK National Amyloidosis Centre
NBS	Norm-Based Domain Scores
NQ	Non-Quantifiable
NT pro-BNP	N-terminal pro b-type Natriuretic Peptide
PCI	Potential Clinical Importance
PCS	Physical Component Summary
PD	Pharmacodynamic
PK	Pharmacokinetic
PMM	Pattern Mixture Model
PopPK	Population PK
PT	Preferred Term
PYP/^{99m}Tc-PYP	^{99m}Tc-Pyrophosphate
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
RV	Right Ventricular
SAA	Serum Amyloid A Protein
SAC	Statistical Analysis Complete
SAP	Serum Amyloid P Component
SD	Standard Deviation
SOC	System Organ Class
SV	Stroke Volume
TFL	Tables, Figures & Listings
tmax	The Time Associated with Cmax
TTR	Transthyretin
ULN	Upper Limit of Normal
VPC	Visual Predictive Check

10.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

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

10.11. Appendix 11: List of Data Displays

Unless otherwise specified, data displays will be paginated by study groups. Study groups will be displayed by ascending order.

Note that initial interims may only include one study group based on the interim triggering rules defined in Section 3.1.

10.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Pharmacodynamic and / or Biomarker	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Efficacy	5.1 to 5.n	5.1 to 5.n
Quality of Life	6.1 to 6.n	6.1 to 6.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up display provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln

NOTES:

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

10.11.3. Deliverable [Priority]

For a description of interim analysis trigger and corresponding analysis selection, refer to Section 3.1.

Delivery [Priority] [1]	Description
IA1 [X]	Interim Analysis Selection #1
IA2 [X]	Interim Analysis Selection #2
SAC [X]	Full RAP Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated.

10.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition		SAC [3]
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC [3]
1.3.	Enrolled	NS1	Summary of Number of Subjects by Country and Centre ID		SAC [3]
1.4.	Safety	SD1	Summary of Treatment Status and Reason for Discontinuation of Study Treatment		SAC [3]
Protocol Deviations					
1.5.	Safety	DV1	Summary of Important Protocol Deviations		SAC [3]
Populations Analysed					
1.6.	Screened	SP1	Summary of Study Populations		SAC [3]
Demography					
1.7.	Safety	DM1	Summary of Demographic Characteristics		SAC [3]
1.8.	Enrolled	DM11	Summary of Age Ranges		SAC [3]
1.9.	Safety	DM6	Summary of Race and Racial Combination Details		SAC [3]
1.10.	Standard of Care	DM1	Summary of Demographic Characteristics		SAC [3]
1.11.	Standard of Care	DM11	Summary of Age Ranges		SAC [3]
1.12.	Standard of Care	DM6	Summary of Race and Racial Combination Details		SAC [3]

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Concomitant Medications					
1.13.	Safety	CM1	Summary of Concomitant Medications		SAC [3]
Medical Conditions					
1.14.	Safety	MH1	Summary of Current Medical Conditions		SAC [3]
1.15.	Safety	MH1	Summary of Past Medical Conditions		SAC [3]
Exposure					
1.16.	Safety	EX1	Summary of Exposure to CPHPC	Display overall and by treatment session	SAC [3]
1.17.	Safety	EX1	Summary of Exposure to anti-SAP mAb	Display overall and by treatment session	SAC [3]

10.11.5. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Pharmacodynamic/Biomarker Endpoint					
2.1.	Safety	Non-standard PD_T1	Summary of LV mass (g) Measured by CMR Over Time	Includes absolute values and changes from baseline	IA1 [1], IA2[1], SAC [1]
2.2.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV mass (g) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[1], SAC [1]
2.3.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[1], SAC [1]
2.4.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV mass (g) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Non-Future Dependency	Include all Bayesian model parameters.	SAC [1]
2.5.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Non-Future Dependency	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [1]
2.6.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV mass (g) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Based on Standard of Care Data	Include all Bayesian model parameters.	SAC [1]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.7.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Based on Standard of Care Data	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [1]
2.8.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV mass (g) Measured by CMR, Model: Two-Piece Linear Model (Model 2), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[1], SAC [1]
2.9.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by CMR with Posterior Probabilities of Interest, Model: Two-Piece Linear Model (Model 2), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[1], SAC [1]
2.10.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV mass (g) Measured by CMR, Model: Including Restricted Cubic Splines (Sensitivity Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[1], SAC [1]
2.11.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by CMR with Posterior Probabilities of Interest, Model: Including Restricted Cubic Splines (Sensitivity Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[1], SAC [1]
2.12.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV mass (g) Measured by CMR, Model: Including Polynomial Terms (Sensitivity Model 2), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[1], SAC [1]
2.13.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by CMR with Posterior Probabilities of Interest, Model: Model: Including Polynomial Terms (Sensitivity Model 2), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[1], SAC [1]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.14.	Standard of Care	Non-standard PD_T1	Summary of LV mass (g) Measured by CMR Over Time	Includes absolute values and changes from first scan	SAC [1]
2.15.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV mass (g) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope).	SAC [1]
2.16.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [1]
Secondary Imaging Markers of Cardiac Dysfunction					
2.17.	Safety	Non-standard PD_T1	Summary of Imaging Markers of Cardiac Dysfunctions Over Time	Several endpoints: GLS by CMR & ECHO (tagging, feature tracking, speckle tracking), LV Twist by CMR, SV by CMR & ECHO, EF by CMR & ECHO, EDV by CMR & ECHO, E/e' ratio by ECHO (lateral and septal) Includes absolute values and changes from baseline.	IA1 [2], IA2[2], SAC [2]
2.18.	Standard of Care	Non-standard PD_T1	Summary of Imaging Markers of Cardiac Dysfunctions Over Time	Several endpoints, where available for the Standard of Care population: GLS by CMR & ECHO (tagging, feature tracking, speckle tracking), LV Twist by CMR, SV by CMR & ECHO, EF by CMR & ECHO, EDV by CMR & ECHO, E/e' ratio by ECHO (lateral and septal) Includes absolute values and changes from first scan.	SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Global Longitudinal Strain (<unit>) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters. Paginate by GLS type of measurement: tagging, feature tracking (CMR), speckle tracking (ECHO)	IA2[2], SAC [2]
2.20.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Global Longitudinal Strain (<unit>) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed. Paginate by GLS type of measurement: tagging, feature tracking (CMR), speckle tracking (ECHO)	IA2[2], SAC [2]
2.21.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Global Longitudinal Strain (<unit>) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope). Paginate by GLS type of measurement: tagging, feature tracking (CMR), speckle tracking (ECHO)	SAC [2]
2.22.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Global Longitudinal Strain (<unit>) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed. Paginate by GLS type of measurement: tagging, feature tracking (CMR), speckle tracking (ECHO)	SAC [2]
2.23.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Left Ventricular Twist (<unit>) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[2], SAC [2]
2.24.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Left Ventricular Twist (<unit>) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[2], SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.25.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Left Ventricular Twist (<unit>) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope).	SAC [2]
2.26.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Left Ventricular Twist (<unit>) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [2]
2.27.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Stroke Volume (mL) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[2], SAC [2]
2.28.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Stroke Volume (mL) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[2], SAC [2]
2.29.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Stroke Volume (mL) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope).	SAC [2]
2.30.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Stroke Volume (mL) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [2]
2.31.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Ejection Fraction (%) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[2], SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.32.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Ejection Fraction (%) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[2], SAC [2]
2.33.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Ejection Fraction (%) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope).	SAC [2]
2.34.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Ejection Fraction (%) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [2]
2.35.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of End Diastolic Volume (mL) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[2], SAC [2]
2.36.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in End Diastolic Volume (mL) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[2], SAC [2]
2.37.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of End Diastolic Volume (mL) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope).	SAC [2]
2.38.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in End Diastolic Volume (mL) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.39.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of E/e' Ratio Measured by ECHO, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters. Paginate by type of measurement: lateral, septal	IA2[2], SAC [2]
2.40.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in E/e' Ratio Measured by ECHO with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed. Paginate by type of measurement: lateral, septal	IA2[2], SAC [2]
2.41.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of E/e' Ratio Measured by ECHO, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope). Paginate by type of measurement: lateral, septal	SAC [2]
2.42.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in E/e' Ratio Measured by ECHO with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed. Paginate by type of measurement: lateral, septal	SAC [2]
2.43.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by ECHO, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[2], SAC [2]
2.44.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by ECHO with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[2], SAC [2]
2.45.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by ECHO, Model: Linear Model, Missing Data Imputation: None	If data are available for the Standard of Care population Include all Bayesian model parameters (Intercept and Slope).	SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.46.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in LV Mass (g) Measured by ECHO with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	If data are available for the Standard of Care population Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [2]
2.47.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of ECV (Global) (<unit>) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[2], SAC [2]
2.48.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in ECV (Global) (<unit>) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[2], SAC [2]
2.49.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of ECV (Global) (<unit>) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope).	SAC [2]
2.50.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in ECV (Global) (<unit>) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [2]
2.51.	Safety	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Native T1 (Global) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2[2], SAC [2]
2.52.	Safety	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Native T1 (Global) Measured by CMR with Posterior Probabilities of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	IA2[2], SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.53.	Standard of Care	Non-standard PD_T2	Posterior Distribution of Bayesian Model Parameters for the Analysis of Native T1 (Global) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope).	SAC [2]
2.54.	Standard of Care	Non-standard PD_T3	Posterior Distribution of Mean Change from First Dose of mAb in Native T1 (Global) Measured by CMR with Posterior Probabilities of Interest, Model: Linear Model, Missing Data Imputation: None	Probability thresholds to be confirmed by clinical team before analysis performed.	SAC [2]
Secondary Circulating Markers					
2.55.	Safety	Non-standard PD_T1	Summary of Fluid Phase Complement Markers Over Time	Several endpoints: C3, C4, CH50 Includes absolute values and changes from baseline.	SAC [2]
2.56.	Safety	Non-standard PD_T1	Summary of Inflammatory Biomarkers Over Time	Several endpoints: hsCRP, SAA Includes absolute values and changes from baseline.	SAC [2]
2.57.	Safety	Non-standard PD_T1	Summary of Plasma Cytokines Over Time	Several endpoints: TNFα, IL-8, IL-6, IL-10, IL-13, IL-2, IL-4, IL-12p70, IL 1β, IFNγ Includes absolute values and changes from baseline.	SAC [2]
Exploratory Pharmacodynamic and Biomarker Endpoints					
2.58.	Safety	Non-standard PD_T1	Summary of Cardiac ECV (Global) by CMR Over Time	Includes absolute values and changes from baseline.	IA1 [3], IA2 [3], SAC [3]
2.59.	Safety	Non-standard PD_T1	Summary of Cardiac Biomarkers Over Time	Several endpoints: hs-Troponin T, NT-Pro-BNP Includes absolute values and changes from baseline.	SAC [3]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.60.	Safety	Non-standard PD_T5	Summary of Cardiac Uptake of Radioisotope Bone Tracers at Baseline and 8-week Follow Up	Several categorical endpoints: ^{99m}Tc-DPD, ^{99m}Tc-PYP uptake Group 1 Only. "No data to display" for Groups 2 and 3.	SAC [3]
2.61.	Safety	Non-standard PD_T1	Summary of Overall Body Load and in Affected Organs (Excluding Cardiac Load) on SAP Scan Over Time	Several endpoints: Overall Load and Organ Loads where available Includes absolute values and changes from baseline. Group 2 & 3 Only. "No data to display" for Group 1.	SAC [3]
2.62.	Safety	Non-standard PD_T1	Summary of Imaging Markers of Cardiac Structure as Monitored by CMR and / or ECHO imaging Over Time	Includes LV wall thickness and LV Mass (ECHO) Includes absolute values and changes from baseline.	SAC [3]
2.63.	Safety	Non-standard PD_T1	Summary of Other Imaging Markers of Cardiac Dysfunction as Monitored by CMR and / or ECHO imaging Over Time	Includes several endpoints: Longitudinal, Radial and Circumferential Strain (Global values, CMR and/or ECHO), E/A ratio (ECHO), E-wave deceleration time on the mitral inflow (ECHO), LA volume index (ECHO), RV FAC (ECHO) Includes absolute values and changes from baseline.	IA1 [3], IA2 [3], SAC [3]
2.64.	Safety	Non-standard PD_T1	Summary of Imaging Markers of Cardiac Tissue Characterization as Monitored by CMR Over Time	Includes Native T1 and T2 (Global) Includes absolute values and changes from baseline. For interims: include T1 only	IA1 [3], IA2 [3], SAC [3]
2.65.	Safety	Non-standard PD_T5	Summary of LGE Over Time		SAC [3]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.66.	Safety	Non-standard PD_T1	Summary of DCE-CMR Global Measure of Myocardial Perfusion Over Time	Includes absolute values and changes from baseline.	IA1 [3], IA2 [3], SAC [3]
2.67.	Safety	PK01	Summary of Plasma SAP Concentration-Time Data	By treatment cycle and sampling occasion	SAC [1]
2.68.	Safety	Non-standard PD_T4	Summary of Association Between Biomarkers and CMR Measures by Timepoint	Association between a selection of markers (NT proBNP, hs-Troponin-T and cytokines: TNF-α, IL-6 and IL-8) and CMR measures (LV Mass, GLS and ECV respectively)	SAC [3]
2.69.	Safety	Non-standard PD_T4	Summary of Association Between DCE-CME Global Measure of Myocardial Perfusion and CMR Measures by Timepoint	Association between DCE-CME measure of myocardial perfusion and CMR measures (LV Mass, GLS and ECV respectively)	SAC [3]
Immunogenicity Endpoints					
2.70.	Safety	Non-standard PD_T5	Summary of Antidrug Antibodies		SAC [3]
2.71.	Safety	Non-standard PD_T1	Summary of Immune Complexes	Includes absolute values only (no post-baseline value).	SAC [3]
2.72.	Safety	Non-standard PD_T5	Summary of Auto-antibodies		SAC [3]

10.11.6. Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Pharmacodynamic/Biomarker Endpoint					
2.1.	Safety	Non-standard PD_F1	Profile Plot of LV Mass (g) Measured by CMR Over Time by Subject	Includes only one endpoint: LV mass	IA1 [1], IA2 [1], SAC [1]
2.2.	Safety	Non-standard PD_F2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2 [1], SAC [1]
2.3.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [1], SAC [1]
2.4.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in LV Mass Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [1], SAC [1]
2.5.	Safety	Non-standard PD_F2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Non-Future Dependency	Include all Bayesian model parameters.	SAC [1]
2.6.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Non-Future Dependency	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [1]
2.7.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in LV Mass Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Non-Future Dependency		SAC [1]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	Safety	Non-standard PD_F2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by CMR, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Based on Standard of Care Data	Include all Bayesian model parameters.	SAC [1]
2.9.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Based on Standard of Care Data	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [1]
2.10.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in LV Mass Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: Based on Standard of Care Data		SAC [1]
2.11.	Safety	Non-standard PD_F2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by CMR, Model: Two-Piece Linear Model (Model 2), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2 [1], SAC [1]
2.12.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by CMR at Timepoints of Interest, Model: Two-Piece Linear Model (Model 2), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [1], SAC [1]
2.13.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in LV Mass Measured by CMR Over Time, Model: Two-Piece Linear Model (Model 2), Missing Data Imputation: None		IA2 [1], SAC [1]
2.14.	Safety	Non-standard PD_F2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by CMR, Model: Including Restricted Cubic Splines (Sensitivity Model 1), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2 [1], SAC [1]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.15.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by CMR at Timepoints of Interest, Model: Including Restricted Cubic Splines (Sensitivity Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [1], SAC [1]
2.16.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in LV Mass Measured by CMR Over Time, Model: Including Restricted Cubic Splines (Sensitivity Model 1), Missing Data Imputation: None		IA2 [1], SAC [1]
2.17.	Safety	Non-standard PD_F2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by CMR, Model: Including Polynomial Terms (Sensitivity Model 2), Missing Data Imputation: None	Include all Bayesian model parameters.	IA2 [1], SAC [1]
2.18.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by CMR at Timepoints of Interest, Model: Including Polynomial Terms (Sensitivity Model 2), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [1], SAC [1]
2.19.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in LV Mass Measured by CMR Over Time, Model: Including Polynomial Terms (Sensitivity Model 2), Missing Data Imputation: None		IA2 [1], SAC [1]
2.20.	Standard of Care	Non-standard PD_F1	Profile Plot of LV Mass Measured by CMR Over Time by Subject	Includes only one endpoint: LV mass	SAC [1]
2.21.	Standard of Care	Non-standard PD_F2	Posterior Distribution of Bayesian Model Parameters for the Analysis of LV Mass (g) Measured by CMR, Model: Linear Model, Missing Data Imputation: None	Include all Bayesian model parameters (Intercept and Slope)	SAC [1]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.22.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [1]
Secondary Imaging Markers of Cardiac Dysfunction					
2.23.	Safety	Non-standard PD_F1	Profile Plot of Imaging Markers of Cardiac Dysfunction Over Time by Subject	Several endpoints: GLS by CMR & ECHO (tagging, feature tracking, speckle tracking), LV Twist by CMR, SV by CMR & ECHO, EF by CMR & ECHO, EDV by CMR & ECHO, E/e' ratio by ECHO (lateral, septal)	IA1 [2], IA2 [2], SAC [2]
2.24.	Standard of Care	Non-standard PD_F1	Profile Plot of Imaging Markers of Cardiac Dysfunction Over Time by Subject	Several endpoints where available for the Standard of Care population: GLS by CMR & ECHO (tagging, feature tracking, speckle tracking), LV Twist by CMR, SV by CMR & ECHO, EF by CMR & ECHO, EDV by CMR & ECHO, E/e' ratio by ECHO (lateral, septal)	SAC [2]
2.25.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Global Longitudinal Strain (<unit>) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months) Paginate by type of measurement: tagging, feature tracking (CMR), speckle tracking (ECHO)	IA2 [2], SAC [2]
2.26.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in Global Longitudinal Strain (<unit>) Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Paginate by type of measurement: tagging, feature tracking (CMR), speckle tracking (ECHO)	IA2 [2], SAC [2]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Global Longitudinal Strain (<unit>) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months) Paginate by type of measurement: tagging, feature tracking (CMR), speckle tracking (ECHO)	SAC [2]
2.28.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Left Ventricular Twist (<unit>) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [2], SAC [2]
2.29.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in Left Ventricular Twist (<unit>) Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [2], SAC [2]
2.30.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Left Ventricular Twist (<unit>) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [2]
2.31.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Stroke Volume (mL) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [2], SAC [2]
2.32.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in Stroke Volume (mL) Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [2], SAC [2]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.33.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Stroke Volume (mL) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [2]
2.34.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Ejection Fraction (%) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [2], SAC [2]
2.35.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in Ejection Fraction (%) Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [2], SAC [2]
2.36.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Ejection Fraction (%) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [2]
2.37.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in End Diastolic Volume (mL) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [2], SAC [2]
2.38.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in End Diastolic Volume (mL) Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [2], SAC [2]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.39.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in End Diastolic Volume (mL) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [2]
2.40.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in E/e ratio' Measured by ECHO at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (1, 2, 3, 4, 5, 6, 8, 11 and 17 months) Paginate by type of measurement: lateral, septal	IA2 [2], SAC [2]
2.41.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in E/e ratio' Measured by ECHO Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Paginate by type of measurement: lateral, septal	IA2 [2], SAC [2]
2.42.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in E/e ratio' Measured by ECHO at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (1, 2, 3, 4, 5, 6, 8, 11 and 17 months) Paginate by type of measurement: lateral, septal	SAC [2]
2.43.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV mass (g) Measured by ECHO at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (1, 2, 3, 4, 5, 6, 8, 11 and 17 months)	IA2 [2], SAC [2]
2.44.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by ECHO Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [2], SAC [2]
2.45.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in LV Mass (g) Measured by ECHO at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	If data are available for the Standard of Care population. Include all timepoints of interest (1, 2, 3, 4, 5, 6, 8, 11 and 17 months)	SAC [2]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.46.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in ECV (Global) (<unit>) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [2], SAC [2]
2.47.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in ECV (Global) (<unit>) Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [2], SAC [2]
2.48.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in ECV (Global) (<unit>) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [2]
2.49.	Safety	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Native T1 (Global) (<unit>) Measured by CMR at Timepoints of Interest, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	IA2 [2], SAC [2]
2.50.	Safety	Non-standard PD_F4	Posterior Mean Change from First Dose of Anti-SAP mAb in Native T1 (Global) (<unit>) Measured by CMR Over Time, Model: Three-Piece Linear Model (Model 1), Missing Data Imputation: None		IA2 [2], SAC [2]
2.51.	Standard of Care	Non-standard PD_F3	Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in Native T1 (Global) (<unit>) Measured by CMR at Timepoints of Interest, Model: Linear Model, Missing Data Imputation: None	Include all timepoints of interest (2, 3, 4, 5, 8, 11 and 17 months)	SAC [2]
Secondary Circulating Markers					
2.52.	Safety	Non-standard PD_F1	Profile Plot of Fluid Phase Complement Markers Over Time by Subject	Includes several endpoints: C3, C4, CH50. **At interims C3 only**	IA1 [2], IA2 [2], SAC [2]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.53.	Safety	Non-standard PD_F1	Profile Plot of Inflammatory Biomarkers Over Time by Subject	Includes several endpoints: hsCRP, SAA	IA2 [2], SAC [2]
2.54.	Safety	Non-standard PD_F1	Profile Plot of Plasma Cytokines Over Time by Subject	Includes several endpoints: TNFα, IL-8, IL-6, IL-10, IL-13, IL-2, IL-4, IL-12p70, IL 1β, IFNγ	IA2 [2], SAC [2]
Exploratory Pharmacodynamic and Biomarker Endpoints					
2.55.	Safety	Non-standard PD_F1	Profile Plot of Cardiac Extracellular Volume (Global and Segmental) by CMR Over Time by Subject	Includes Global and Segmental values. For segmental data: All segment curves should be displayed on the same plot, with segment identifiers as legend.	IA1 [3], IA2 [3], SAC [3]
2.56.	Safety	Non-standard PD_F1	Profile Plot of Cardiac Biomarkers Over Time by Subject	Includes several endpoints: hs-Troponin T, NT Pro-BNP	IA1 [3], IA2 [3], SAC [3]
2.57.	Safety	Non-standard PD_F1	Profile Plot of Amyloid Load on SAP Scan Over Time by Subject	Includes several endpoints: Overall Body Load and in Affected Organs (Excluding Cardiac Load), where available Group 2&3 Only. “No data to display” for Group 1.	SAC [3]
2.58.	Safety	Non-standard PD_F1	Profile Plot of Imaging Markers of Cardiac Structure by Serial CMR and/or ECHO Imaging Over Time by Subject	LV wall thickness (CMR and ECHO), LV mass (ECHO)	SAC [3]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.59.	Safety	Non-standard PD_F1	Profile Plot of Other Imaging Markers of Cardiac Dysfunction by Serial CMR and/or ECHO Over Time by Subject	Includes several endpoints: Longitudinal, Radial and Circumferential Strain (Global, Segmental by CMR and/or ECHO), E/A ratio (ECHO), E-wave deceleration time on the mitral inflow (ECHO), LA volume index (ECHO), RV FAC (ECHO) Do not include GLS as already reported as secondary endpoint. For endpoints with segmental values: All segment curves should be displayed on the same plot, with segment identifiers as legend.	IA1 [3], IA2 [3], SAC [3]
2.60.	Safety	Non-standard PD_F1	Profile Plot of Imaging Markers of Cardiac Tissue Characterization as Monitored by CMR Over Time by Subject	LGE, native T1 (Global, Segmental), native T2 (Global, Segmental) For endpoints with segmental values: All segment curves should be displayed on the same plot, with segment identifiers as legend. For interims: Include T1 only	IA1 [3], IA2 [3], SAC [3]
2.61.	Safety	Non-standard PD_F1	Profile Plot of DCE-CMR Global and Segmental Measures of Myocardial Perfusion Over Time by Subject	For endpoints with segmental values: All segment curves should be displayed on the same plot, with segment identifiers as legend.	IA1 [3], IA2 [3], SAC [3]
2.62.	Safety	Non-standard PK_F1	Individual Plasma SAP Concentration-Time Plot (Linear and Semi-Log) by Treatment Cycle with Subject Identifiers		IA1 [1], IA2 [1], SAC [1]

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.63.	Safety	Non-standard PD_F5	Scatter Plots of Biomarkers versus CMR Measures by Timepoint with Subject Identifiers	Scatter plots between a selection of markers (NT ProBNP, hs-Troponin-T and cytokines: TNF-α, IL-6 and IL-8) and CMR measures (LV Mass, GLS and ECV)/	SAC [3]
2.64.	Safety	Non-standard PD_F5	Scatter Plots of DCE-CME Global Measure of Myocardial Perfusion versus CMR/ECHO Measures by Timepoint with Subject Identifiers	Scatter plots between DCE-CMR measure of myocardial perfusion and following CMR measures; LV Mass, GLS and ECV.	SAC [3]

10.11.7. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term		SAC [1]
3.2.	Safety	AE3	Summary of Most Frequent Adverse Events by Overall Frequency		SAC [1]
3.3.	Safety	AE1	Summary of Drug Related Adverse Events by System Organ Class and Preferred Term		SAC [1]
3.4.	Safety	Non-Standard AE_T1	Summary of Posterior Probabilities for Specific Adverse Events	AE posterior probabilities may be provided after 10 subjects complete at least 3 courses of Anti-SAP treatment in a given cohort (not at first interim)	IA2 [1], SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.5.	Safety	AE15	Summary of Common (≥5%) Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurences)		SAC [1]
Serious and Other Significant AEs					
3.6.	Safety	AE1	Summary of Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
3.7.	Safety	AE1	Summary of Drug-Related Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
3.8.	Safety	AE1	Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
3.9.	Safety	AE1	Summary of Drug-Related Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC [1]
3.10.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC [1]
3.11.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term		SAC [1]
Rashes					
3.12.	Safety	AE5B	Summary of Rashes by System Organ Class and Preferred Term and Maximum CTCAE Grade		SAC [1]
Chemistry					
3.13.	Safety	LB1	Summary of Chemistry Change from Baseline		SAC[1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hematology					
3.14.	Safety	LB1	Summary of Hematology Change from Baseline		SAC [1]
3.15.	Safety	LB1	Summary of Haemoglobin Change from Baseline Relative to Clinical Importance Ranges		SAC [1]
Urinalysis					
3.16.	Safety	LB1	Summary of Urinalysis Change from Baseline	Quantitative results only. Other results to be listed.	SAC [1]
Hepatobiliary (Liver)					
3.17.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC [1]
3.18.	Safety	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria		SAC [1]
ECG					
3.19.	Safety	EG1	Summary of ECG Findings		SAC [1]
3.20.	Safety	CP_EG11	Summary of Maximum Emergent QTc Values by Category		
3.21.	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC [1]
3.22.	Safety	CP_EG12	Summary of Maximum Change from Baseline in QTc Values by Category		SAC [1]
Vital Signs					
3.23.	Safety	VS1	Summary of Change From Baseline in Vital Signs		SAC [1]

10.11.8. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.1.	Safety	Non-standard PD_F1	Profile Plot of Liver Function Parameters Over Time by Subject		IA2 [1], SAC [1]
3.2.	Safety	Non-standard PD_F1	Profile Plot of Renal Function Parameters Over Time by Subject	Serum creatinine and eGFR only for interim IA1	IA1 [1], IA2 [1], SAC [1]
3.3.	Safety	Non-standard PD_F1	Profile Plot of Haemoglobin Over Time by Subject		IA2 [1], SAC [1]
3.4.	Safety	Non-standard PD_F1	Profile Plot of Vital Signs Parameters Over Time by Subject	Blood pressure and heart rate only for interims	IA1 [1], IA2 [1], SAC [1]
3.5.	Safety	Non-standard PD_F6	Scatter Plot of Maximum vs. Baseline for ALT		SAC [1]
3.6.	Safety	Non-standard PD_F6	Scatter Plot of Maximum ALT vs Maximum Total Bilirubin		SAC [1]

10.11.9. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK concentration data					
4.1.	Safety	PK01	Summary of Plasma GSK2398852 Pharmacokinetic Concentration-Time Data	By treatment cycle and sampling occasion	SAC [1]
4.2.	Safety	PK01	Summary of Plasma GSK2315698 Pharmacokinetic Concentration-Time Data	By treatment cycle and sampling occasion Group 3 Only	SAC [1]

10.11.10. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK concentration data					
4.1.	Safety	Non-standard PK_F1	Individual Plasma GSK2398852 Concentration-Time Plot (Linear and Semi-Log) by Treatment Cycle with Subject Identifiers	For each of the 3 groups, a landscape grid plot of 2 rows by 3 columns for the 6 treatment cycles. Plot drug concentrations versus time. Connect individual data with lines. Symbol code by dose. Colour code by ID. Do this separately on log and linear scales.	IA1 [1], IA2 [1], SAC [1]

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.2.	Safety	Non-standard PK_F2	Median Plasma GSK2398852 Concentration-Time Plot (Linear and Semi-Log) by Treatment Cycle with Group Identifier	A landscape grid plot of 2 rows by 3 columns for the 6 treatment cycles. Plot group median of drug concentrations versus time. Connect group data with lines. Colour code by group. Do this separately on log and linear scales.	IA1 [1], IA2 [1], SAC [1]
4.3.	Safety	Non-standard PK_F1	Individual Plasma GSK2315698 Concentration-Time Plot (Linear and Semi-Log) by Treatment Cycle with Subject Identifiers	A landscape grid plot of 2 rows by 3 columns for the 6 treatment cycles. Plot drug concentrations versus sampling occasion Day/Hour (1/0, 2/0, 2/2, 3/0). Connect individual data with lines. Symbol code by dose. Colour code by ID. Do this separately on log and linear scales. Group 3 Only	IA1 [1], IA2 [1], SAC [1]
4.4.	Safety	Non-standard PK_F2	Median Plasma GSK2315698 Concentration-Time Plot (Linear and Semi-Log) by Treatment Cycle	A single plot of cycle median of drug concentrations versus sampling occasion Day/Hour (1/0, 2/0, 2/2, 3/0). Connect cycle data with lines. Colour code by treatment cycle. Do this separately on log and linear scales. Group 3 only	IA1 [1], IA2 [1], SAC [1]

10.11.11. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exploratory Efficacy					
5.1.	Safety **Group 1&2 Only**	Non-standard PD_T1	Summary of 6 Minute Walking Test (6MWT) Over Time	Includes absolute values and changes from baseline.	IA1 [3], IA2 [3], SAC [3]

10.11.12. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exploratory Efficacy					
5.1.	Safety **Group 1&2 Only**	Non-standard PD_F1	Profile Plot of 6 Minute Walking Test (6MWT) Over Time by Subject	Includes only one endpoint:6WMT	IA1 [3], IA2 [3], SAC [3]

10.11.13. Quality of Life Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exploratory Efficacy					
6.1.	Safety	Non-standard PD_T1	Summary of SF-36 Domain and Overall Scores at Baseline and 8-week Follow Up	Includes absolute values and changes from baseline.	SAC [3]
6.2.	Safety	Non-standard PD_T1	Summary of KCCQ Scores at Baseline and 8-week Follow Up	Includes absolute values and changes from baseline.	SAC [3]
6.3.	Safety	Non-standard PD_T1	Summary of EORTC QLQ-C30 Scores at Baseline and 8-week Follow Up	Includes absolute values and changes from baseline.	SAC [3]
6.4.	Safety	Non-standard PD_T1	Summary of DLQI Overall and Section Scores at Baseline and 8-week Follow Up	Includes absolute values and changes from baseline.	SAC [3]

10.11.14. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen failures		SAC [3]
2.	Safety	ES2	Listing of Reasons for Study Withdrawal		SAC [3]
3.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC [3]
Protocol Deviations					
4.	Safety	DV2	Listing of Important Protocol Deviations		SAC [3]
5.	Safety	IE3	Listing of Subjects with Inclusion/ Exclusion Criteria Deviations		SAC [3]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Populations Analysed					
6.	Safety	SP3	Listing of Subjects Excluded from Safety Population		SAC [3]
Demography					
7.	Safety	DM2	Listing of Demographic Characteristics		SAC [3]
8.	Safety	DM9	Listing of Race		SAC [3]
Concomitant Medications					
9.	Safety	CP_CM3	Listing of Concomitant Medications		SAC [3]
Medical Conditions					
10.	Safety	MH2	Listing of Medical Conditions		SAC [3]
Exposure					
11.	Safety	EX3	Listing of Exposure to CPHPC		SAC [3]
12.	Safety	EX3	Listing of Exposure to anti-SAP mAb		SAC [3]
Adverse Events					
13.	Safety	AE8CP	Listing of All Adverse Events		IA1 [1], IA2 [1], SAC [1]
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC [1]
15.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC [1]
Serious and Other Significant Adverse Events					
16.	Safety	AE8CP	Listing of Fatal Serious Adverse Events		SAC [1]
17.	Safety	AE8CP	Listing of Non-Fatal Serious Adverse Events		SAC [1]
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
19.	Safety	AE8CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC [1]
20.	Safety	AE8CP	Listing of Anti-SAP mAb Infusion Related Reactions	Filtering on PTs identified by clinical team as infusion-related reactions.	SAC [1]
21.	Safety	AE8CP	Listing of Adverse Events Related to Treatments other than Study Drug		SAC [1]
Rashes					
22.	Safety	AE8CP	Listing of Adverse Events of Rashes		SAC [1]
23.	Safety	Non-Standard AE_L1	Listing of Rash Details		IA1 [1], IA2 [1], SAC [1]
Chemistry					
24.	Safety	LB5	Listing of Clinical Chemistry Values		IA1 [1], IA2 [1], SAC [1]
Hematology					
25.	Safety	LB5	Listing of Hematology Values		IA1 [1], IA2 [1], SAC [1]
26.	Safety	LB5	Listing of Haemoglobin Change from Baseline Values		IA2 [1], SAC [1]
Urinalysis					
27.	Safety	UR2A	Listing of Urinalysis Data		IA1 [1], IA2 [1], SAC [1]
Hepatobilary (Liver)					
28.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
29.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		SAC [1]
All Laboratory					
30.	Safety	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Concern/Potential Clinical Importance		IA2 [1], SAC [1]
31.	Safety	LB5	Listing of Laboratory Values of Potential Clinical Importance		IA2 [1], SAC [1]
ECG					
32.	Safety	EG3	Listing of All ECG Data for Subjects with Any Value of Potential Clinical Importance		IA1 [1], IA2 [1], SAC [1]
33.	Safety	EG3	Listing of ECG Values of Potential Clinical Importance		IA1 [1], IA2 [1], SAC [1]
34.	Safety	EG5	Listing of Abnormal ECG Findings		IA1 [1], IA2 [1], SAC [1]
Echocardiogram and Cardiac Monitoring					
35.	Safety	Non-standard PD_L1	Listing of Cardiac Monitoring Values		SAC [1]
36.	Safety	Non-standard PD_L1	Listing of All Echocardiogram Results for Subjects Requiring Unscheduled Assessments		IA1 [1], IA2 [1], SAC [1]
Vital Signs					
37.	Safety	VS4	Listing of Vital Signs Values		SAC [1]
38.	Safety	CP_VS4	Listing of Vital Signs of Potential Clinical Importance		SAC [1]
39.	Safety	CP_VS4	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance		SAC [1]

10.11.15. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic and Biomarkers					
40.	Safety	PD_L1	Listing of Cardiac MRI Data		IA2 [1], SAC [1]
41.	Safety	PD_L1	Listing of ECHO Data		IA2 [2], SAC [2]
42.	Safety	PD_L1	Listing of SAP Scan Data		IA1 [3], IA2 [3], SAC [3]
43.	Safety	PD_L1	Listing of Bone Scan Data		IA1 [3], IA2 [3], SAC [3]
44.	Safety	PD_L1	Listing of Complement and Inflammatory Biomarkers		IA1 [2], IA2 [2], SAC [2]
45.	Safety	PD_L1	Listing of hs-Troponin T and NT-ProBNP		IA1 [3], IA2 [3], SAC [3]
46.	Safety	PD_L1	Listing of Anti-Drug Antibody (anti-SAP mAb)		SAC [3]
47.	Safety	PD_L1	Listing of Auto-Antibodies		SAC [3]
48.	Safety	PD_L1	Listing of mAb/SAP Immune Complex		SAC [3]
Quality of Life					
49.	Safety	PD_L1	Listing of MOS SF-36 data		SAC [3]
50.	Safety	PD_L1	Listing of KCCQ data		SAC [3]
51.	Safety	PD_L1	Listing of EORTC data		SAC [3]
52.	Safety	PD_L1	Listing of DLQI questionnaire		SAC [3]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Efficacy					
53.	Safety	PD_L1	Listing of 6MWT data		IA2 [3], SAC [3]
Pharmacokinetics					
54.	Safety	PK07	Listing of PK plasma concentrations (GSK2315698 & GSK2398852)		SAC [1]

10.12. Appendix 12: Example Mock Shells for Data Displays

Example : PD_T1 Page 1 of n
Protocol : 201464
Population : Safety

Table x.x
Summary of <Endpoint (unit) or Endpoint Type> Over Time

Cohort: <Study Group X>
Parameter: <Endpoint (unit)>
Derivation: <Absolute value> / <Change from Baseline >

Planned Period	Planned Visit	n	Mean	SD	Median	Min.	Max.
Screening	Screening	x	x.xx	x.xxx	x.xx	x.x	x.x
Baseline	Baseline	x	x.xx	x.xxx	x.xx	x.x	x.x
Treatment Session 1	Session Day X	x	x.xx	x.xxx	x.xx	x.x	x.x
	Session Day X	x	x.xx	x.xxx	x.xx	x.x	x.x
	Etc.	x	x.xx	x.xxx	x.xx	x.x	x.x
Treatment Session 2	Session Day X	x	x.xx	x.xxx	x.xx	x.x	x.x
	Session Day X	x	x.xx	x.xxx	x.xx	x.x	x.x
Etc.	Etc.	x	x.xx	x.xxx	x.xx	x.x	x.x
Follow up	8-week follow up	x	x.xx	x.xxx	x.xx	x.x	x.x
	Etc.	x	x.xx	x.xxx	x.xx	x.x	x.x

Programming notes: Absolute value and Change from baseline to be subsequently presented for a given endpoint. Some tables may display results for several endpoints (table repeated for each endpoint). Planned time may need to be displayed within planned timepoint for endpoints with multiple assessments within the same day, as necessary.

Example : PD_T2
Protocol : 201464
Population : Safety

Table x.x
Posterior Distribution of Bayesian Model Parameters for the Analysis of <Endpoint (unit)>
Model: <Three-Piece Linear Model / Three-Piece Model with Restricted Cubic Spline Parameters / Other Model as Appropriate>
Missing Data Imputation: <None / Non-Future Dependence Multiple Imputation / Multiple Imputation Based on Standard of Care Data>

Cohort: <Study Group X>

				95% Credible Interval	
Parameter	Mean	SD	Median	Lower	Upper
Intercept	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx
<Pre-treatment slope (unit/month) >	x.xx	x.xxx	x.xx	x.xx	x.xx
<On-treatment slope (unit/month)>	x.xx	x.xxx	x.xx	x.xx	x.xx
<Post-treatment slope (unit/month)>	x.xx	x.xxx	x.xx	x.xx	x.xx

Programming note: include all Bayesian model parameters as appropriate

Example : PD_T3
Protocol : 201464
Population : Safety

Table x.x
Posterior Distribution of Mean Change from First Dose of mAb in <Endpoint (unit)> with Posterior Probabilities of Interest
Model: <Three-Piece Linear Model / Three-Piece Model with Restricted Cubic Spline Parameters / Other Model as Appropriate>
Missing Data Imputation: <None / Non-Future Dependence Multiple Imputation / Multiple Imputation Based on Standard of Care Data>

Cohort: <Study Group X>

Parameter	Mean	SD	Median	95% Credible Interval		Prob. <Chg<0g> (%)	Prob. <Chg<-50g> (%)	Prob. <Chg<-70g> (%)
				Lower	Upper			
Change from first mAb dose at 2 months	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	xx.x
Change from first mAb dose at 3 months	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	xx.x
Change from first mAb dose at 4 months	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	xx.x
Change from first mAb dose at 5 months	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	xx.x
Change from first mAb dose at 8 months	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	xx.x
Change from first mAb dose at 11 months	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	xx.x
Change from first mAb dose at 17 months	xxx.xx	xx.xxx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	xx.x

Programming note: probability thresholds to be adapted or removed as required

Example : PD_T4 Page 1 of n
Protocol : 201464
Population : Safety

Table x.x
Summary of Association between <Endpoint Type 1/ Endpoint 1 (unit)> and <Endpoint Type 2 / Endpoint 2 (unit)> by Timepoint

Cohort: <Study Group X>
Endpoints: <Endpoint 1 (unit)> vs <Endpoint 2 (unit)>

Planned Period	Planned Visit	n	Corr.	95% CI
Screening	Screening	x	x.xx	x.xx, x.xx
Baseline	Baseline	x	x.xx	x.xx, x.xx
Treatment Session 1	Session Day X	x	x.xx	x.xx, x.xx
	Session Day X	x	x.xx	x.xx, x.xx
	Etc.	x	x.xx	x.xx, x.xx
Treatment Session 2	Session Day X	x	x.xx	x.xx, x.xx
	Session Day X	x	x.xx	x.xx, x.xx
Etc.	Etc.	x	x.xx	x.xx, x.xx
Follow up	8-week follow up	x	x.xx	x.xx, x.xx
	Etc.	x	x.xx	x.xx, x.xx

Note: Spearman correlation coefficients and corresponding 95% confidence intervals derived based on available pairs of endpoint measurements.
Programming note: Planned time may need to be displayed within planned timepoint for endpoints with multiple assessments within the same day, as necessary.

Example : PD_T5
Protocol : 201464
Population : Safety

Table x.x
Summary of <Categorical Endpoint or Categorical Endpoint Type> Over Time

Cohort: <Study Group X>
Parameter: <Categorical Endpoint>

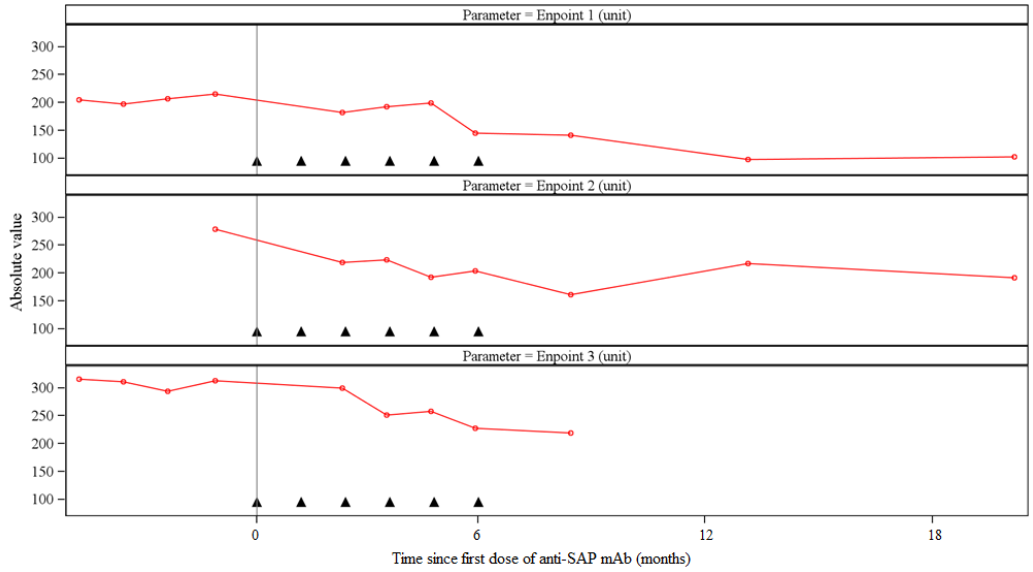
Planned Period	Planned Visit	N	Category	n (%)
Baseline	Baseline	x	<Category 1>	xx (xx.x%)
			<Category 2>	xx (xx.x%)
			<Category 3>	xx (xx.x%)
Treatment Session X	Session Day X	x	<Category 1>	xx (xx.x%)
			<Category 2>	xx (xx.x%)
			<Category 3>	xx (xx.x%)
Follow up	8-week follow up	x	<Category 1>	xx (xx.x%)
			<Category 2>	xx (xx.x%)
			<Category 3>	xx (xx.x%)
	Etc.			

Programming note: Some tables may display results for several endpoints (table repeated for each endpoint).

Example : PD_F1
Protocol : 201464
Population : Safety

Figure x.x
Profile Plot of <Endpoint (unit) or Endpoint Type> Over Time by Subject

Cohort: <Study Group X>, Subject: XXX



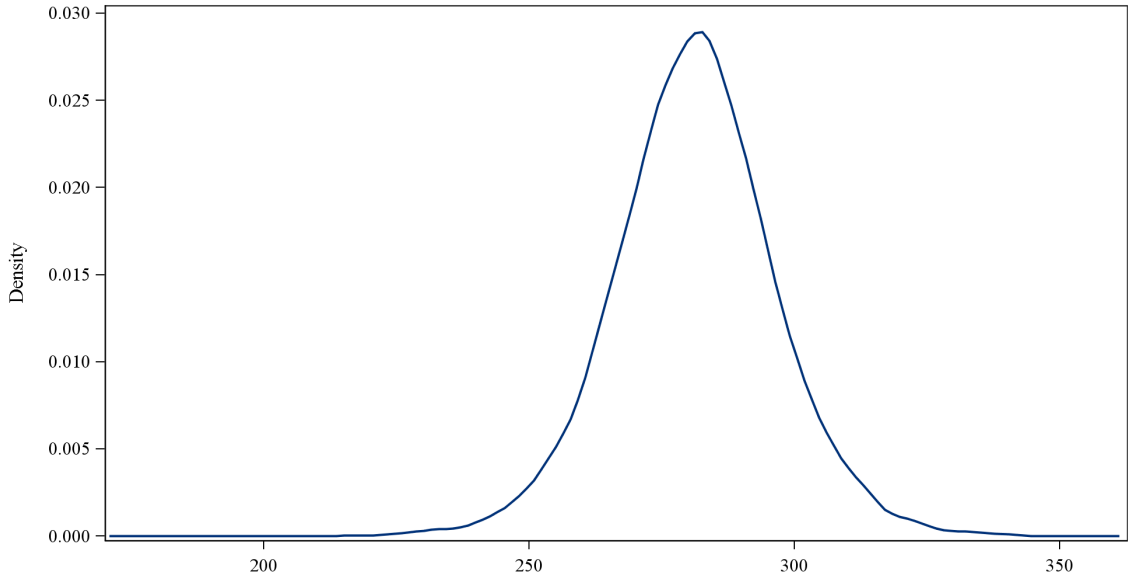
Note: Black triangles are treatment session first dose of anti-SAP mAb. Vertical Line is first dose of anti-SAP mAb of the first treatment session.

Programming notes: Include as many panels as endpoints. If more than 4 panel rows introduce a second column. If more than 4 rows x 2 columns consider moving panels to second page. For imaging markers with segmental values, include as many curves as segments on the same plot (with segments identified in legend).

Example : PD_F2
Protocol : 201464
Population : Safety

Figure x.x
Posterior Distribution of Bayesian Model Parameters for the Analysis of <Endpoint (unit)>
Model: <Three-Piece Linear Model / Three-Piece Model with Restricted Cubic Spline Parameters / Other Model as Appropriate>
Imputation: <None / Non-Future Dependence Multiple Imputation / Multiple Imputation Based on Standard of Care Data>

Cohort: <Study Group X>
Model Parameter: <Intercept / Pre-treatment Slope / On-treatment Slope / Post-treatment Slope / On/post-treatment RCS parameters...>



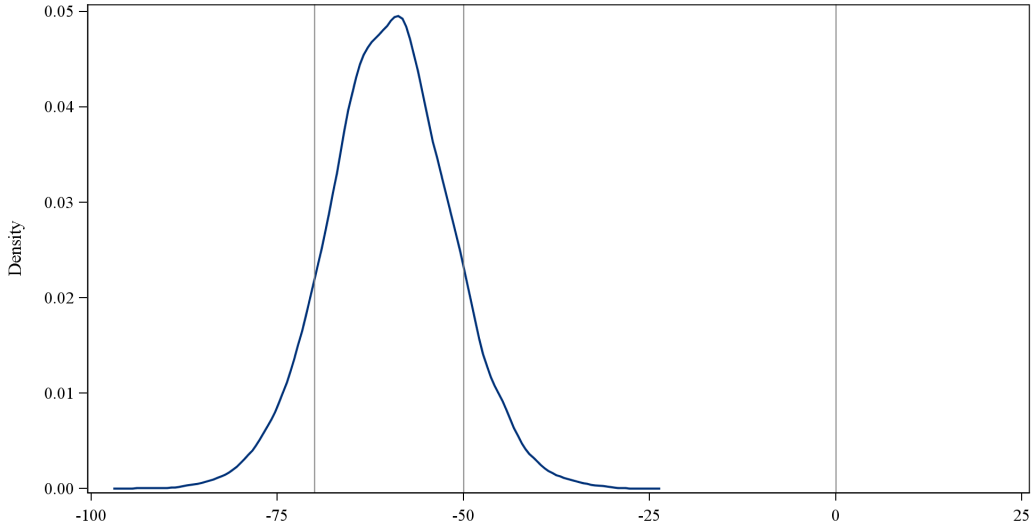
<Intercept / Pre-treatment Slope / On-treatment Slope / Post-treatment Slope / On/post-treatment RCS parameters...>

Programming note: include all Bayesian model parameters as appropriate, one by page (as many pages as parameters)

Example : PD_F3
Protocol : 201464
Population : Safety

Figure x.x
Posterior Distribution of Mean Change from First Dose of Anti-SAP mAb in <Endpoint (unit)> at Timepoints of Interest
Model: <Three-Piece Linear Model / Three-Piece Model with Restricted Cubic Spline Parameters / Other Model as Appropriate>
Imputation: <None / Non-Future Dependence Multiple Imputation / Multiple Imputation Based on Standard of Care Data>

Cohort: <Study Group X>
Timepoint: <2/3/4/5/8/11/17> Months



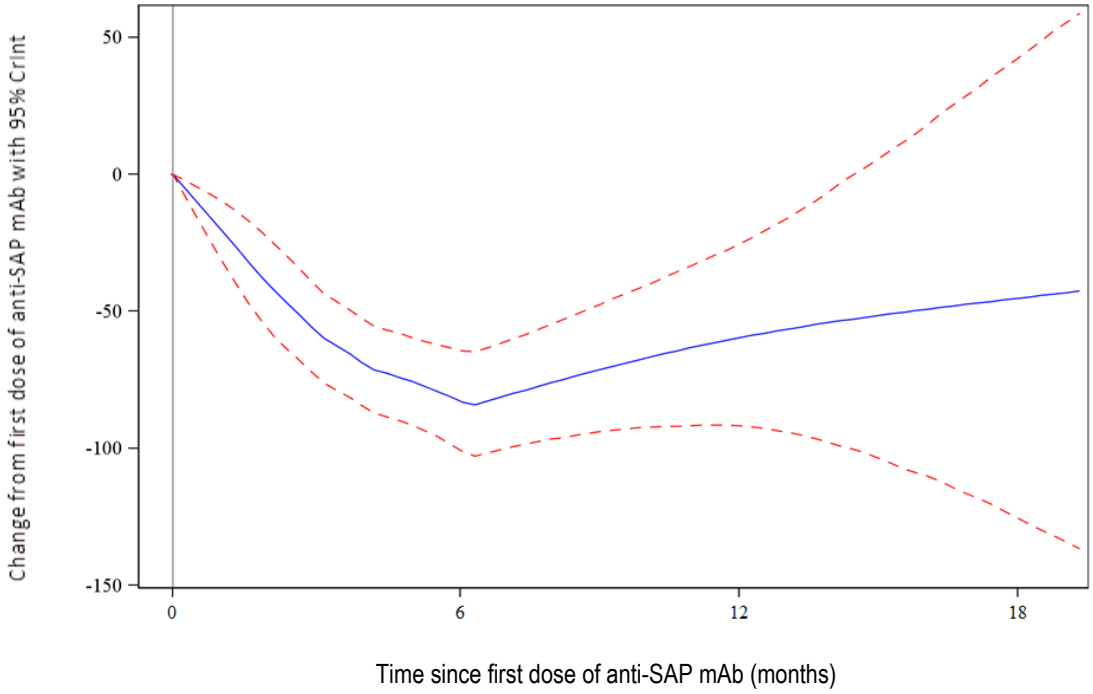
<Note: Vertical lines are thresholds of changes from first dose of anti-SAP mAb for values <-70, -50, 0>>

Programming note: include all timepoints as appropriate (2,3,4,5,8,11,17 months), one by page (as many pages as timepoints)

Example : PD_F4
Protocol : 201464
Population : Safety

Figure x.x
Posterior Mean Change from First Dose of Anti-SAP mAb in <Endpoint (unit)> Over Time
Model: <Three-Piece Linear Model / Three-Piece Model with Restricted Cubic Spline Parameters / Other Model as Appropriate>
Imputation: <None / Non-Future Dependence Multiple Imputation / Multiple Imputation Based on Historical Data>

Cohort: <Study Group X>

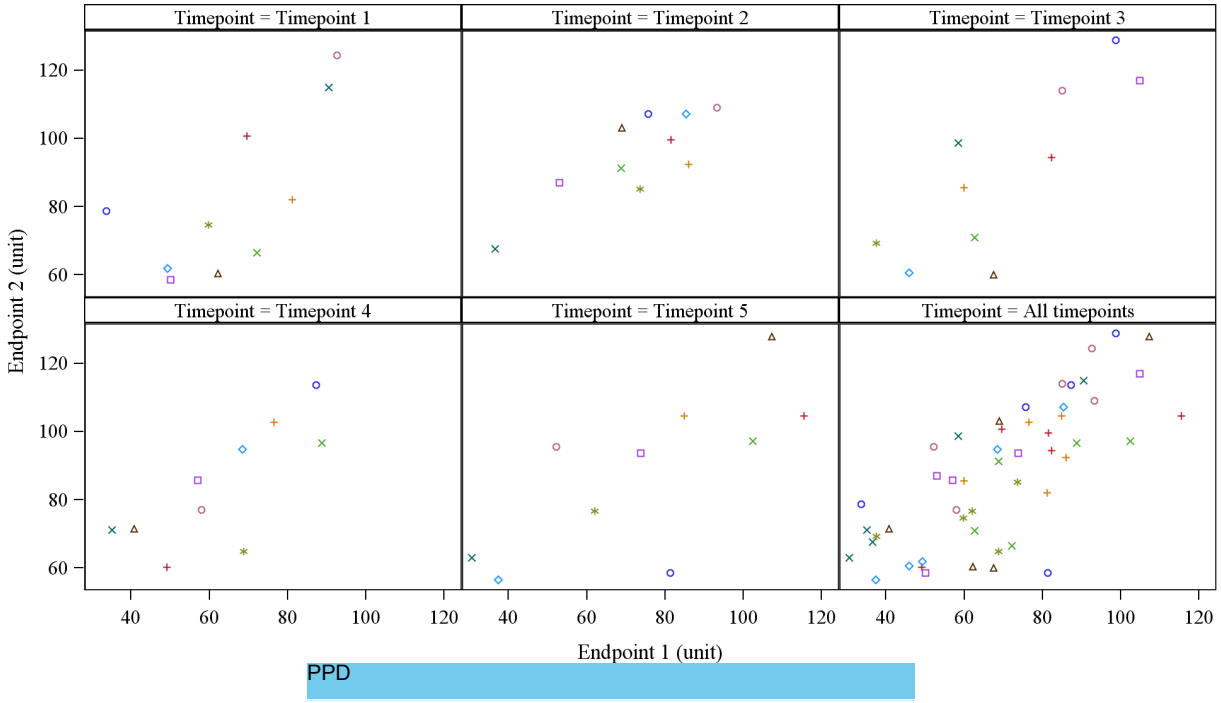


Note: Vertical Line is First Dose of Anti-SAP mAb.

Example : PD_F5
Protocol : 201464
Population : Safety

Figure x.x
Scatter Plot of <Endpoint Type / Endpoint 1 (unit)> versus <Endpoint Type / Endpoint 2 (unit)> by Timepoint with Subject Identifiers

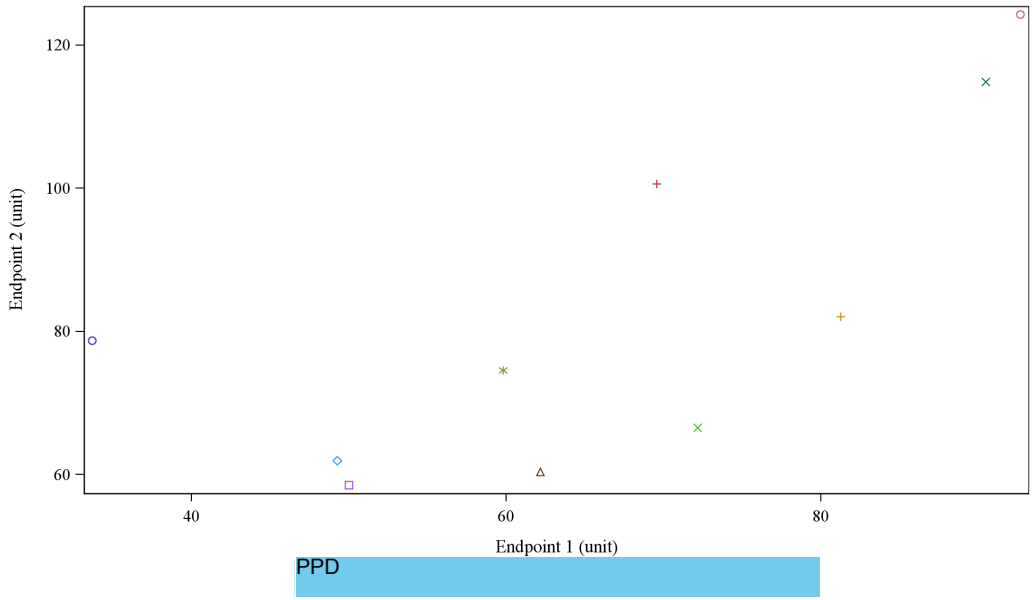
Cohort: <Study Group X>
Endpoints: <Endpoint 1 (unit)> vs <Endpoint 2 (unit)>



Example : PD_F6
Protocol : 201464
Population : Safety

Figure x.x
Scatter Plot of < Endpoint 1 (unit)> versus <Endpoint 2 (unit)>

Cohort: <Study Group X>
Endpoints: <Endpoint 1 (unit)> vs <Endpoint 2 (unit)>



Example : AE_T1
Protocol : 201464
Population : Safety

Table x.x
Summary of Posterior Probabilities for Specific Adverse Events

Cohort: <Study Group X>

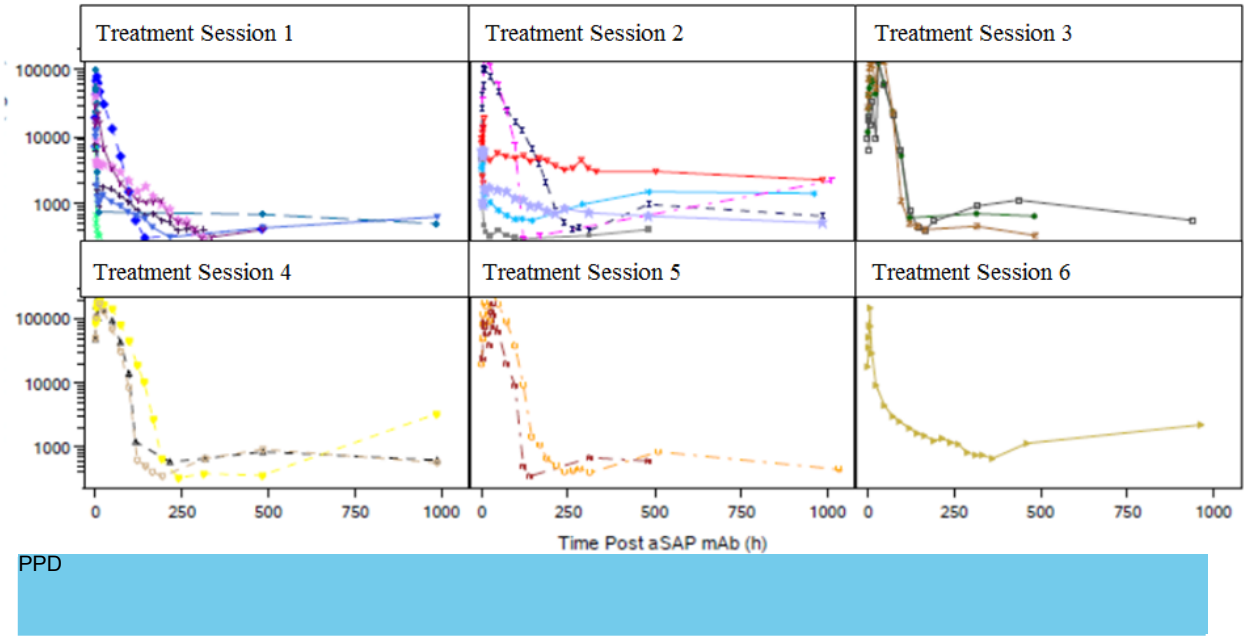
			95% Credible Interval		Prob. of true subject rate > x% given observed data		
Preferred Term	n / N	Observed subject rate	Lower Limit	Upper Limit	>10%	>30%	>50%
PreferredTerm1	xx / xx	0.xx	0.xx	0.xx	0.xx	0.xx	0.xx
PreferredTerm2	xx / xx	0.xx	0.xx	0.xx	0.xx	0.xx	0.xx
PreferredTerm3	xx / xx	0.xx	0.xx	0.xx	0.xx	0.xx	0.xx
PreferredTerm4	xx / xx	0.xx	0.xx	0.xx	0.xx	0.xx	0.xx
PreferredTerm5	xx / xx	0.xx	0.xx	0.xx	0.xx	0.xx	0.xx
PreferredTerm6	xx / xx	0.xx	0.xx	0.xx	0.xx	0.xx	0.xx
...	xx / xx	0.xx	0.xx	0.xx	0.xx	0.xx	0.xx

Note: Probabilities derived within a Bayesian framework with a non-informative conjugate prior distribution, Beta (1/3,1/3)

Example : PK_F1
Protocol : 201464
Population : Safety

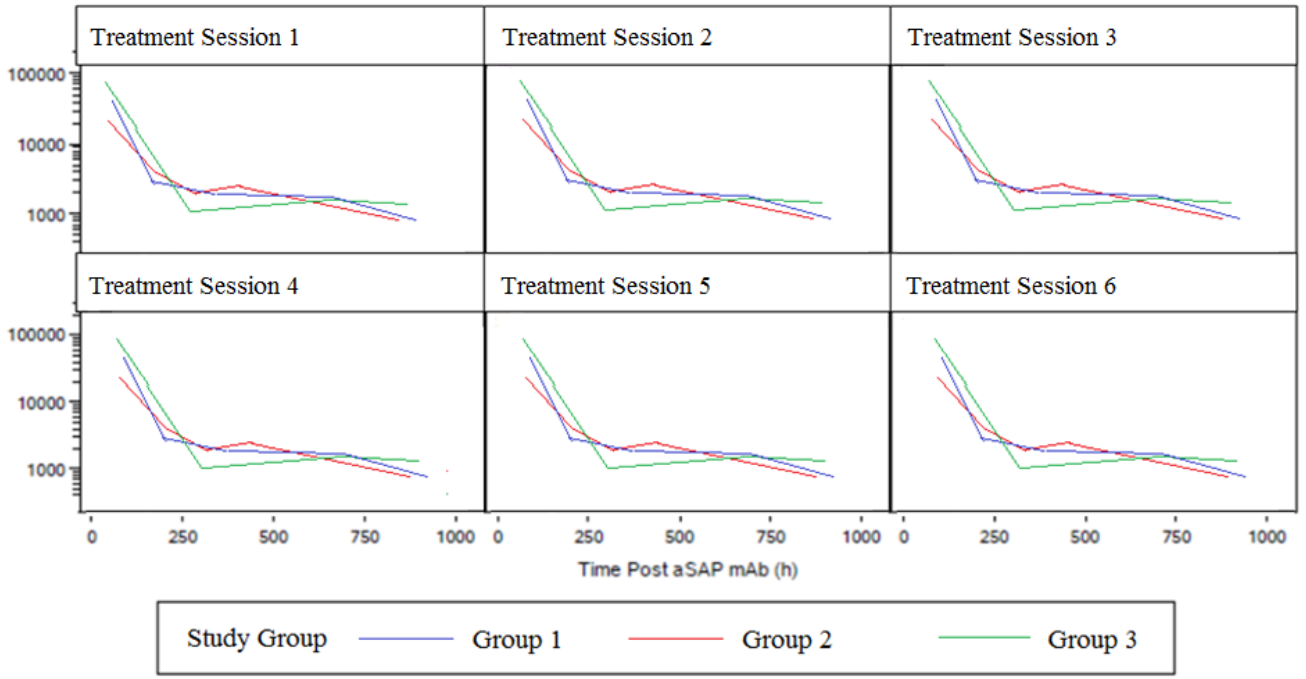
Figure x.x
Individual Plasma <GSKXXXXXX> Concentration-Time Plot (Linear and Semi-Log) by Treatment Session with Subject Identifiers
Y axis scale: <Linear / Semi-Log> (Repeat on two pages)

Cohort: <Study Group X>



Example : PK_F2
Protocol : 201464
Population : Safety

Figure x.x
Median Plasma <GSKXXXXXX> Concentration-Time Plot (Linear and Semi-Log) by Treatment Session with Group Identifier
Y axis scale: <Linear / Semi-Log> (Repeat on two pages)



Example : PD_L1
Protocol : 201464
Population : Safety

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

Cohort: <Study Group X>

				<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.

Example : AE_L1
Protocol : 201464
Population : Safety

Listing x.x
Listing of Rash Details

Cohort: <Study Group X>

Site Id./ Unique Subject Id.	Assessment Date/ Time	Rash Form Item	Value
PPD	DDMMMYY/ xx:xx	Type or Rash	Maculopapular, Urticarial
		Most Severe	Maculopapular
		Appearance of lesions	Yes
		Percentage of total body surface covered in rash	17%
		Rash Location	Head, Trunk
		Etc.	Etc.

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