

## TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Protocol Amendment

<b>Title:</b>	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
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Regulatory input from the FDA on clarifying requirements for recruitment. Define plasma SAP depletion target level of <3 mg/L. Inclusion criterion for LVmass updated for Groups 2 and 3 to reflect the AL patient population. Reflect regulatory safety update information for Gadolinium contrast agents. Dermatology review timings adjusted for grade 3 rash incidences. Other changes made for clarity and to correct minor typographical errors.		

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201464

**SPONSOR SIGNATORY**

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**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number: 201464

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

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# 1. PROTOCOL SYNOPSIS FOR STUDY 201464

## Rationale

The study is intended to evaluate whether repeated courses of administration of GSK2315698 (carboxy pyrrolidine hexanoyl pyrrolidine carboxylate [CPHPC]) followed by GSK2398852 (monoclonal anti-serum amyloid p component antibody [anti-SAP mAb]) is associated with a reduction in cardiac amyloid load in patients with transthyretin cardiomyopathy (ATTR-CM) and immunoglobulin light chain (AL) systemic amyloidosis, monitored by cardiac magnetic resonance imaging (CMR) and echocardiography (ECHO), and whether this is associated with an improvement in cardiac function.

In this document GSK2315698 is referred to as **CPHPC** and GSK2398852 is referred to as **anti-SAP mAb**. The administration of CPHPC and anti-SAP mAb is referred to in this document as **Anti-SAP treatment**.

The study will also evaluate the systemic and cardiac safety of repeated administrations of CPHPC followed by anti-SAP monoclonal antibody (mAb), as well as the pharmacodynamic compatibility of CPHPC and anti-SAP mAb with chemotherapy regimens in patients with newly diagnosed AL amyloidosis.

## Objective(s)/Endpoint(s)

Objectives	Endpoints
<b>Primary (all groups)</b>	
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 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 follow-up  Incidence and grading of skin rashes classified using the Common Terminology Criteria for Adverse Events (CTCAE)
<b>Secondary</b>	
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	Descriptive pharmacokinetic (PK) parameters including the maximum concentration (C <sub>max</sub> ), the time associated with C <sub>max</sub> (T <sub>max</sub> ), and the area under the

Objectives	Endpoints
	concentration-time profile (AUC).
Assessment of changes in circulating markers associated with pharmacodynamic effect during repeated administrations	Circulating biomarkers including but not limited to classical complement pathway components, acute phase proteins (e.g. c reactive protein [CRP], SAA) and cytokines (e.g. IL6, IL8, IL10, TNF $\alpha$ ).
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 follow-up
<b>Exploratory</b>	
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 extracellular volume (ECV) over time from baseline to 8-week follow-up
Assessment of effects of Anti-SAP treatment on individual patient quality of life	Change in individual patient quality of life as measured by the MOS SF-36, KCCQ, DLQI and EORTC QLQ 30 questionnaires over time from baseline to 8-week 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 follow-up.  Change in NT-proBNP from baseline to 8-week follow-up
Assessment of reduction in cardiac uptake of radioisotope bone tracers (Group 1 only)	Change in $^{99m}\text{Tc}$ -DPD or $^{99m}\text{Tc}$ -PYP uptake from baseline to 8-week follow-up
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 follow-up
Assess the correlation between circulating biomarkers and structural and functional CMR measures	Circulating biomarkers (e.g. cardiac - NT-proBNP and Troponin T, cytokines) over time  Structural, Functional, and Tissue Characterization CMR measures over time, as data permit

Objectives	Endpoints
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 structure LV wall thickness (CMR and/or ECHO), and LV mass (ECHO) over time from baseline to 8-week 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 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 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
<b>Long term follow-up</b>	
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 AntiSAP treatment outcomes at 6 and 12 months post last anti-SAP mAb dose	<p>Long term changes in LV mass over time up to 12-month follow-up</p> <p>Long term changes in imaging markers from CMR and / or ECHO over time up to 12-month follow-up (as per 8-week follow-up)</p> <p>Long term changes in NT-proBNP over time up to 12-month follow-up</p> <p>Long term changes in 6MWT distance over time up to 12-month follow-up (Groups 1 and 2).</p> <p>Measurement of anti-drug antibodies at 6 and 12 month follow-up</p>

## Overall Design

This is an open label, non-randomised, three-group, monthly repeat Anti-SAP treatment study in systemic amyloidosis patients with cardiac dysfunction caused by cardiac amyloidosis. 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.

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. Subjects will attend a follow-up visit 8 weeks after final dose of anti-SAP mAb.

Subjects will attend 2 further follow-up sessions at 6 and 12 months after last Anti-SAP treatment session. Maximum total duration for a subject in the study is approximately 18 months.

## Treatment Groups and Duration

Three patient Groups will be studied:

**Group 1: Cardiac TTR patients (mutant genotypes primarily associated with familial amyloidotic cardiomyopathy (FAC) & wild-type TTR)** with clinical cardiac dysfunction measurable by CMR. Subjects will be evaluated for the cardiac / systemic safety, and overall magnitude of cardiac amyloid load reduction, with repeated administrations of Anti-SAP treatment on a monthly schedule for up to 6 courses.

**Group 2: Post-Chemotherapy AL amyloidosis patients** whom have attained either a very good partial response (VGPR), or complete response (CR), to systemic chemotherapy (including autologous stem cell transplantation), and have residual clinical cardiac dysfunction that is measurable by CMR. Subjects will be evaluated for cardiac / systemic safety, and overall magnitude of cardiac amyloid load reduction, with repeated administrations of Anti-SAP treatment on a monthly schedule for up to 6 courses.

**Group 3: Newly diagnosed Mayo stage II or IIIa AL amyloidosis patients**, and with plasma NT-proBNP levels  $\leq 8500$  ng/L, who have attained a free light chain CR following first-line chemotherapy cycles 1, 2 or 3 where at least the first cycle of chemotherapy has been cyclophosphamide, bortezomib, dexamethasone (CyBorD). Subjects in Group 3 will be evaluated for cardiac / systemic safety, and overall magnitude of cardiac amyloid reduction, with repeated administrations of Anti-SAP treatment on a monthly schedule for a total of up to 6 courses.

AntiSAP treatment will commence during the last week of the *next* scheduled cycle of chemotherapy immediately after the preceding cycle in which a free light chain CR status was attained, and in those patients where there is no intent to immediately proceed to an autologous stem cell transplant.

The Study is a three-group study. 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.

## **Type and Number of Subjects**

A minimum of 30 subjects will be recruited initially, comprising 10 subjects per group. Additional subjects may be enrolled in each of the three groups to assist in interpretation of safety and / or pharmacodynamic (PD) data based on emerging data.

## **Analysis**

### *Hypotheses*

No formal statistical hypothesis tests are planned in this study.

### *Interim analyses*

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

Study specific decisions will be supported by the periodic review of study data. The first review will take place once 5 subjects have completed at least 3 courses of Anti-SAP treatment. Outcomes from the periodic data reviews may include:

- Regulatory interactions and initiation of recruitment in to Group 3
- Triggering of phase 3 planning and related regulatory interactions
- Sample size re-estimation/adjustment
- Adjustment of the schedule and timing of assessments
- Confirmed continuation of the study

An interim analysis on a clean data cut will be conducted once at least 10 subjects per group have completed their 8-week follow-up visit. Further details will be provided in the Reporting and Analysis Plan (RAP) regarding key deliverables for this interim.

The final analyses will be conducted once all subjects have completed their 12-month follow-up visit.

### *Primary analyses - LV mass*

Analyses detailed below will be performed on data from each study group separately.

Individual subject profiles over time for LV mass will be plotted using historical pre-trial standard of care subject data, where available, and within-study data on the same subject, pre and post Anti-SAP treatment. Absolute values and changes from baseline in LV mass will also be summarized over time.

The longitudinal profile of LV mass post Anti-SAP treatment will be analyzed using a Bayesian linear mixed model (LMM). The intention is to also include two sources of historical MRI data in the model from one participating site that will be informative of the standard of care LV mass profile over time:

1. Pre-trial MRI data for patients enrolling in the study, collected as part of their medical history, where available
2. Repeat historical MRI data for patients not enrolled in the study (2 to 3 scans per patient)

For subjects who prematurely discontinue treatment, follow-up MRI scans at 8 weeks, 6 months and 12 months post last dose will be performed where possible. All retrieved LV mass data post treatment-discontinuation will be incorporated directly within the model. This will be achieved in two ways: (i) fitting a LMM following a Pattern Mixture Model (PMM) framework, uniquely identifying patterns of treatment discontinuation; and (ii) fitting a LMM to all data ignoring whether subjects prematurely discontinued Anti-SAP treatment.

Any missing data will be imputed assuming a Missing Not at Random mechanism with the historical MRI data acting as reference.

Posterior distributions at time points of interest post Anti-SAP treatment (e.g. after 3 doses, at 8-week follow-up) will be presented graphically. Probability statements around the magnitude of LV mass and/or the reduction in LV mass post Anti-SAP treatment at selected time points will also be presented. Similarly, posterior distributions and probability statements will be presented for standard of care.

Further details will be provided in the RAP.

#### *Primary analyses – Safety*

Safety data (e.g. AEs, vital signs, haematology, biochemistry, urinalysis, ECGs, holter, rash) will be summarized by study group in tabular and/or graphical format. Posterior probabilities of a true adverse event rate being  $> 10\%$ ,  $> 30\%$  and  $> 50\%$  will be presented for specific AEs (e.g. rash, anti-SAP mAb infusion-related reactions, cardiac AEs), derived within a Bayesian framework with a neutral non-informative conjugate Beta(1/3,1/3) prior distribution.

Further details will be provided in the RAP.

## 2. INTRODUCTION

Carboxy pyrrolidine hexanoyl pyrrolidine carboxylate (CPHPC) + anti- serum amyloid p component (SAP) monoclonal antibody (mAb) is a novel combination therapy, in fact an obligate therapeutic partnership, which promotes clearance of amyloid deposits from the tissues and is being developed in order to treat patients with systemic amyloidosis and alleviate the cardiac and other organ dysfunction caused by amyloid.

The heart is probably the most commonly clinically affected organ in systemic amyloidosis. Myocardial deposition of amyloid in transthyretin (ATTR-CM) and immunoglobulin light chain (AL) amyloidosis causes restrictive cardiomyopathy and arrhythmias. Cardiac dysfunction is a major cause of morbidity and the main determinant of disease-related survival. Removal of amyloid deposits from the myocardium could thus improve cardiac function, reduce symptoms and prolong survival in patients with ATTR and AL amyloidosis.

### 2.1. Study Rationale

The principal aim of this phase 2 study is to investigate the extent of cardiac amyloid removal, the associated improvement in cardiac function, and the cardiac / systemic safety profile of Anti-SAP treatment (GSK2315698 + GSK2398852), given monthly for up to 6 sessions.

### 2.2. Brief Background

In systemic amyloidosis normally soluble plasma proteins misfold and then aggregate as abnormal insoluble fibrils in the extracellular space, disrupting the architecture and function of affected tissues and organs, causing disease which is usually fatal [Pepys, 2006]. About 30 different proteins are known to form amyloid fibrils in different types of amyloidosis. The most common types are AL amyloidosis, caused by monoclonal immunoglobulin light chains, and ATTR amyloidosis, caused by wild type or variant (mutant) transthyretin (TTR). Involvement of the heart is the most important determinant of outcome in both these forms of amyloidosis, leading to restrictive cardiomyopathy with predominantly diastolic dysfunction and heart failure with normal ejection fraction. Amyloid is deposited early in the subendocardium, causing a high incidence of arrhythmias, and deposition then proceeds asymmetrically, usually predominantly affecting the interventricular septum and left ventricular wall.

Existing treatment for systemic amyloidosis comprises maintenance and/or replacement of the function of amyloidotic organs and also, if possible, reduction of the production of the protein precursors of the amyloid fibrils. However, even when these approaches are successful, regression of amyloid deposits is very variable and is always very slow. No approved treatments exist which impact cardiac amyloid deposits. A new approach, directly targeting amyloid deposits for clearance from the tissues, would have the potential to deliver substantial clinical benefit. The approach here is based on targeting of human serum amyloid P component (SAP).



SAP is a normal, circulating, constitutive plasma glycoprotein which is always present as a minor component of all human amyloid deposits of all types. SAP is a member of the pentraxin protein family which is characterized by calcium dependent binding to various ligands. SAP avidly binds specifically but reversibly to all amyloid fibrils and in patients with systemic amyloidosis there is a dynamic equilibrium between SAP bound to the amyloid deposits and about 50-150 mg of SAP free in the plasma and extracellular fluid. SAP is produced only by hepatocytes and its plasma concentration is rather tightly maintained regardless of the presence, absence and extent of amyloid deposition. In contrast the amyloid bound SAP pool reflects the mass of the amyloid fibrils present and can comprise grams of SAP.

The drug (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) efficiently and highly specifically depletes circulating SAP from the plasma for as long as the drug is administered [Pepys, 2002; Sahota, 2015]. This treatment also removes some SAP from the amyloid deposits but it does not remove it all. After depletion of plasma SAP by CPHPC, anti-SAP antibodies can be given without being consumed by interaction with circulating SAP and without causing formation of large amounts of immune complexes in the circulation. The antibodies can then reach and bind to residual SAP in the amyloid deposits and trigger the normal opsonophagocytic processes for removal of abnormal debris from the extracellular space.

In Amyloid A (AA) amyloidotic mice engineered or treated to have human SAP in their amyloid deposits, administration of a single dose of polyclonal or monoclonal antibodies to human SAP produced almost complete clearance of massive amyloid deposits from the liver and spleen [Bodin, 2010]. Cardiac amyloid deposits were significantly reduced after two doses of anti-SAP antibody [Simons, 2013]. The amyloid clearance was dependent on binding of the antibody to the amyloid deposits, activation of the classical complement pathway, complement deposition on the amyloid, and availability of macrophages. Destruction of amyloid was mediated by macrophage derived multinucleated giant cells (MGCs) which surrounded, engulfed and degraded the amyloid fibrils [Milde, 2015]. The whole process was completed within about 16 days from antibody dosing and was well tolerated without evidence of additional organ dysfunction. Normal histology was restored with amyloid absent and no residual infiltrating or inflammatory cells. A major reason for using SAP as the target in this approach is its universality in all amyloid deposits in all forms of amyloidosis, so that the same therapeutic mechanism should operate in all types and tissues.

GSK is developing this approach comprising an obligate therapeutic partnership, involving prior administration of CPHPC to deplete SAP from the plasma so that a fully humanized IgG1 monoclonal anti-SAP antibody (GSK2398852) can then be given to target systemic amyloid deposits for clearance from the tissues.

### **2.3. Summary of First In Human (FIH) Findings**

A GSK-sponsored phase 1 study is complete. The study demonstrated proof-of-pharmacology for the obligate therapeutic partnership of CPHPC + anti-SAP mAb in patients with AL amyloidosis, AA amyloidosis and patients with different types of hereditary systemic amyloidoses, all with predominantly abdominal organ involvement

GlaxoSmithKline Document Number 2012N141587, GSK2398852 + GSK2315698 Investigator's Brochure].

- Overall Anti-SAP treatment was associated with an acceptable systemic safety profile in patients whose amyloid predominantly involved the abdominal viscera.
- The following risks were identified:
  - Administration of anti-SAP mAb was associated with an infusion reaction. This was substantially mitigated by premedication with hydrocortisone and antihistamine.
  - Rashes were commonly reported following anti-SAP mAb infusion (refer to Section 12.3 Appendix 3 Rash and investigator's brochure (IB GlaxoSmithKline Document Number 2012N141587, GSK2398852 + GSK2315698 Investigator's Brochure)] for more information and mitigation plans).
  - Transient pain and erythema at sites of injection and infusion of CPHPC were common but not treatment limiting.
- Preliminary results in a small number of AL and ATTR patients with cardiac amyloidosis showed Anti-SAP treatment at doses of mAb up to 1200mg were generally well-tolerated with a similar safety profile to those subjects without evidence of cardiac amyloid.
- Patients showing reduction of amyloid load following Anti-SAP treatment in the FIH study generally also had substantial reduction in total plasma C3 concentration, consistent with the mechanism of action characterized in the preclinical model.
- Plasma cytokine assays in subjects in the first in human (FIH) study showed increases in circulating IL-10, IL-8, TNF $\alpha$ , and IL-6 values typically within the first 6 hours of anti-SAP mAb administration. Subjects showing reduction of amyloid load following treatment in the FIH study also typically had acute phase responses of C-reactive protein (CRP) and serum amyloid A protein (SAA).
- There were no preliminary clinical safety signals in the FIH study suggesting any direct visceral organ toxicity after one or more courses of anti-SAP mAb treatment in patients with systemic AL, ATTR, apolipoprotein A-I amyloidosis (AApoAI), fibrinogen A alpha chain amyloidosis (AFib), ATTR or AA amyloidosis, although one subject who developed hypotension during the immediate infusion reaction to anti-SAP mAb had a transient increase in plasma creatinine.

## 2.4. Purpose of phase 2 Study

The principal aim of this study is to investigate the benefit-risk profile of Anti-SAP treatment administered monthly for up to 6 treatments. Prognosis in AL and ATTR amyloidosis mostly depends on cardiac involvement and removal of cardiac amyloid will

be quantitatively monitored by comprehensive imaging evaluation coupled with detailed assessment of cardiac function and cardiac safety. The main adverse events observed in the FIH study (Study SAP115570), specifically at anti-SAP mAb doses  $\geq 600\text{mg}$ , were skin rashes and these will therefore be closely monitored and thoroughly investigated.

#### **2.4.1. Multimodality cardiac imaging**

This will consist of serial cardiac magnetic resonance imaging (CMR) and echocardiography (ECHO).

CMR methods precisely and specifically quantify the left ventricle (LV) mass and the cardiac extracellular volume (ECV), both of which are increased by the presence and extent of cardiac amyloid deposition. Raised ECV values have been shown to be associated with a worse clinical prognosis in AL amyloidosis [[Banyersad, 2015](#)]. Neither LV mass nor ECV measurements have previously been shown to be markers of clinically beneficial regression of cardiac amyloid, both because these CMR parameters have only recently become available and because there are no existing therapies that reliably promote significant clearance of cardiac amyloid. However, knowledge of the pathogenic mechanisms by which amyloid deposits cause dysfunction in the heart and other organs, coupled with the favourable evidence on liver function from Study SAP115570 strongly suggest that reduction in cardiac amyloid load detected by sufficient reduction towards normal of LV mass and cardiac ECV is likely to be accompanied by improved cardiac function and symptomatic improvement, and will be assessed in this study in an exploratory manner.

In addition, bone tracer scintigraphy using either  $^{99\text{m}}\text{Tc}$ -3,3-diphosphono-1,2-propanodicarboxylic acid ( $^{99\text{m}}\text{Tc}$ -DPD) or  $^{99\text{m}}\text{Tc}$ -pyrophosphate ( $^{99\text{m}}\text{Tc}$ -PYP) will also be performed in Group 1 only (patients with ATTR-CM). It has been shown that  $^{99\text{m}}\text{Tc}$ -DPD and  $^{99\text{m}}\text{Tc}$  PYP in routine use for many years as bone scan agents in the United Kingdom and United States of America respectively, can also be used to image cardiac amyloid in patients with ATTR [[Rapezzi, 2011](#)].

### 3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
<b>Primary (all groups)</b>	
Assessment of reduction in cardiac amyloid load after repeated administrations of Anti-SAP treatment as evaluated by CMR in all study groups	Change in LV mass over time from baseline to 8-week 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 follow-up  Incidence and grading of skin rashes classified using the Common Terminology Criteria for Adverse Events (CTCAE)
<b>Secondary</b>	
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	Descriptive pharmacokinetic (PK) parameters including the maximum concentration (C <sub>max</sub> ), the time associated with C <sub>max</sub> (t <sub>max</sub> ), 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, TNF $\alpha$ ).
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 follow-up
<b>Exploratory</b>	
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 follow-up

Objectives	Endpoints
Assessment of effects of Anti-SAP treatment on individual patient quality of life	Change in individual patient quality of life as measured by the MOS SF-36, KCCQ, DLQI and EORTC QLQ 30 questionnaires over time from baseline to 8-week 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 follow-up  Change in N-terminal pro b-type Natriuretic Peptide (NT-proBNP) from baseline to 8-week follow-up
Assessment of reduction in cardiac uptake of radioisotope bone tracers (Group 1 only)	Change in <sup>99m</sup> Tc-DPD or <sup>99m</sup> Tc-PYP uptake from baseline to 8-week follow-up.
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 follow-up
Assess the correlation between circulating biomarkers and structural and functional CMR measures	Circulating biomarkers (e.g. cardiac - NT proBNP and 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 structure LV wall thickness (CMR and/or, ECHO), and LV mass (ECHO) over time from baseline to 8-week 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 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 follow-up)

Objectives	Endpoints
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
<b>Long term follow-up</b>	
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	<p>Long term changes in LV mass over time up to 12-month follow-up</p> <p>Long term changes in imaging markers from CMR and / or ECHO over time up to 12-month follow-up (as per 8-week follow-up)</p> <p>Long term changes in NT-proBNP over time up to 12 month follow-up</p> <p>Long term changes in 6MWT distance over time up to 12-month follow-up (Groups 1 and 2).</p> <p>Measurement of anti-drug antibodies (6 and 12 month follow-up)</p>

## 4. STUDY DESIGN

### 4.1. Overall Design

This is an open label, non-randomised, three-group, monthly repeat Anti-SAP treatment study in systemic amyloidosis patients with cardiac dysfunction caused by cardiac amyloidosis. 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.

**Figure 1 Schematic of study groups**

<b>Group 1</b>  Wild-type and variant ATTR-CM  N=10	Monthly Anti-SAP treatment - up to 6 treatment sessions		
<b>Group2</b>  AL amyloidosis with cardiac dysfunction  ≥6 months post chemotherapy or autologous stem cell (CR/VGPR)  N=10			
Group 3 will be initiated following a review of safety in cohorts 1 and 2 (See Section <a href="#">10.8</a> )	<b>Group 3</b>  Mayo II/IIIa. AL amyloidosis with cardiac dysfunction  Free light chain CR during first three cycles of chemotherapy where at least the first cycle was CyBorD	Monthly CPHPC + anti-SAP mAb up to 6 treatment sessions  Initial dose of anti-SAP mAb defined by review of cohorts 1 and 2  N=10	

N = number of subjects

A screening visit and baseline assessments will be conducted prior to the first Anti-SAP treatment session. Cardiac pharmacodynamic assessments will consist of CMR imaging and ECHO. Contrast-enhanced CMR imaging to assess changes in cardiac amyloid (including ECV) and cardiac safety will be performed at baseline, following the third



anti-SAP mAb treatment, and at the 8-week follow-up visit approximately 8 weeks after final dose of anti-SAP mAb (see Section 7.6.2 & Cardiac Imaging Manual). Non contrast-enhanced CMR imaging will be scheduled to be performed following the second, fourth and fifth anti-SAP mAb treatment to assess changes in cardiac amyloid and safety. ECHO will be performed in all subjects prior to the first treatment session (baseline), at monthly intervals up to the final treatment session, and at the 8 week follow-up visit (see Section 7.4.6 & Cardiac Imaging Protocol). <sup>99m</sup>Tc-DPD or <sup>99m</sup>Tc-PYP scintigraphy will be performed at baseline and at 8 week follow-up in Group 1 (Figure 2). SAP scan to assess total and individual organ amyloid load will be performed at baseline and at 8 week follow-up in Groups 2 and 3 (UK sites only)

There will be a minimum of 1 month between the start of anti-SAP mAb treatments. If a subject shows, on CMR, a reduction in amyloid load consistent with clearance of amyloid then Anti-SAP treatment will cease and they will proceed to 8-week follow-up.

Subjects will return to clinic for long term follow-up of safety and functional status (including CMR and ECHO), 6 and 12 months post last anti-SAP mAb treatment.

No more than two subjects will be in treatment session 1 (up to Day 24) at each study site at any given time.

**Figure 2**      **Schedule of Anti-SAP Treatment sessions and cardiac imaging**

Screening	Baseline	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6	Follow up	Long term follow up	
42 days		Monthly intervals						8 Weeks post final mAb dose	6 month post final mAb dose	12 month post final mAb dose
MRI with contrast				MRI with contrast +ECHO				MRI with contrast + ECHO	MRI with contrast + ECHO	MRI with contrast + ECHO
	ECHO	ECHO	MRI+ ECHO		MRI+ ECHO	MRI+ ECHO	ECHO			
	Bone tracer scintigraphy (Group 1 only)							Bone tracer scintigraphy (Group 1 only)		

**Table 1 Anti-SAP treatment session**

Treatment session					
Day	Day -2 & -1	Day 1/2/3	Day 4-11	Day 17	Day 24 ± 1d
Setting	Inpatient			Outpatient	Outpatient
Activity	<b>Plasma SAP depletion</b>  Administration of CPHPC 48 to 72 hours IV  Blood SAP concentration checked before anti-SAP mAb infusion.	<b>Administration of anti-SAP mAb</b>  Each infusion of anti-SAP mAb over 6 to 8 hours  Dose will be split over 2 days [day 1 + day 3]  CPHPC continues SC Subjects closely monitored.	<b>Inpatient safety follow up</b>  Administration of CPHPC SC continues until Day 11	<b>Safety follow up</b> Including cardiac monitoring	<b>Safety follow up</b> Including cardiac monitoring  PD assessments

SC = sub-cutaneous IV = intravenous

## 4.2. Treatment Groups and Duration

**Group 1: Cardiac TTR amyloidosis (ATTR-CM) patients, ((mutant genotypes primarily associated with familial amyloidotic cardiomyopathy (FAC) & wild-type TTR))** with clinical cardiac dysfunction measurable by CMR. Subjects will be evaluated for cardiac / systemic safety and extent of cardiac amyloid load reduction in response to repeated monthly administration of up to 6 Anti-SAP treatments.

Subjects with clinically significant polyneuropathy will not be enrolled.

**Group 2: Post-chemotherapy AL amyloidosis patients** who have clinical cardiac dysfunction measurable by CMR after having had either a complete response (CR) or a very good partial response (VGPR) to chemotherapy or autologous stem cell transplantation will be evaluated for cardiac/systemic safety and extent of cardiac amyloid load reduction in response to repeated monthly administration of up to 6 Anti-SAP treatments.

**Group 3: Newly diagnosed Mayo stage II or IIIa AL amyloidosis patients** (plasma NT-proBNP levels ≤ 8500 ng/L) who have attained a free light chain CR during the first three cycles of first-line chemotherapy where the first cycle was cyclophosphamide, bortezomib, dexamethasone (CyBorD) will be evaluated for cardiac/systemic safety and extent of cardiac amyloid load reduction in response to repeated monthly administration of up to 6 Anti-SAP treatments. Anti-SAP treatment will commence during the next scheduled cycle of chemotherapy *after* the cycle in which a free light chain CR was attained (see Section 4.4.1 & Figure 3).

Group 1 and Group 2 will begin recruitment first. Recruitment into Group 3 will start only after data has been reviewed and regulatory interaction sought as detailed in Section 10.8.2.

### **4.3. Number of Subjects**

**Group 1:** Sufficient subjects will be recruited to ensure that at least 10 subjects receive at least 3 sessions of Anti-SAP treatment.

**Cohort 2:** Sufficient subjects will be recruited to ensure that at least 10 subjects receive at least 3 sessions of Anti-SAP treatment.

**Cohort 3:** Sufficient subjects will be recruited to ensure that at least 10 subjects receive at least 3 sessions of Anti-SAP treatment.

If subjects prematurely discontinue the study, additional replacement subjects may be recruited at the discretion of the Sponsor in consultation with the Investigator (see Section 5.5).

### **4.4. Justification of the study design**

It is not feasible to include a control group in the study for reasons as outlined below.

#### **Placebo control**

In a severe and life-threatening disease such as systemic amyloidosis, the administration of a blinded placebo treatment of this complexity and invasiveness is considered inappropriate and would not maintain study blind for the following reasons. Both elements are given parenterally, require dose individualization, and in the case of anti SAP mAb may require individual dose adaption as treatment progresses. Furthermore, it is recommended that subjects receive premedication with a modest dose of hydrocortisone (100 mg) and an antihistamine to mitigate the infusion response related to the mechanism of action of anti SAP mAb. Administration of premedication or placebo premedication to a control group is also considered inappropriate.

Anti-SAP mAb treatment is associated with characteristic adverse effects: specifically an infusion reaction (substantially mitigated by premedication) and common appearance of rash, thus attempts at blinding would likely be compromised. These features lead us to conclude that use of a blinded control arm is impractical.

#### **No treatment concurrent control**

The intensity of study assessments required for evaluation of safety, pharmacokinetics, and pharmacodynamics including the need for prolonged inpatient assessment are such that a 'no treatment' arm would be inappropriate.

### **Dose-response concurrent control**

In order to safeguard patient safety it is important to have the ability to adapt the dose administered at each dosing session. If two dose groups were included, this would lead to convergence of the doses administered in the two groups and thus frustrate the analysis of the two groups. Evaluation of a larger cohort following a single dose adaption regimen is expected to provide a more complete assessment of dose response.

### **Active control**

There are no approved treatments which lead to active removal of amyloid or the treatment of systemic amyloidosis and therefore an appropriate active control is not available.

No disease modifying interventions are approved for cardiac ATTR amyloidosis. Although there may be periods of relative clinical stability, cardiac ATTR amyloidosis progresses inexorably with clinical deterioration. In cardiac AL amyloidosis, cardiac function sometimes stabilises and may even improve after induction of CR by chemotherapy but the process is very slow, taking at least 18 months or more. Recent unpublished CMR work from the UK National Amyloidosis Centre (personal correspondence with PPD *et al*; 2016) has for the first time documented regression of cardiac AL amyloid deposits in some such patients. In contrast, the encouraging results of the FIH study indicate that, if the present intervention is efficacious in clearing cardiac amyloid, clear differences in cardiac function from both the natural history of ATTR and the post-chemotherapy course of AL cardiac amyloidosis is likely to be apparent within the 6 month treatment duration of this study.

#### **4.4.1. Combining Anti-SAP Treatment with Chemotherapy**

Subjects in Group 3 will have attained a free light chain complete response (CR) during the first three cycles of chemotherapy where at least the first cycle was CyBorD.

Subjects will not receive Anti-SAP treatment until a CR has been achieved to mitigate against any impact of an interaction between chemotherapy and Anti-SAP treatment.

The total number of chemotherapy cycles which shall be administered, and the specific dosages of each individual chemotherapy constituent, for each subject will be at the discretion of the Investigator.

The preferred timing for the first Anti-SAP treatment session is during the last week of the next scheduled chemotherapy cycle after the cycle in which a free light chain CR was confirmed.

Administration of the first Anti-SAP treatment session can be delayed at Investigator discretion based upon an individual subject's chemotherapy-related toxicity profile and clinical cardiac status. The first Anti-SAP should be at the earliest possible opportunity during any week of chemotherapy between cycles 2 - 4.

A subject will be withdrawn from the study if the first Anti-SAP treatment session cannot be started by the end of the last week of cycle 4 chemotherapy.

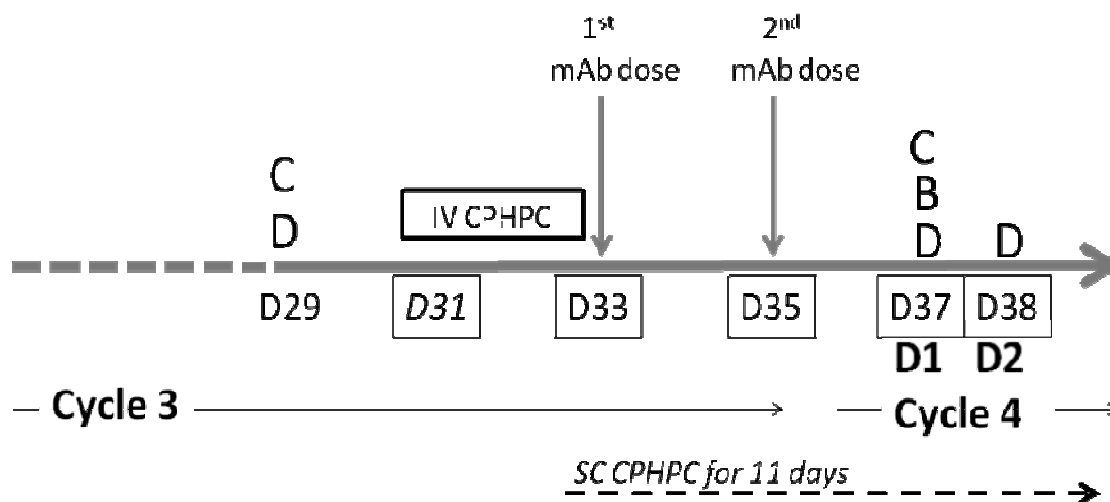
Changes to the chemotherapy regimen may be made by the treating haematologist based on emerging data but these will be discussed with the Medical Monitor. If the change calls for the use of a prohibited medication (Section 6.10.2) the subject will be withdrawn.

#### **4.4.1.1. Scheduling of Anti-SAP Treatment with Chemotherapy**

Two specific Anti-SAP treatment scheduling conditions will apply in Group 3 to reduce the potential for development of overlapping toxicities between the individual constituents of Anti-SAP treatment and chemotherapy:

- 1. IV CPHPC** - IV CPHPC infusion must **not** be on the same day(s) as chemotherapy is administered. Maintenance subcutaneous (SC) CPHPC administration is permitted.
- 2. Anti-SAP mAb** - There must be at least a 2 day interval between the:
  - a).** Last administered sub-cycle of chemotherapy and the first split dose of anti-SAP mAb;
  - b).** Second split anti-SAP mAb dose and the next scheduled sub-cycle of chemotherapy.

As outlined as an example in [Figure 3](#), the inter-cycle (and / or intra-cycle) scheduling of chemotherapy can be modified at the discretion of the Investigator to facilitate the delivery of Anti-SAP treatment following the above two conditions.

**Figure 3 Scheduling of Chemotherapy - example for CyBorD**

C = Cyclophosphamide

B = Bortezomib

D = Dexamethasone

Illustrative example in which the first Anti-SAP treatment is administered during the last week of Cycle 3 CyBorD in a subject who has attained a free light chain CR by completion of cycle 2 - *Note the 2 day interval on either side of Anti-SAP treatment constituents and CyBorD chemotherapy*

Anti-SAP treatment will be given on a monthly basis for up to five further treatment sessions. When chemotherapy has been completed (i.e. maximal haematological response has been attained) or discontinued (e.g. chemotherapy related toxicities), Anti-SAP treatment may continue to be administered as planned on a monthly schedule until completion of up to six treatment sessions.

The Investigator may delay administration of the next scheduled Anti-SAP treatment session by a maximum of 1 month thereby extending the interval between Anti-SAP treatment sessions up to a maximum of 8 weeks to facilitate sufficient resolution of chemotherapy-related toxicities (see Section 6.2.3 & Figure 4).

## 4.5. Justification of Dosing Regimen

### 4.5.1. GSK2315698 (CPHPC - Plasma SAP Depleter)

In the FIH study (SAP115570), the standard dosing regimen of CPHPC consisted of an IV infusion of 20 mg/hour for 72 hours prior to anti-SAP mAb administration. This regimen was reliably effective in depleting circulating SAP to <2 mg/L (using a Hycult ELISA assay). The current study is using a MSD assay and due to difference in SAP concentration scale between the assay types, a SAP concentration of <3 mg/L will be the target plasma SAP depletion level in this study. Since there is no precedent for the



present treatment, this empirical target SAP concentration was adopted on the basis of evaluation of the potential for formation of harmful circulating immune complexes and safety evaluation in the FIH study did not identify signals suggestive of adverse effects from residual SAP.

CPHPC is predominantly cleared from the plasma by the kidneys and excreted in the urine. CPHPC doses will therefore be adjusted (see Section 6.2.1, Table 2) based on individual renal function as measured by glomerular filtration rate (eGFR) using the existing pharmacokinetics/pharmacodynamics (PK/PD) model of CPHPC [Sahota, 2015].

Subjects in the FIH study achieved the target plasma SAP by 48 hours CPHPC IV treatment and therefore the duration of the initial CPHPC infusion prior to administration of anti-SAP mAb has been shortened in this study. On retrospective analysis most, but not all, subjects in the FIH study had achieved the target plasma SAP depletion by 24 hours CPHPC (IV) with further depletion to 48 hours. Blood SAP concentration will be checked after 24 hours of administration of CPHPC to confirm administration of anti-SAP mAb on the next day. If at the 24 hour timepoint the target SAP level is not achieved, a check at 48 hours will be performed and, if target achieved, subjects will receive anti-SAP mAb on the following day (i.e. after ~72 hours of CPHPC IV).

A retrospective analysis of PK shows that 9 days post mAb infusion is sufficient for anti-SAP mAb to fall to a low level at the dose levels proposed in this phase 2 study. Therefore in each treatment session, from the day of first IV infusion of anti-SAP mAb, CPHPC will be administered by SC injection for 11 days in order to maintain the depletion of circulating SAP while anti-SAP antibody remains in the plasma. Thereafter, as observed in the FIH study, only minimal traces of anti-SAP mAb are detectable, with almost no binding activity for SAP. Return of the normal circulating SAP concentration after stopping CPHPC therefore poses a low risk of formation of potentially harmful immune complexes.

#### **4.5.2. GSK2398852 (anti-SAP mAb)**

The proposed starting dose level of anti-SAP mAb dose in this study is 600mg given as a divided dose of two infusions of 300 mg over 6-8 hours each on Days 1 and 3. This dose level and regimen is expected to be well tolerated based on previous experience and to be pharmacologically active in a proportion of patients (estimated to be 30% based on previous experience).

Dose escalation on subsequent sessions will be considered on a case by case basis based on tolerability and evidence of pharmacodynamic effect. It is proposed that the dose in subsequent treatment sessions will be maximally 1200 mg, given as two infusions over 6-8 hours each, on Days 1 and 3. The dose and regimen is based on the results of the FIH study (SAP115570), and has been selected to promote rapid elimination of amyloid deposits whilst minimising adverse effects.

**Efficacy considerations.** The therapeutic mechanism by which anti-SAP antibody mediates amyloid clearance has been characterized in the pre-clinical model and is dependent on classical complement pathway activation triggered by binding of the antibody to SAP coating the amyloid fibrils. Initiation of the classical pathway requires formation of hexameric assemblies of IgG antibody molecules bound to their cognate

antigen in order to fix C1q. In the FIH clinical study, just as in the pre-clinical model, the therapeutic anti-SAP mAb was very swiftly cleared from the circulation. The rate of decline in plasma concentration was related to the whole body amyloid load and was most rapid in subjects with substantial hepatic amyloidosis who had by far the greatest total amyloid burden. The dose of anti-SAP antibody was progressively increased in consecutive subjects in the FIH study, amyloid removal first being seen at 246 mg with reduction in hepatic amyloid load. Incrementally increased single doses in subsequent individual subjects up to a maximum of 2000 mg were generally well tolerated. In subjects in whom amyloid clearance was subsequently observed, anti-SAP mAb administration was generally associated with an initial pro-inflammatory cytokine spike followed by an acute phase response of CRP and SAA, accompanied by a decrease in plasma C3 concentration.

Consistent with the pre-clinical mechanism and the established molecular stoichiometry of classical pathway complement activation, the FIH study showed a close relationship between the estimated whole body load of amyloid-associated SAP and the dose of anti-SAP mAb required to trigger the systemic inflammatory response, plasma complement consumption and amyloid clearance. The available evidence is consistent with the antibody most easily and rapidly accessing amyloid deposits in the liver and spleen which have sinusoidal capillary endothelium specialised for maximal filtration of the blood through the parenchyma. By contrast cardiac capillaries have tight endothelial junctions in cardiac capillaries which is likely to restrict access to the myocardial extracellular space. Nevertheless pre-clinical work showed reduction in myocardial amyloid deposits with repeat anti-SAP dosing [Simons, 2013], and preliminary observations in the FIH study showed some evidence of engagement of target mechanism in the heart.

Although doses up to 2000 mg were well tolerated in those with a large (hepatic) amyloid load, much of the target patient population for this phase 2 study will have a small to moderate amyloid load. The dose response information from the FIH study in those with renal amyloidosis (also a small/moderate load population) show that a dose level of 600 mg is effective in about one third of the subjects treated but at a dose level of 1200 mg the response rate is substantially higher (>80%). It is recognized that while the dose of 1200 mg is associated with a high rate of amyloid clearance, it is also associated with rash which has been severe in one case. At this time the most likely causes of the rash are related to the peak concentration of the anti-SAP mAb. For this reason the anti-SAP mAb dose in this study will be split: administered as two infusions (duration of 6-8hr) on Days 1 and 3. This will have the effect of blunting the maximum concentration while maintaining a moderate concentration in the plasma for longer. This approach may also enhance delivery of anti-SAP mAb to the heart.

**Safety considerations.** Most subjects receiving more than 200 mg of anti SAP antibody in the FIH study experienced reactions varying in incidence and severity, which included headache; flushing; hot or cold feelings; chest discomfort; chills; facial, orbital and peripheral oedema; nausea; vomiting; diarrhoea; fatigue; tachycardia; pre-syncope. These symptoms were reduced by slowing or temporarily interrupting the infusion and were further mitigated by pre medication with a modest dose of hydrocortisone and chlorphenamine. However, over the next few days many recipients of anti-SAP antibody doses of 600 mg or more developed mild or moderate urticarial and/or macular rashes of

variable and sometimes extensive distribution. Urticaria responded well to antihistamine. Macular lesions were more persistent but resolved spontaneously without sequelae.

The risk of skin rashes will be mitigated by giving the anti-SAP mAb dose in two slowly infused portions on Days 1 and 3, with availability of a reduced dose schedule according to the safety assessment algorithm in Section 6.2. Emerging results will be reviewed regularly to enable dose reduction if necessary and to select the appropriate starting dose for Group 3.

#### **4.5.3. Dosing schedule for GSK2315698 (CPHPC) + GSK2398852 (anti-SAP mAb)**

There is an urgent need for rapid reduction in cardiac amyloid load in both AL and ATTR amyloidosis. The FIH study showed the anti-SAP intervention can remove systemic amyloid deposits from the abdominal viscera. The rate of amyloid clearance was apparently also similar in the patients as had been documented in the mouse model, with improvement towards normal hepatic stiffness indicating that the effect on liver amyloid of a single antibody dose is apparent by 2 weeks. The mechanistic basis for amyloid removal by Anti-SAP treatment is the same in the heart as in other tissues but there are no readily tractable experimental animal models of cardiac amyloidosis. Nevertheless in a transgenic mouse SAA model in which some cardiac amyloid is present, the deposits were reduced one month after two doses of anti-SAP administered a month apart [Simons, 2013]. Six patients with abundant cardiac amyloid were treated in the FIH study with up to 3 doses of anti-SAP mAb but the shortest interval between doses was 2 months. One subject showed a reduction in LV mass; others showed biomarker evidence of engagement of the PD mechanism and some evidence of this in the heart (transient rise in NT-proBNP). In order to achieve optimal efficacy as quickly as possible, Anti-SAP treatment will be administered monthly for up to six cycles in the present study. More frequent antibody dosing is not possible because it would require uninterrupted depletion of plasma SAP by continuous CPHPC dosing. This would risk excessive depletion of the amyloid-associated SAP target for the antibody, a sufficient density of binding to which is essential for triggering the crucial complement activation which attracts macrophages to form the MGCs and remove the amyloid.

Emerging results will be reviewed regularly to enable appropriate adjustment of initial and ongoing doses (Section 6.2.2)

#### **4.6. Benefit:Risk Assessment**

The purpose of the phase 2 study is to evaluate the benefit:risk profile of Anti-SAP treatment in ATTR and AL systemic amyloidosis patients with cardiac involvement. Summaries of the pre-clinical and clinical studies conducted with CPHPC alone and with CPHPC + anti-SAP mAb are presented in the IB [GlaxoSmithKline Document Number 2012N141587, GSK2398852 + GSK2315698 Investigator's Brochure].

#### **4.6.1. Risk Assessment**

The main identified risk for the phase 2 study is rash associated with administration of the anti-SAP mAb. The engagement of the antibody, complement and macrophage mechanisms of amyloid clearance within the myocardium carries a potential risk of cardiotoxicity.

##### **4.6.1.1. Potential for Cardiotoxicity**

The intended and desired PD mechanism by which anti-SAP mAb treatment mediates clearance of amyloid deposits from the extracellular space is absolutely dependent on antibody binding to amyloid deposits in the heart, activation of complement and attraction of macrophage infiltration and fusogenic activation to form MGCs. The clinical experience to date has been reassuring that these processes or the consequent removal of amyloid do not have adverse effects on tissues or organs, including the heart. However it could be speculated that cardiac function could be impaired through disturbance of electrophysiology and/or myocardial contractility or perfusion.

The present study design therefore includes comprehensive assessment and monitoring designed specifically to detect and characterize these and any other adverse cardiac effects which may arise. Baseline will include leadless non-implantable ECG analysis, for example using BodyGuardian, to provide the individual's own control profile for any changes following treatment. Monitoring during the study will comprise in-patient telemetry, out-patient leadless ECG analysis (e.g. BodyGuardian) between treatment sessions, monthly ECHO & CMR imaging, and serial monitoring of cardiac blood biomarkers. Any adverse effects on cardiac function will thus be detected promptly, enabling swift and appropriate intervention and management.

##### **4.6.1.2. Summary of rashes**

Many subjects who received 600 mg or more of anti-SAP mAb in the FIH study (SAP115570) developed variably, polymorphic urticarial and/or macular skin rashes with a range of different anatomical distribution, severity and persistence; though all but one were self-limiting. Skin biopsy in one affected subject shows leukocytoclastic vasculitis but importantly with no evidence of either fibrinoid changes or necrosis. There was also no demonstrable deposition of immunoglobulins, complement or immune complexes in the tissues. One AL amyloidosis patient who was concomitantly receiving an immunomodulatory drug (IMiD) (i.e. lenolidamide), had an erythema multiforme-like rash which rapidly responded to a short course of treatment with 60 mg oral prednisolone.

The pathogenic mechanism responsible for these rashes is not known but, importantly, it was not associated with any systemic symptoms, signs or organ dysfunction, and in particular, there was no evidence of arthritis or systemic vasculitis in the eye, kidneys or elsewhere.

In the present study subjects will be carefully monitored by the Investigator for development of any rash during or between treatment cycles, with additional timely review by a dermatologist if clinically indicated. Management of the rash specified in

Section [12.3 Appendix 3](#) may be modified during the study in light of emerging new immunological and pathological information.

#### **4.6.1.3. Potential for Circulating Immune Complex Formation**

Depletion of plasma SAP by CPHPC is never complete because the liver continues to produce about 100 mg of SAP daily. Infusion of anti-SAP mAb must therefore inevitably lead to formation of SAP-anti-SAP mAb immune complexes in the circulation. Initially these complexes must be in antibody excess and both experimental and clinical studies of immune complex disease indicate this antigen:antibody ratio is least likely to be pro-inflammatory. However as the anti-SAP antibody is rapidly cleared from the plasma due to its binding to the SAP target in amyloid deposits, formation of potentially inflammatory immune complexes could contribute to the infusion reactions and skin rashes caused by anti-SAP mAb treatment.

In order to mitigate this potential risk, blood samples for determination of SAP/anti-SAP mAb immune complexes will be taken from all subjects in this study as a safety measurement at the time-points specified in the Time & Events tables (Section [7.1](#)) and in the event of a rash. Timing of the assessments may be adjusted based on emerging data.

#### **4.6.1.4. Surveillance for Long-Term Toxicities**

All subjects will be asked to return for follow up assessments including cardiac imaging at 6 and 12 months post last anti-SAP mAb dose.

#### 4.6.2. Risk Assessment Table

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Investigational Product (IP) [GSK2398852; anti-SAP mAb]</b>		
Acute onset rash within first 7 days of infusing anti-SAP mAb	<p>Many patients who received 600 mg or more of anti-SAP mAb in the FIH study (SAP115570) developed variable polymorphic urticarial and/or macular skin rashes with a range of different anatomical distributions, severity, and persistence, with all but one case being self-resolving and self-limiting.</p> <p>Skin biopsy in one AL amyloidosis patient who had a diffuse maculopapular rash after being administered 600mg anti-SAP mAb on the first treatment session was reported as a leukocytoclastic vasculitis (LCV). In this biopsy sample there was no demonstrable deposition of immunoglobulins, complement or immune complexes in the tissues.</p> <p>A second AL amyloidosis patient with improving liver load (after 1<sup>st</sup> treatment session) had a diffuse rash after receiving 1G anti-SAP mAb on their 2<sup>nd</sup> treatment session. The morphological changes on skin biopsy would be consistent with a lymphocytic vasculitis/LCV although no definitive conclusion was reached by the reporting pathologist.</p>	<p>Dermatological monitoring</p> <p>Prompt clinical dermatology review and skin biopsy after onset of any skin rash (i.e. grade <math>\geq 1</math>)</p> <p>Use of topical or systemic anti-inflammatory medications including corticosteroids and anti-histamines</p> <p>Reduction of anti-SAP mAb dose and/or frequency if the mitigation strategies are not sufficient (see Section 6.2.2 &amp; Section 6.2.3)</p> <p>Discontinuation of anti-SAP mAb if rash persists or worsens despite mAb dose reduction and the subject is severely affected</p> <p>Immunosuppressive effects of dexamethasone and cyclophosphamide in the CyBorD chemotherapy regimen may suppress the rash</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Post-inflammatory hyperpigmentation (PIH)	<p>Some FIH study patients who experienced repeated rashes with repeat anti-SAP mAb dosing developed variable PIH.</p> <p>PIH is benign but may only resolve fully after weeks or months especially in darker skinned individuals. Subjects with hereditary cardiac amyloidosis caused by the V122I TTR variant, which is very largely confined to ethnicities originating in Africa, will thus be at greater risk.</p>	<p>All subjects who develop PIH will be monitored clinically for cumulative progression of PIH after each successive session of Anti-SAP treatment</p> <p>Dermatology review for all PIH occurrences</p> <p>DLQI questionnaire will be used for both acute rashes and PIH</p>
Infusion Reactions	<p>Most subjects receiving more than 200 mg of anti SAP antibody in the FIH study experienced reactions varying in incidence and severity, which included headache; flushing; hot or cold feelings; chest discomfort; chills; facial, orbital and peripheral oedema; nausea; vomiting; diarrhoea; fatigue; tachycardia; pre-syncope. These symptoms were reduced by slowing or temporarily interrupting the infusion and were further mitigated by pre-medication with a modest dose of hydrocortisone and chlorphenamine.</p>	<p>Total anti-SAP mAb dose given slowly over 6-8 hours, 2 days apart.</p> <p>Interrupting the infusion and/or reducing the rate of administration of each mAb infusion</p> <p>Hydrocortisone premedication with a single 100 mg IV bolus</p> <p>Antihistamine premedication</p> <p>Careful monitoring of blood pressure, fluid balance and urine output with immediate access to IV fluids, especially in subjects with any impairment of renal function and or development of hypotension and/or vomiting and/or arrhythmias.</p> <p>Use of anti-emetics for nausea &amp; vomiting</p>
Myocarditis Cardiac remodelling associated with removal of amyloid	<p>The intended and desired PD mechanism by which anti-SAP mAb treatment mediates clearance of amyloid deposits from the extracellular space is absolutely dependent on antibody binding to amyloid deposits in the heart, activation of complement and attraction of</p>	<p>Comprehensive inpatient and outpatient cardiac monitoring comprising:</p> <p>Serial heart rate and blood pressure measurement</p> <p>Continuous inpatient telemetry during and after each infusion</p>



Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>macrophage infiltration and fusogenic activation to form MGCs. The clinical experience to date has been reassuring that these processes or the consequent removal of amyloid do not have adverse effects on tissues or organs, including the heart. However it could be speculated that cardiac function could be impaired through disturbance of electrophysiology and/or myocardial contractility or perfusion.</p>	<p>of anti-SAP mAb</p> <p>Serial 12-lead ECG recording</p> <p>Serial assay of plasma cardiac troponin T and NT-proBNP concentration</p> <p>Serial ECHO</p> <p>Serial CMR imaging</p> <p>CMR &amp; ECHO imaging at 6 &amp; 12 months after the final anti-SAP mAb treatment</p> <p>Non-implantable, ECG recording devices (e.g. BodyGuardian) will be used to detect abnormalities in cardiac electrophysiology on discharge from in-patient stay and at 8-week and 6-month follow-up</p>
<b>Investigational Product (IP) [GSK2315698 - CPHPC]</b>		
Epistaxis	<p>Small volume nose bleeds have been noted in a few subjects in previous studies. These events have been self-limiting and not associated with any evidence of thrombocytopenia or coagulopathy. The relationship to Anti-SAP treatment is not apparent.</p> <p>Group 3 patients will receive GSK2315698 at the same time as CyBorD chemotherapy which is known to cause thrombocytopenia and anaemia, potentially increasing the severity of epistaxis.</p>	<p>Serial blood haematology and baseline and session 1 post dose coagulation assessment.</p> <p>Serial coagulation if epistaxis or other bleeding abnormalities occur. If abnormalities are observed in coagulation tests, additional investigations including platelet function tests may be performed.</p> <p>Serial heart rate and blood pressure measurement</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Chemotherapy</b>		
Overlapping of acute toxicity between anti-SAP mAb and bortezomib-containing chemotherapy	Cyclophosphamide, bortezomib & dexamethasone (CyBorD) and other cytotoxic chemotherapy regimens used in AL amyloidosis have systemic adverse effects including nausea, vomiting, hypotension and diarrhoea, which are also symptoms of the infusion reactions caused by anti-SAP mAb	Anti-SAP mAb will be administered at least 48 hours before the start of a chemotherapy cycle to minimise overlap of acute toxicity.
Attenuation of PD efficacy of anti-SAP antibody by chemotherapy agents	Amyloid clearance mediated by anti-SAP antibody depends absolutely on attraction of macrophages to the amyloid deposits, their fusion into MGCs and the efficient functioning of these cells. The effects on these processes of high dose dexamethasone and of the cytotoxic chemotherapy agents within the drug combinations used in AL amyloidosis are not known.	Anti-SAP mAb will be administered at least 48 hours before the start of a chemotherapy cycle to minimise risk of attenuation of the efficacy of anti-SAP mAb by the anti-inflammatory and cytotoxic actions of the chemotherapy drugs.
Myelosuppression, thrombocytopenia, neutropenia and sepsis	Cyclophosphamide, bortezomib & dexamethasone (CyBorD) and other cytotoxic chemotherapy regimens used in AL amyloidosis have inevitable myelosuppressive effects, often leading to symptomatic anemia and other cytopenias and their complications, including sepsis	<p>Serial haematology</p> <p>Platelet and red blood cell replacement / transfusion, and / or use of granulocyte colony stimulating factor for severe neutropenia, as directed by the treating haematologist</p> <p>Serial monitoring of body temperature, CRP, heart rate and blood pressure</p> <p>Sepsis management according to standard local procedures for neutropenic patients.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Bortezomib-induced rashes	There are limited data on bortezomib-induced rashes in AL amyloidosis chemotherapy. However, in patients with recurrent, treatment refractory, multiple myeloma, bortezomib when incorporated into similar chemotherapy regimens has been reported to cause rashes in approximately 20% of recipients, predominantly CTC grades 1 -2 with severe CTC grades 3 – 4 in < 1% [Richardson, 2003]. The rashes are polymorphic in clinical characteristic with different histological appearances including leukocytoclastic vasculitis [Agterof , 2005], and lymphocytic vasculitis [Pour, 2005].	The intermediate dose CyBorD schedule which will be used in Group 3 subjects. - weekly administration of bortezomib during a 5-week cycle, this provides a high clonal response rate [Kropff, 2007] and is known to cause fewer rashes than CyBorD regimens that involve biweekly administration of bortezomib [Case, 2012]
<b>CMR Contrast Agent - gadolinium (Gd)</b>		
Delayed excretion and tissue accumulation of gadolinium contrast agent after repeated contrast CMR scans	<p>Gadolinium is mostly excreted in the urine and this is impaired in subjects with reduced renal function. Patients with systemic AL amyloidosis very often have renal amyloid and impaired renal function while cardiac ATTR patients are all elderly and therefore may also have non-amyloid chronic kidney disease. All these individuals are therefore at increased risk of Gd accumulation.</p> <p>FDA and MHRA have issued an alert for tissue accumulation of Gd in organs including the brain following its repeated use, including some patients with normal renal function, although no new neurological complications have been reported to date</p>	<p>Exclusion of patients with GFR &lt; 40 mL/min</p> <p>GFR will be checked prior to each Gd contrast CMR and if GFR is &lt;40mL/min then CMR without Gd contrast will be performed</p> <p>Gd contrast CMR will be performed at five scheduled visits over the 18 month study period</p> <p>Other CMR scans will be without Gd contrast</p> <p>Gd contrast agents for this study are gadoteric acid, gadoteridol, and gadobutrol.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Nephrogenic systemic fibrosis (NSF) / dermatopathy (NSD)	A very rare cause of cutaneous and, even more rarely, systemic fibrosis, including in the heart, caused by Gd contrast agents, with typical rash and characteristic histopathology. Possibly related to impaired renal function.	Exclusion of patients with GFR < 40 mL/min (see exclusion criteria) Serial monitoring of serum creatinine Dermatological inspection for rashes. Skin biopsy if clinically indicated.
Allergic reactions to Gd contrast	Gd contrast agents can cause allergic reactions especially with IV bolus administration	History before infusion regarding any reactions to previous imaging contrast agents. Slow IV infusion of Gd contrast with ability to stop immediately if subject develops symptoms.
<b>Procedural risks</b>		
Skin biopsy	Skin biopsy is a minimally invasive procedure but has been associated with scarring, bleeding and infection.	Skin biopsies will be taken from non-sensitive areas only. Biopsies will not be taken from the head, neck, hands, feet or genitalia. To minimise the risk of bleeding the biopsy site will be sutured or 'steri-strip' applied as per site policy All skin biopsies should be undertaken by trained individuals under aseptic conditions according to site policy
Cumulative radioactivity from scans	Ionising radiation exposure from SAP scan (UK Groups 2&3 only) comes from the administered radioligand and CT examination. The total radiation burden per subject is calculated as 8 mSv per SAP scan; total 16 mSv for two scans and this corresponds to a lifetime risk of a fatal malignancy of about 1 in 1250 [ICRP, 2007]. Group 1 subjects will undergo a <sup>99m</sup> Tc-DPD or <sup>99m</sup> Tc-PYP	Subjects will undergo baseline and post treatment scan thus will remain below the 20mSv exposure limit recommendation. The scans are medically justified and provide proven evidence of changes in amyloid load.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>bone scan and will be exposed to 6.7mSv per scan, total 13.4 mSv for two scans and this corresponds to a lifetime risk of a fatal malignancy of about 1 in 1500 [ICRP, 2007]</p> <p>Subjects will receive either an SAP scan or a DPD scan, not both.</p> <p>The International Commission on Radiological Protection (ICRP) 2007 has recommended a maximum occupational adult effective dose limit of 20 mSv per year, averaged over a defined period of 5 years (not exceeding 50 mSv in a single year) [ICRP, 2007]</p>	

#### **4.6.3. Benefit Assessment**

Extracellular deposition of amyloid fibrils is the major and overwhelmingly most important cause of organ damage and disease in systemic amyloidosis. Study SAP115570 confirmed that clearance of amyloid from the tissues (liver) improved function towards normal. The major causes of cardiac dysfunction in cardiac amyloidosis are restrictive cardiomyopathy, which is directly related to the myocardial stiffness produced by infiltration of the heart with stiff inelastic amyloid, and arrhythmias. Thus a reduction in cardiac amyloid load by Anti-SAP treatment has the potential to improve diastolic filling, increase stroke volume and restore cardiac output towards normal. Similarly normalisation of myocardial architecture with reduction of the ECV, which is substantially expanded and distorted by amyloid, has the potential to reduce the electrophysiological instability responsible for arrhythmias.

#### **4.6.4. Overall Benefit:Risk Conclusion**

Cardiac involvement in AL and ATTR-CM amyloidosis is the major cause of morbidity and mortality. If Anti-SAP treatment reduces the cardiac amyloid load sufficiently to improve cardiac function, alleviate heart failure and prevent ventricular arrhythmias, it has the potential to have a substantial impact on quality and duration of life in these conditions whilst also reducing hospital admissions and other medical treatment. The infusion reactions and skin rashes experienced so far are considered manageable and mitigation plans are in place. The hypothetical cardiac risks are important but preliminary safety in six patients with cardiac amyloidosis is encouraging.

On the basis that this treatment has potential for substantial benefit that cannot be obtained from existing treatments, the potential and identified risks are considered manageable and thus acceptable.

## 5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigators Brochure [IB GlaxoSmithKline Document Number [2012N141587](#)].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

### 5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Between 18 and 80 years of age inclusive, at the time of signing the informed consent.

SEX
<p>2. <b>Gender:</b> Male and female.</p> <p><b>Males:</b></p> <p>Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication for a cycle of spermatogenesis following five terminal half-lives after the last dose of study medication.</p> <ol style="list-style-type: none"> <li>Vasectomy with documentation of azoospermia.</li> <li>Male condom plus partner use of one of the contraceptive options below: <ul style="list-style-type: none"> <li>Contraceptive subdermal implant</li> <li>Intrauterine device or intrauterine system</li> <li>Combined Oral Contraceptive [<a href="#">Hatcher</a>, 2007] or Injectable progestogen [<a href="#">Hatcher</a>, 2007]</li> <li>Contraceptive vaginal ring [<a href="#">Hatcher</a>, 2007]</li> <li>Percutaneous contraceptive patches [<a href="#">Hatcher</a>, 2007]</li> </ul> </li> </ol> <p>This is an all-inclusive list of those methods that meet the following GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. For non-product methods (e.g., male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [<a href="#">ICH, M3 (R2)</a>]</p>

2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

### Females

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative Urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:

- Documented tubal ligation
- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy

- Postmenopausal defined as:

≥60 years old

Twelve(12) months of spontaneous amenorrhea with an appropriate clinical profile, e.g. age appropriate, > 45 years, in the absence of hormone replacement therapy (HRT) or medical suppression of the menstrual cycle (e.g. leuprolide treatment) in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and oestradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on HRT and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see [Appendix 6](#)) from 30 days prior to the first dose of study medication and until 3 months after the last dose of study medication.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception

### INFORMED CONSENT

3. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form

### OTHER

4. Late-Gadolinium enhancement (LGE) on CMR indicative of cardiac amyloidosis



## Inclusion Criteria for Group 1

[1] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
<p>5. ATTR cardiomyopathy (ATTR-CM)</p> <p>a) Subjects with a diagnosis of hereditary ATTR amyloidosis should have a known amyloidogenic TTR mutation demonstrated by genotyping AND is recognised to be primarily associated with cardiomyopathy AND one of the following:</p> <p>Definite histochemical identification of amyloid by Congo red staining and green birefringence in crossed polarised light in cardiac or other tissue biopsy and identification of TTR as the amyloid fibril protein either by immunohistochemistry or proteomic analysis.</p> <p>Note: Subjects with a confirmed mutation but who have not been biopsied may be eligible if they have an affected close blood relative whose amyloid has been confirmed histochemically. Such cases should be discussed with the Medical Monitor.</p> <p>OR</p> <p>Scintigraphy: <sup>99m</sup>Tc-DPD with Grade 2 cardiac uptake or <sup>99m</sup>Tc-PYP with either Grade 2 or 3 cardiac uptake.</p> <p>b) Subjects with a diagnosis of wild type ATTR-CM must be negative by genotyping AND have one of the following:</p> <p>Definite histochemical identification of amyloid by Congo red staining and green birefringence in crossed polarised light in cardiac or other tissue biopsy <b>and</b> identification of TTR as the amyloid fibril protein either by immunohistochemistry or proteomic analysis</p> <p>OR</p> <p>Scintigraphy <sup>99m</sup>Tc-DPD with Grade 2 cardiac uptake or <sup>99m</sup>Tc-PYP with Grade 2 or 3 cardiac uptake.</p> <p>6. LVmass on CMR &gt; 200g</p> <p>7. Clinically stable in New York heart association (NYHA) class 2 or 3 for the 3 months preceding screening</p>

**Inclusion Criteria for Group 2**

[1] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
<p>8. Subject medically diagnosed with AL amyloidosis that has required chemotherapy or an autologous stem cell transplant based upon:</p> <p>AL amyloidosis confirmed by biopsy with immunohistochemical staining or proteomic identification of AL amyloid fibril type, in subjects with definite monoclonal gammopathy in whom causative mutations of amyloidogenic genes have been excluded</p> <p>9. Clinically stable in NYHA class 2 or 3 for the 3 months preceding screening</p> <p>10. <math>\geq 6</math> months after completing any line of chemotherapy, or after autologous stem cell transplantation, and having attained either a very good partial response (VGPR) or a complete response (CR), and without the need for haematological maintenance therapies</p> <p>11. LV mass on CMR <math>&gt; 150</math>g</p>

**Inclusion Criteria for Group 3**

[1] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
<p>12. Newly diagnosed AL amyloidosis based upon:</p> <p>AL amyloidosis confirmed by biopsy with immunohistochemical staining or proteomic identification of AL amyloid fibril type in subjects with definite monoclonal gammopathy in whom causative mutations of amyloidogenic genes have been excluded</p> <p>13. Mayo stage II or IIIa</p> <p>14. Confirmed free light chain complete response (CR) during the first three cycles of first-line chemotherapy where at least the first cycle has been with CyBorD</p> <p>15. LV mass on CMR <math>&gt; 150</math>g</p>

## 5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
<ol style="list-style-type: none"> <li>1. Cardiomyopathy primarily caused by non-amyloid diseases (e.g. ischemic heart disease; valvular heart disease)</li> <li>2. Interval from the Q wave on the ECG to point T using Fredericia's formula (QTcF) &gt; 500 msec</li> <li>3. Sustained / symptomatic monomorphic ventricular tachycardia (VT), or rapid polymorphic VT, at screening</li> <li>4. Unstable heart failure defined as emergency hospitalization for worsening, or decompensated heart failure, or syncopal episode within 1 month of screening.</li> <li>5. Implantable cardiac defibrillator (ICD) or permanent pacemaker (PPM) at screening</li> <li>6. NT-proBNP &gt;8500ng/L</li> <li>7. Glomerular filtration rate (GFR) at Screening &lt; 40 mL/min</li> <li>8. Any active and persistent dermatological condition</li> <li>9. Existing diagnosis of any type of dementia</li> <li>10. History of allogeneic stem cell transplantation, prior solid organ transplant, or anticipated to undergo solid organ transplantation, or left ventricular assist device (LVAD) implantation, during the course of the study.</li> <li>11. Malignancy within last 5 years, except for basal or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix that has been successfully treated. <i>Note: Subjects with a history of other malignancies that have been curatively treated may be eligible, but must be discussed with and approved by the Medical Monitor.</i> Previous or current diagnosis of symptomatic multiple myeloma</li> <li>12. Acute coronary syndrome, or any form of coronary revascularization procedure (including coronary artery bypass grafting [CABG]), within 6 months of screening.</li> <li>13. Stroke within 6 months of screening, or transient ischaemic attack (TIA) within 3 months of screening</li> <li>14. Symptomatic, clinically significant autonomic neuropathy which the Principal Investigator (PI) feels will preclude administration of study treatment</li> <li>15. Hypoalbuminaemia (serum albumin &lt; 30 g/L)</li> <li>16. Uncontrolled hypertension during screening</li> <li>17. Alanine transaminase ALT &gt;3x upper limit of normal (ULN) AND bilirubin &gt;1.5xULN (isolated bilirubin &gt;1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin &lt;35%)</li> </ol>

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
18. Peripheral oedema at Screening that in the opinion of the PI or designee might prevent adequate absorption of subcutaneously administered CPHPC
19. Urine dipstick positive (>1+) for blood during screening with investigation indicating glomerular haematuria. If other causes are identified, subjects may be enrolled on resolution of the abnormality
20. Presence of any co-morbid or an uncontrolled medical condition (e.g. diabetes mellitus), which in the opinion of the investigator would increase the potential risk to the subject. <i>Investigator should liaise with the Medical Monitor where there is uncertainty as to the eligibility of a patient</i>
21. Positive test for hepatitis B hepatitis C, and / or human immunodeficiency virus (HIV) during screening, or within 3 months prior to first dose of study treatment
22. Unwillingness or inability to follow the procedures outlined in the protocol

CONCOMITANT MEDICATIONS
23. Use of GSK2315698 (CPHPC), or participation in a separate clinical trial involving CPHPC within 3 months of screening
24. Any prohibited concomitant medication as per Section 6.10.2 within 28 days of screening

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
25. Donation of blood or blood products in excess of 500 mL within 84 days of screening
26. Lactating females
27. Poor or unsuitable venous access
OTHER
28. Treatment with another investigational drug, biological agent, or device within 6 months of screening, or 5 half-lives of the study agent, whichever is longer.
CONTRAINDICATIONS
29. History of sensitivity to any of the study medications, or metabolite thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation

CARDIAC MAGNETIC RESONANCE (CMR) SCANNING
<p>30. Orthopnoea of sufficient severity to preclude supine scanning as determined at screening</p> <p>31. Contraindication to MRI contrast agents</p> <p>32. Inability to fit inside scanner due to body size (girth)</p> <p>33. Contraindication for MRI scanning (as assessed by local MRI safety questionnaire), which includes but is not limited to:</p> <ul style="list-style-type: none"> <li>a. Intracranial aneurysm clips (except Sugita) or other metallic objects</li> <li>b. Intra- orbital metal fragments that have not been removed</li> <li>c. Pacemakers or other implanted cardiac rhythm management/monitoring devices and non-MR conditional heart valves</li> <li>d. Inner ear implants</li> <li>e. History of claustrophobia</li> </ul>

<sup>99m</sup> Tc-PYP OR <sup>99m</sup> Tc-DPD BONE TRACER RADIOSCINTOGRAPHY
<p>34. Orthopnoea of sufficient severity to preclude supine scanning as determined at Screening</p> <p>35. Previous allergic reaction to radioisotope bone tracers</p> <p>36. Previous inclusion in a research protocol involving nuclear medicine, positron emission tomography (PET) or radiological investigations with significant radiation burden (a significant radiation burden being defined as 10 mSv in addition to natural background radiation, in the previous 3 years).</p>

### Exclusion Criteria for Group 1

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
<p>37. Has any of the following:</p> <ul style="list-style-type: none"> <li>a. Fulfilment of diagnostic criteria for AL amyloidosis</li> <li>b. TTR polyneuropathy and / or intracranial TTR involvement including ophthalmological disease</li> </ul> <p>38. Non-amyloidosis related chronic liver disease (with the exception of Gilbert's syndrome or clinically asymptomatic gallstones) Note: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice</p> <p>39. Platelet count &lt; 125x10<sup>9</sup> / L</p>

**Exclusion criteria for Group 2**

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
40. Chronic liver disease or current active liver or biliary disease not attributable to amyloidosis (with the exception of Gilbert's syndrome or asymptomatic gallstones). <i>Note: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice</i>

**Exclusion criteria for Group 3**

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
41. Chronic liver disease or current active liver or biliary disease not attributable to amyloidosis (with the exception of Gilbert's syndrome or asymptomatic gallstones). <i>Note: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice</i>
42. Platelet count < 75x10 <sup>9</sup> /L

**5.3. Screening/Baseline/Run-in Failures**

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently enrolled. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory Authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.4).

**5.4. Withdrawal/Stopping Criteria**

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last

known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Individual subjects may be withdrawn at the Investigator's discretion at any time during the Study, provided there is a valid and confirmable clinical reason. The presence of severe AEs predefined as stopping criteria below in Section 5.4, or severe adverse events (SAE) as defined in Section 12.5, Appendix 5, will lead to the withdrawal of an individual subject. Withdrawn subjects will be replaced by new subjects as per the guidance in Section 5.5

**Whenever possible subjects must complete CPHPC maintenance following anti-SAP mAb dose for safety reasons (Section 4.5).**

#### **5.4.1. Liver Chemistry Stopping Criteria**

**Liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the food & drug administration [FDA] premarketing clinical liver safety guidance).  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Liver Safety Required Actions and Follow-up Assessments Section can be found in Section 12.2, Appendix 2.

##### **5.4.1.1. Study Treatment Restart or Rechallenge**

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

#### **5.4.2. Renal Function Stopping Criteria**

Dosing of a subject with study treatment will be stopped permanently if 24-hour creatinine clearance is confirmed as  $< 30\text{mL/min}$ .

If a subject's estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) is  $< 40\text{ mL/min/1.73m}^2$  or if the eGFR by MDRD decreases from baseline by  $> 50\%$ , this will trigger a further investigation.

Subjects who have eGFR  $30 - 40\text{ mL/min/1.73m}^2$  (or 24-hour creatinine clearance [CrCl] of  $30 - 40\text{ mL/min}$ ) will continue treatment at the discretion of the Investigator in consultation with the Medical Monitor. If the GFR or CrCl remains below 40

mL/min/1.73m<sup>2</sup> or mL/min respectively at the time of the next scheduled contrast enhanced CMR then a non-enhanced CMR will be performed. If the CrCl recovers to  $\geq 40$  mL/min then a contrast enhanced CMR should be performed at the next scheduled CMR).

Whenever possible subjects must complete CPHPC maintenance following anti-SAP mAb dose for safety reasons (dose adjustment of CPHPC may be necessary - see [Table 2](#)).

#### **5.4.3. Platelet Stopping Criteria**

In the event of a platelet count  $<30 \times 10^9/L$  no further AntiSAP treatment will be administered until the platelet count returns to  $\geq 30 \times 10^9/L$ .

#### **5.4.4. Neutrophil Stopping Criteria**

In the event of a neutrophil count  $\leq 0.5 \times 10^9 / L$  no further AntiSAP treatment will be administered until the neutrophil count returns to  $> 0.5 \times 10^9 / L$ .

Subjects who experience a septic episode during the study, febrile neutropenia or otherwise, should be treated with antibiotics according to local study site protocols, and must not receive any further AntiSAP treatment until sufficient clinical resolution from the septic episode has occurred as determined by the Investigator.

#### **5.4.5. Cardiovascular Safety Stopping Criteria**

##### **5.4.5.1. Individual subject cardiovascular stopping criteria**

A subject who meets any criterion below will be withdrawn from the study.

1. Acute coronary syndrome or myocardial infarction
2. Decompensated heart failure, or worsening heart failure that is refractory to medical management
3. **New** & symptomatic bradyarrhythmia
4. **New** sustained monomorphic VT, or development of new rapid polymorphic VT, or new VF
5. Symptomatic myocarditis
6. Requirement for LVAD implantation, or consideration of urgent cardiac transplantation during the Study
7. Development of any rhythm disorder during the study which requires *treatment* with a permanent cardiac pacemaker, or ICD. Subjects who require insertion of a permanent cardiac pacemaker or an ICD for prophylactic reasons may continue—see Section [7.4.7.3](#)



#### **5.4.6. QTc Stopping Criteria**

- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

##### **5.4.6.1. Individual Subject QTcF Stopping Criteria**

A subject who meets either criterion below will be withdrawn from the study treatment.

QTcF correction formula should be used throughout, including at screening and for discontinuation of any individual subject at any time during the study.

QTcF  $\geq$  530msec, irrespective of bundle branch block status

or,

Change from baseline: QTcF  $>$  60 msec

#### **5.4.7. Dermatological Toxicity Stopping Criteria**

##### **5.4.7.1. Individual subject dermatological stopping criteria**

A subject who meets any criterion below will be withdrawn from further treatment in the study.

- Grade 4 Common Terminology Criteria (CTC) skin rash
- Peripheral oedema which is deemed by the Investigator to be affecting the systemic absorption of SC CPHPC (CPHPC administration should continue by intravenous (IV) infusion to Day 11)
- Skin toxicity of any CTC grade which is refractory to dermatological treatment
- Clinical evidence of skin necrosis, irrespective of CTC rash grade, at any time during the study
- Symptoms of a systemic vasculitis, including but not restricted to, development of new arthritis or iritis, vasculitic purpura or other lesions of skin and/or mucous membranes and/or retina, and / or clinical evidence of organ dysfunction (e.g. nephritis)

#### **5.4.8. Haematological Stopping Criteria (Groups 2 & 3)**

##### **5.4.8.1. Individual subject haematological stopping criteria**

A subject who meets any criterion below will be withdrawn from the study.

- Confirmed haematological clonal relapse requiring immediate chemotherapy

#### **5.4.9. Study Safety Stopping Criteria**

If any of the following are recorded and considered potentially related to Anti-SAP treatment this will trigger a full safety review and no new recruitment into the study will occur:

**Cardiac:** Development of symptomatic myocarditis

**Dermatological:** Development of CTC Grade 4 rash

**Immunological:** Clinical evidence of a systemic vasculitis affecting any visceral organ

In the event that recruitment is temporarily halted, this will be reported to relevant regulatory and ethics authorities. Resumption of recruitment will only take place with the permission of the relevant authorities.

#### **5.5. Subject Withdrawal Procedures**

Subjects withdrawn following one or more administrations of anti SAP mAb should follow the procedures at the 8 week follow-up visit shown in the Time and Events Table.

Subjects withdrawn following administration of CPHPC but no administration of anti SAP mAb should follow the procedures at the 8 week follow-up visit shown in the Time and Events Table, with the exception of: Blood sampling for anti-SAP mAb, Cardiac MRI, ECHO, <sup>99m</sup>Tc-DPD / PYP scans (Group 1 only), SAP Scan (Groups 2 & 3, UK only) or out-patient cardiac monitoring.

#### **5.6. Replacement of Withdrawn Subjects**

For each group, subjects withdrawn from study treatment prior to completion of three Anti-SAP treatment sessions will be replaced. Subjects requiring insertion of a PPM or ICD prior to completion of three Anti-SAP treatment sessions will also be replaced.

#### **5.7. Subject and Study Completion**

A completed subject is one who has completed at least three courses of AntiSAP treatment and including the 8 week follow-up visit.

The end of the study is defined as the last subject's last visit.

## 6. STUDY TREATMENT

### 6.1. Investigational Product and Other Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments

#### 6.1.1. Anti-SAP treatment

	<b>Study Treatment</b>	
<b>Product name:</b>	GSK2315698 (CPHPC)	GSK2398852 (anti-SAP mAb)
<b>Dosage form:</b>	GSK2315698 Solution for Subcutaneous Injection or Intravenous Infusion, 200 mg/mL	GSK2398852 Concentrate for Solution for Infusion, 100 mg/mL
<b>Unit dose strength(s)/Dosage level(s):</b>	Unit dose strength: 200mg/mL provided as 2mL solution per vial Dosage levels: variable dependent on renal function	Unit dose strength: 100 mg/mL provided as 1 mL solution per vial.  Dosage levels variable (1200mg, 900mg, 600mg or 300mg)
<b>Route/ Administration/ Duration:</b>	Intravenous infusion usually for 48 hours and up to 72 hours Subcutaneous injection up to 3x daily for 11 days from initial mAb dose per treatment session	Intravenous infusion to be administered over 2 days (Day 1 and Day 3) with 6-8h infusion/day.
<b>Dosing instructions:</b>	Study medication will be diluted in 0.9% w/v sodium chloride and administered by intravenous infusion by study personnel following specified regimens and by subcutaneous injection by study personnel in in-patient setting and by subject in out-patient setting	Study medication will be diluted in 0.9% w/v sodium chloride and administered by intravenous infusion by study personnel following specified regimens
<b>Manufacturer/ source of procurement:</b>	Manufactured and supplied by GSK [0.9% w/v sodium chloride for dilution sourced locally by site]	Manufactured and supplied by GSK [0.9% w/v sodium chloride for dilution sourced locally by site]

## 6.2. Planned Dose Adjustments- Subject Specific Dose Adjustment Criteria

### 6.2.1. CPHPC dosing regimen according to renal function

**Table 2 CPHPC dosing regimen according to renal function**

Renal Function eGFR <sup>a</sup> (mL/min/1.73m <sup>2</sup> )	IV dose level	SC dose regimen	Time points of SC administration		
			Day 1 <sup>b</sup> 1st mAb dose per treatment session	Subsequent days (Days 2-10)	Subsequent day (Day 11)
≥ 64	20mg/hour	60 mg t.i.d	14:00, 22:00	08:00, 14:00, 22:00	08:00
≥ 46 and < 64	10mg/hour	60 mg t.i.d	14:00, 22:00	08:00, 14:00, 22:00	08:00
≥ 39 and < 46	10mg/hour	60 mg b.i.d	21:00	09:00, 21:00	09:00
≥ 33 and < 39	5mg/hour	60 mg b.i.d	21:00	09:00, 21:00	09:00
≥ 27 and < 33	5mg/hour	60 mg o.d	-	09:00	09:00

- a. eGFR determined by MDRD must be used to define CPHPC dose based on renal function. The most recent eGFR value available at the time of the pharmacy prescription being prepared will be used to determine the CPHPC dosing requirement for the treatment session. Should subsequent eGFR results within that treatment session show a change in eGFR, the CPHPC dosing requirement will not be altered as a result. Changes to eGFR which the Investigator considers to be a safety concern should be discussed with the Medical Monitor.
- b. IV CPHPC on Day 1 stops at ~09:00  
t.i.d. = three times daily; b.i.d. = two times daily; o.d. = once daily

### 6.2.2. Dose-Level Reduction Schedule for anti-SAP mAb Due to Adverse Events

**When it is deemed clinically appropriate, the Investigator is advised to maintain the dose-intensity of anti-SAP mAb throughout the study.**

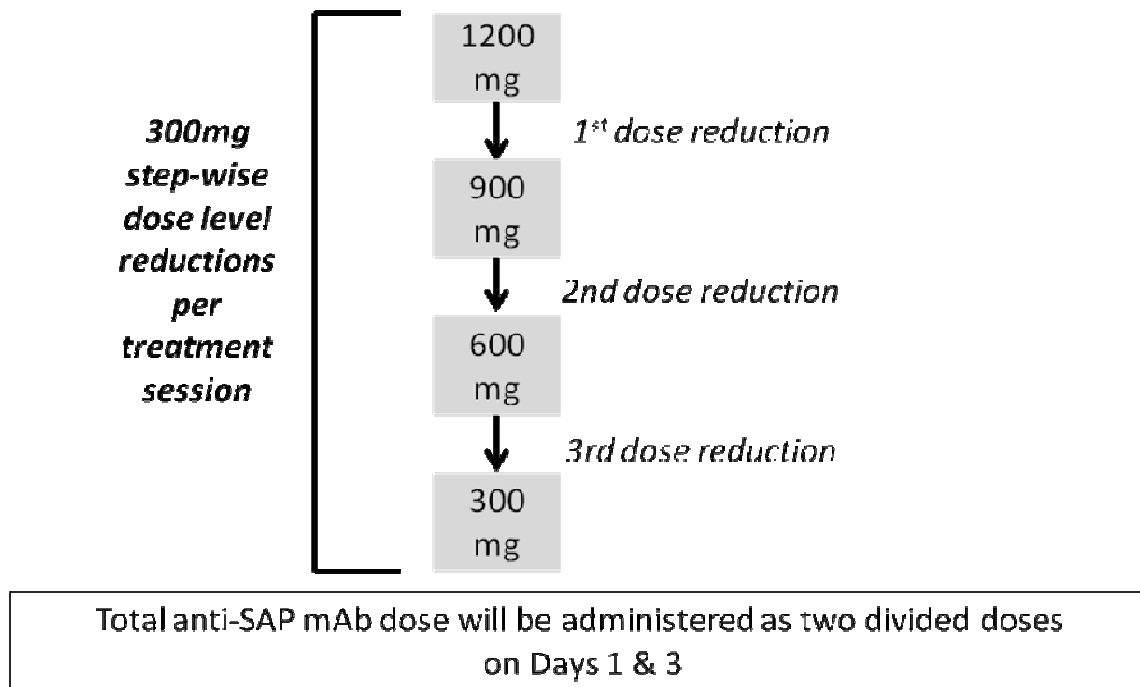
Reductions in dose level are at the discretion of the Investigator in consultation with the GSK study team during the dose confirmation meeting, and can be triggered based upon the intensity of the adverse event (AE) which is observed during any treatment session and is reasonably attributable to anti-SAP mAb. (See [Figure 4](#)). The recommended dose reduction scheme is provided in [Figure 4](#) although greater than 300 mg reductions would be allowed based on clinical tolerability.

- First dose reduction will be to 900 mg (300mg on D1, 600mg on D3)
- Second dose reduction to 600mg (300mg on D1, 300mg on D3)
- Third dose reduction to 300mg (150mg on D1, 150mg on D3)

**No further dose modifications will be permitted below the 300mg dose level.**

**Note:** If a dose reduction is required following Session 1, then the Session 2 mAb dose level will be 300mg ('c' in the above list).

If tolerability is unacceptable at the 300mg dose level, the Investigator must withdraw the subject from further study treatment, and inform the Medical Monitor at the earliest possible opportunity.

**Figure 4      Dose-Reduction Schedule for anti-SAP mAb****6.2.3.      Dose-Interval Extension between Anti-SAP Treatment Sessions**

At the Investigator's discretion and in consultation with the GSK study team during the dose confirmation meeting an Anti-SAP treatment session may be delayed up to a maximum of 1 month (i.e. maximum anti-SAP mAb treatment interval of 8 weeks) to allow for clinical stabilisation and / or recovery of incompletely resolved adverse events caused by any constituent of Anti-SAP treatment, or chemotherapy in Group 3 patients.

**The Investigator must review the affected subject's status on at least a weekly basis (or more frequently based on the AE) until the AE(s) has completely resolved.**

Administration of the next Anti-SAP treatment should be scheduled at the earliest possible opportunity after the Investigator has deemed the subject to have recovered sufficiently to continue treatment.

Subjects must be withdrawn from further study treatment if the persistent AE(s) is still deemed by the Investigator to be insufficiently resolved to allow further treatment 8 weeks after administration anti-SAP mAb.

Please refer to [Appendix 3](#) for detailed management of anti-SAP mAb skin rashes

**6.2.4.      Dose Modifications for Skin Rashes**

Refer to Section [12.3 Appendix 3](#)

Dose reduction of anti-SAP mAb will be based upon the clinical grade (intensity) of the rash and its duration (persistence) until complete resolution of active lesions during each monthly Anti-SAP treatment session.

The available clinical, immunological and pathological findings from each rash affected subject (see Section 12.3, Appendix 3) will be discussed at the Individual Subject Review meeting (see Section 10.8.1) before administration of the next scheduled Anti-SAP treatment session.

### **6.3. Blinding**

This is a non-randomised open-label study. All Investigators and GSK Study Team members, except those involved in central imaging core laboratory review, have direct access to the subject's individual study treatment and dosing schedules for each constituent drug.

All CMR & ECHO cardiac imaging investigations, but not the  $^{99m}\text{Tc}$ -DPD or  $^{99m}\text{Tc}$ -PYP scintigraphy, will be centrally reviewed at designated central core laboratories.

CMR & ECHO after each Anti-SAP treatment session will be assessed at the study site as part of safety evaluation.

### **6.4. Packaging and Labelling**

The contents of the label will be in accordance with all applicable regulatory requirements.

### **6.5. Preparation/Handling/Storage/Accountability**

A description of the methods and materials required for preparation of GSK2398852 and GSK2315698 will be detailed in a Study Specific Technical Agreement/Memo (TTS) or Pharmacy Manual which will be accompanied by a Quality Agreement.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the study reference manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case

of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- Material Safety Data Sheets (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

## **6.6. Compliance with Study Treatment Administration**

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

Subjects will be dosed at the site, and will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

CPHPC (prior to anti-SAP mAb administration) and anti-SAP mAb will be intravenously administered to subjects at the site. Administration will be documented in the source documents and reported in the CRF.

## **6.7. Treatment of Study Treatment Overdose**

For this study, any dose of CPHPC or anti-SAP mAb greater than the intended dose within the scheduled dosing period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

## **6.8. Treatment after the End of the Study**

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Given the lack of information about the safety and efficacy of Anti-SAP treatment in AL and ATTR-CM, treatment will not be provided after the end of the study. This may be reviewed once more information is available.

## **6.9. Lifestyle and/or Dietary Restrictions**

The following restrictions apply from recruitment into the study and until the 8 week follow-up visit

### **6.9.1. Alcohol, and Tobacco**

During each resident dosing session, subjects will abstain from alcohol and tobacco for 12 hours prior to admission and until discharge.

**6.9.2. Activity**

Subjects will abstain from strenuous exercise for at least 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during in-patient part of the study (e.g., watch television, read).

**6.10. Concomitant Medications and Non-Drug Therapies****6.10.1. Permitted Medications and Non-Drug Therapies**

Subjects usual medication can be continued during this study with the exception of those listed in Section [6.10.2](#).

Paracetamol can be administered if clinically indicated at the discretion of the Investigator up to and including the recommended maximum total daily dose.

New chronic concomitant medication should be discussed with the GSK Medical Monitor.

**Pre-medication prior to anti-SAP mAb**

A non-selective antihistamine (e.g. Chlorphenamine 10-20 mg) and hydrocortisone 100 mg (or equivalent) should be given prior to each infusion of anti-SAP mAb. Additional administrations of either or both medications are permitted at discretion of Investigator or designee if symptoms require this.

**Prophylactic treatments for rash**

If a rash and associated symptoms (e.g. pruritus) are experienced by a subject at a treatment session, during subsequent treatment sessions prophylactic treatment (any first and / or second generation H<sub>1</sub> antihistamine) are permitted at discretion of Investigator or designee.



**6.10.2. Prohibited Medications and Non-Drug Therapies**

The following restrictions apply from pre-screening up to the 8 week follow-up visit.

<b>Medication</b>	<b>Pre-screen restriction</b>
Tafamidis, diflunisal, doxycycline, tauroursodeoxycholic acid (TUDCA)	28 days
Green tea extract	28 days
Immunomodulatory drug (e.g. IMiD)	12 weeks
Disease-modifying drug for any type of autoimmune disease (e.g. rheumatoid arthritis), including but not restricted to, methotrexate, cyclophosphamide, or anti-cytokine antibodies	12 weeks
Antibody therapy for amyloidosis treatment	At any time
Conditioning chemotherapy for stem cell harvesting)	6 weeks

Where these are deemed to be clinically necessary by the treating physician the individual subject will be withdrawn from the study.

## **7. STUDY ASSESSMENTS AND PROCEDURES**

This section lists the parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 7.1). Detailed procedures for obtaining each assessment are provided in the SPM. Whenever vital signs, 12-lead ECGs and blood sampling are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time when applicable.

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be approved and documented by GSK, but this will not constitute a protocol amendment. The Institutional Review Board/Institutional Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 500 mL of blood will be taken for each Anti-SAP treatment.

## 7.1. Time and Events Table

**Table 3 Overview All Groups (for details of inpatient stay see Table 4)**

			Session 1			Session 2			Session 3			Session 4			Session 5			Session 6			Follow-up		
	Screening <sup>1</sup>	Baseline <sup>2</sup>	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 <sup>3</sup>	6 months <sup>3</sup>	12 months <sup>3</sup>
Inpatient stay at unit <sup>4, 14</sup>			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 <sup>5</sup>	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 <sup>6</sup> 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 <sup>7</sup>		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 <a href="#">Table 6</a>	X																						
Urine $\beta$ hCG <sup>8</sup>	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 <sup>9</sup>	X	X			X			X			X			X			X			X		X	
HepB/Hep C/HIV	X																						

			Session 1			Session 2			Session 3			Session 4			Session 5			Session 6			Follow-up		
	Screening <sup>1</sup>	Baseline <sup>2</sup>	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 <sup>3</sup>	6 months <sup>3</sup>	12 months <sup>3</sup>
Blood biomarkers																							
Complement and Inflammatory markers		X	X			X			X			X			X			X					
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 <sup>10</sup>																							
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 <sup>13</sup>	X <sup>1</sup>									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 <sup>11</sup>			(X)			(X)			(X)			(X)			(X)			(X)					
6MWT - Groups 1 & 2		X								X											X	X	X
Genetic sample <sup>12</sup> (optional)		X																					
Exit Interview																					X		

			Session 1			Session 2			Session 3			Session 4			Session 5			Session 6			Follow-up		
	Screening <sup>1</sup>	Baseline <sup>2</sup>	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 <sup>3</sup>	6 months <sup>3</sup>	12 months <sup>3</sup>
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 4](#) for details of monthly inpatient visit
5. Complete examination at screening only, brief examination at all other time-points. Weight will be recorded at Baseline, D17 and D24. Abdominal girth will be recorded at Baseline.
6. EORTC Groups 2 and 3 only
7. Out-patient cardiac recording using suitable device see 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. 24hr collection - 3.5ml serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples. Day indicated in Table represents the end of the 24hr collection period.
10. Sampling time points in [Table 4](#) and [Table 5](#)
11. In the event of rash, assessments to be performed (see [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<sup>2</sup>, 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 4 Inpatient stay**

Study procedures	Day -2 <sup>13</sup> pre-CPHPC dose	Day -2	Day -1	Day 1-3 anti-SAP mAb dose <sup>1</sup>	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Safety Assessments												
Brief physical examination (including skin) <sup>14</sup>	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			←-----→									
Cardiac monitoring <sup>2</sup>						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 <sup>3</sup>									
Administration of CPHPC (SC )				X	X	X	X	X	X	X	X	X <sup>12</sup>
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 <sup>4</sup>				X			X					X
Urine microscopy <sup>5</sup>	X					X	X					X
Blood biomarkers												
Complement and Inflammatory Markers				X		X	X					
Cytokines	X			X	X	X						
Troponin T/NT-ProBNP	X			X	X	X	X	X	X	X	X	X
Blood sampling for mAb/SAP immune complex <sup>6</sup>	X			X								
Pharmacokinetics/SAP												
Blood sampling for SAP	X		X <sup>7</sup>	X	X			X				

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

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

1. See [Table 5](#) 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 [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. Day 6 represents the start of the collection period, Day 11 represents the end of the collection period. See [Table 5](#) for details of Day 1-3.
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.  $\geq$  Grade 1) and will be decided by clinical judgement of the Investigator  $\pm$  dermatologist (see [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 [Table 8](#)
12. Morning dose only to be administered (see [Table 2](#))
13. Subjects are allowed to be admitted on Day -3 to allow for pre-dose assessments to be performed
14. Weight should be recorded on D-2, D5, D8 and D11. Abdominal girth should be recorded on D-2 and D11

**Table 5 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	24h	28h	32h	36h	40h	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	←----->																									
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	
Study drug administration																										
Administration of CPHPC (SC)- see <a href="#">Table 2</a>	X										X					X										
Administration of anti-SAP mAb		X										n/a					X									
Clinical lab assessments																										
Haem/clin chem/urinalysis	X										X <sup>8,9</sup>					X										
24h Urine collection for protein and creatinine <sup>1</sup>	X															X										
Urine microscopy	X			X			X								X			X			X					
Blood sample mAb/SAP immune complex <sup>2</sup>	X						X <sup>3</sup>														X <sup>3</sup>					
Blood biomarkers																										
Complement & Inflammatory markers	X			X		X		X			X <sup>9</sup>					X			X		X		X			
Cytokines	X		X		X		X				X <sup>9</sup>					X		X		X		X				
Troponin T/NT-proBNP	X										X <sup>9</sup>					X										
Pharmacokinetics																										
Blood sampling - SAP	X						X				X <sup>5</sup>				X						X					
Blood sampling- CPHPC <sup>4</sup>	X										X <sup>5</sup>				X											



Study procedure	Day 1										Day 2					Day 3											
	Pre-dose	0h	1h	2h	3h	4h	6h	8h	12h	16h	24h	28h	32h	36h	40h	Pre-dose	0h	1h	2h	3h	4h	6h	8h	12h	16h		
Blood sampling - anti-SAP mAb	X						X <sup>6</sup>	X	X		X <sup>5</sup>					X						X <sup>6</sup>					
Ongoing subject review																											
Skin biopsy/blood sample/urinalysis/EOSI <sup>7</sup>		(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. Day indicated in the Table represents the start (pre-dose) of the 24hr collection period.
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 [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 [Table 6](#))
9. Time shown to indicate early in the day only – not a specific time. The collection of these should be timed with other pre-dose sample collection in order to minimise inconvenience and needle-sticks for the subjects.

## **7.2. Screening and Critical Baseline Assessments**

### **7.2.1. Demographic/Medical History Assessments**

The following demographic parameters will be captured: year of birth, gender, race and ethnicity.

Medical/medication history will be assessed as related to the eligibility criteria listed in Section 5.

Cardiovascular medical history/risk factors (as detailed in the case report form [CRF]) will be assessed at screening.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study. Whenever available pre-trial magnetic resonance imaging (MRI) data related to the assessments in this study will be obtained from medical history.

## **7.3. Efficacy**

The study is not designed to measure efficacy however the cardiac function assessments i.e. NT-proBNP, Six Minute Walk Test, and Health Outcome Questionnaires may provide some insight into efficacy.

## **7.4. Safety**

Planned time points for all safety assessments are listed in the Time and Events Tables (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

### **7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)**

The definitions of an AE or SAE can be found in Section 12.5, Appendix 5

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### **7.4.1.1. Time period and Frequency for collecting AE and SAE information**

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- AEs will be collected from the start of Study Treatment until the 8 week follow-up contact (see Section 7.4.1.3), at the time points specified in the Time and Events Tables (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.5.6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.5.4.

#### **7.4.1.2. Method of Detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

#### **7.4.1.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Section 12.5.

#### **7.4.1.4. Regulatory Reporting Requirements for SAEs**

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will

comply with country specific regulatory requirements relating to safety reporting to the regulatory authority IRB/IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

#### **7.4.2. Pregnancy**

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until final study follow-up.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 6](#)

#### **7.4.3. Physical Exams**

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Skin, Gastrointestinal and Neurological systems. Height and weight (and girth) will also be measured and recorded.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight and abdominal girth measurements will also be included at times stated in the Time and Events Table.
- Investigators should pay special attention to clinical signs related to previous serious illnesses

#### **7.4.4. Vital Signs**

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

#### **7.4.5. Electrocardiogram (ECG)**

- Single 12-lead ECGs will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section [5.4.6](#) for QTc withdrawal criteria and additional QTc readings that may be necessary.
- In-patient Lead II continuous telemetry will be used during in-patient AntiSAP treatment sessions. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

#### **7.4.6. Echocardiography (ECHO)**

ECHO methodology will be detailed in a separate Image Acquisition Manual.

Echocardiography (ECHO) will be performed by a qualified echocardiographer or cardiologist at the timepoints detailed in Section 7.1 Time and Events Tables. At the discretion of the Investigator, an ECHO may be requested at any time during the study for safety reasons e.g. increase in NT-ProBNP levels, investigation of suspected myocarditis, or to confirm worsening of cardiac function caused by any study treatment (e.g. bortezomib) or disease.

#### **7.4.7. Cardiac Electrical Monitoring & Implantable Devices.**

##### **7.4.7.1. Lead II Telemetry**

Lead II telemetry will be used for electrical cardiac monitoring during in-patient AntiSAP treatment session as detailed in Section 7.1 Time and Events Tables. A baseline reading will be obtained before administration of anti-SAP mAb with telemetry commencing the day prior to start of anti-SAP mAb infusion (i.e. Day -1 to Day 1 pre anti-SAP mAb infusion).

##### **7.4.7.2. Cardiac Recording**

Cardiac recording devices will be used for electrical cardiac monitoring at the times as detailed in Section 7.1 Time and Events Tables.

The type of device will be at the discretion of the Study site and might include, but is not restricted to, use of a BodyGuardian or Cardio-Net device.

The recording will be analysed prior to the next anti-SAP treatment and the analysis reviewed by the Investigator.

Following confirmation of eligibility, a baseline assessment for up to two weeks will be performed to provide baseline data. Whenever feasible the same device as that used at baseline will be used for subsequent measures.

##### **7.4.7.3. Insertion of a PPM or ICD for Prophylactic Reasons**

Subjects who require insertion of a PPM or ICD for prophylactic reasons during the study can continue to receive Anti-SAP treatment, at the discretion of the Investigator in consultation with the Medical Monitor

A contrast-enhanced CMR should be performed whenever possible before PPM or ICD insertion during study treatment (this will represent the final CMR imaging in these subjects).

For all subjects who have a PPM or ICD inserted it is recommended that they have an implantable device check:

- i). On Day 4
- ii). In the event of a rise in plasma NT-proBNP  $\geq 2$ -fold above baseline
- iii).  $\leq 24$  hours before in-patient discharge

Subjects who have a PPM or ICD implanted during Anti-SAP treatment will have no further CMR and will continue to be imaged with ECHO only ( $\pm$  bone tracer scintigraphy in Group 1 subjects where technically feasible).

There must not be more than an 8 week interval between the last Anti-SAP treatment session and the subsequent one after PPM or ICD insertion, or otherwise, the subject will be withdrawn from further study treatment.

#### **7.4.8. Clinical Safety Laboratory Assessments**

All protocol required laboratory assessments, as defined in [Table 6](#) must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM and/or the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Study-required clinical safety laboratory assessments will be performed by a local laboratory. All other laboratory assessments will be performed by a central laboratory. The results of each test must be entered into the CRF.

Local laboratory results are required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. In this case if a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in [Table 6](#).

**Table 6 Protocol Required Safety Laboratory Assessments**

Laboratory Assessments	Parameters				
Haematology	Platelet Count		<i>RBC Indices:</i>	<i>WBC count with Differential:</i>	
	RBC Count		MCV	Neutrophils	
	Hemoglobin		MCH	Lymphocytes	
	Hematocrit		MCHC	Monocytes	
	WBC count (absolute)			Eosinophils	
	Reticulocyte count			Basophils	
Clinical Chemistry <sup>1</sup>	BUN	Potassium	AST (SGOT)		Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)		Total Protein
	Glucose	Calcium	Alkaline phosphatase		Albumin
	Chloride	Total CO <sub>2</sub>	LDH		
	CK	Uric acid			
Other safety	<ul style="list-style-type: none"><li>• Troponin-T (including High Sensitivity)</li><li>• NT-proBNP</li></ul>				
Routine Urinalysis	<ul style="list-style-type: none"><li>• Specific gravity</li><li>• pH, glucose, protein, blood and ketones by dipstick</li><li>• Microscopic examination</li><li>• Urine creatinine, albumin and protein from 24h collection</li></ul>				
Pregnancy testing	Serum or urine hCG Pregnancy test (as needed for women of child bearing potential)				
Other Screening Tests	<ul style="list-style-type: none"><li>• HIV</li><li>• Hepatitis B (HBsAg)</li><li>• Hepatitis C (Hep C antibody)</li><li>• FSH and estradiol (as needed in women of non-child bearing potential only)</li><li>• Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)</li><li>• Serum or urine hCG Pregnancy test (as needed for women of child bearing potential) <sup>2</sup></li><li>• Clotting tests – PT and APTT</li></ul>				
Further Tests (Session 1, Day 2 only)	<ul style="list-style-type: none"><li>• Clotting tests – PT and APTT</li></ul>				

Laboratory Assessments	Parameters
Investigation of adverse bleeding event	<ul style="list-style-type: none"> <li>• Clotting tests – PT and APTT</li> <li>• Platelet function tests (at discretion of Investigator or designee)</li> </ul>
<p>NOTES :</p> <ol style="list-style-type: none"> <li>1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.1 and <a href="#">Appendix 2</a></li> <li>2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.</li> </ol>	

All laboratory tests with values that are considered clinically significantly abnormal for this patient population during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

## 7.5. Pharmacokinetics

### 7.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of GSK2315698 and GSK2398852 will be collected at the time points indicated in Section 7.1, Time and Events Tables. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

2mL of blood will be collected into ethylenediaminetetraacetic acid (EDTA) tubes.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

### 7.5.2. Sample Analysis

Plasma analysis will be performed under the management of Bioanalysis, Immunogenicity & Biomarkers (BIB), In Vitro In Vivo Translation (IVIVT), PTS, GlaxoSmithKline. Concentrations of CPHPC (GSK2315698) and anti-SAP mAb (GSK2398852) will be determined in plasma samples using the currently approved analytical methodology. Raw data will be stored in the good laboratory practice (GLP) Archives, GlaxoSmithKline.



## **7.6. Biomarker(s) / Pharmacodynamic Markers (PD)**

The following biomarkers and PD markers will be collected at the time points indicated in Section 7.1, Time and Events Tables.

The timing of assessments may be altered as information is obtained. Details of PD assessments and blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

### **Companion Diagnostic Assay Development:**

Aliquots of serum/plasma taken for PD analysis in this study will be stored and may be used in the development and validation of a companion diagnostic assay to measure SAP levels.

### **7.6.1. Pharmacodynamic markers in blood**

Blood samples for pharmacodynamic analysis of the following parameters will be collected at the time points indicated in Section 7.1, Time and Events Tables. The actual date and time of each blood sample collection will be recorded.

The timing of PD samples may be altered as information is obtained. Details of PD blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

- SAP concentration
  - A 4mL blood sample will be collected at the time points as per Section 7.1, Time and Events Tables  
Samples collected Day -1 will be analysed immediately to confirm sufficient SAP depleted to target prior to dosing anti-SAP mAb
- Renal Function and Liver function tests (also collected as safety measures)

### **7.6.2. Imaging**

#### **7.6.2.1. Cardiac Magnetic Resonance (CMR) Imaging**

Subjects will be asked to refrain from alcohol, caffeine, and nicotine on the days of CMR exams. Each CMR imaging session will take approximately 45-60 minutes, with a maximum scan time inside of the scanner of 90 minutes. If a scanning failure occurs at any visit, if feasible a rescan is allowed within 7 days of the failed scan after consultation and agreement with the GSK medical monitor. For scans involving contrast, there will be a minimum of 24 hours prior to rescan.

Contrast enhanced MRI scans using an intravenous injection of a gadolinium based contrast agent (GBCA) will be performed at the time points specified in Time & Events tables (Section 7.1). A GBCA dose less than or equal to 0.1 mmol/kg will be used at each contrast enhanced scanning session. Acceptable GBCA agents for this study are gadoteric acid, gadoteridol, and gadobutrol. Non-contrast enhanced MRI scans will also be performed as indicated in the Time & Events table (Section 7.1).

**Whenever possible, the contrast enhanced MRI scan at screening will be performed after a subject has passed other eligibility requirements. This scan will serve as the baseline examination.**

For each subject, follow-up CMR examinations will be performed on the same scanner as the baseline examination. Where this is not possible (e.g. due to scanner failure), the use of an alternative scanner may be approved by the study team in consultation with the central imaging core lab.

Further details of site training and qualification procedures, and scanning protocols are provided in a dedicated Image Acquisition Manual to ensure consistency across study sites. Additional exploratory CMR endpoints, as detailed in the Imaging Acquisition Guidelines, may also be acquired for exploratory purposes.

All CMR scans will be reviewed at the site for clinical abnormalities. Image analysis for the CMR endpoints will be performed by a central core lab.

#### **7.6.2.2. SAP scan (Groups 2 and 3 and where available)**

Amyloid load in liver, spleen, kidney, bone marrow, other involved organs, except the heart, and total body, will be assessed by SAP scintigraphy at baseline and at 8 week follow-up.

SAP scintigraphy is the most comprehensive method for estimating total body amyloid load [Hawkins, 1988], but it is only available for the UK subjects in this phase 2 study. SAP scintigraphy (SAP scan) will be performed in UK for Groups 2 and 3 only.

Methodology will be detailed in a separate Image Acquisition Manual.

#### **7.6.2.3. <sup>99m</sup>Tc-DPD or <sup>99m</sup>Tc-PYP Radioscintigraphy**

Radioscintigraphy with <sup>99m</sup>Tc-DPD or <sup>99m</sup>Tc-PYP will be used to quantify cardiac amyloid load in Group 1 subjects at the time points specified in Time & Events tables (Section 7.1).

Methodology will be detailed in a separate Image Acquisition Manual.

#### **7.6.3. Exploratory Biomarkers**

With the subject's consent, serum, urine and possibly tissue samples (e.g. skin biopsy) will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence amyloidosis and/or medically related conditions, as well as the biological and clinical responses to Anti-SAP treatment, as well as drug-induced toxicities. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events. Novel candidate biomarkers of the biological response associated with skin rashes and/or the action of GSK2398852 may be identified by application of:

- RNA transcriptome analysis of blood and skin samples.

- Measurement of the levels of a subset of RNA species on blood and skin samples.

Samples will be collected at the time points indicated in Time & Events tables (Section 7.1). The timing of the collections may be adjusted on the basis of emerging data from this study or other new information in order to ensure optimal evaluation of the PD endpoints. Analysis of these samples may not take place if other information from the study would indicate that they will not provide useful additional information.

For further instructions on the collection and handling of samples refer to the Study Reference Manual.

#### **7.6.3.1. Blood biomarkers**

##### **Plasma Cytokines**

5mL blood sample for serum will be collected for the purposes of measuring biomarkers of immune function. These may include but are not limited to  $\text{TNF}\alpha$ , IL-10, IL-8, IL-6, IL-13, IL-2, IL-4, IL-12 (p70), IL1 $\beta$  & IFN $\gamma$ .

##### **Cardiac biomarkers**

3.5mL blood samples for serum will be collected to measure exploratory measures of cardiac efficacy including but not limited to: NT-proBNP.

##### **Inflammatory markers and Fluid phase Complement Markers.**

5mL blood samples for serum will be collected to measure:

- complement markers including but not limited to: C3, C4, CH50 and those listed in Table 8
- inflammatory biomarkers including but not limited to: CRP, high-sensitivity C-reactive protein (hsCRP), SAA

#### **7.6.3.2. RNA Transcriptome Research**

Transcriptome studies may be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each biopsy sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to skin rash, amyloid related diseases or the action of GSK2398852.

A 2.5mL blood sample will be collected and the same samples may also be used to confirm findings by application of alternative technologies.

### **7.6.3.3. RNA Expression Research of a Subset of RNA Species**

RNA expression studies may be conducted using quantitative RT-PCR, and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of hundreds of RNA species resulting in a RNA expression profile for each skin sample. The RNAs assayed may be those involved with the pathogenesis of disease, the absorption, distribution, metabolism, or excretion of study treatment, or in the subject's response to study treatment. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in response to GSK2398852 or the pathogenesis of disease. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to skin rash and disease and medically related conditions or the action of study treatment.

### **7.6.3.4. Access to other biopsy tissue**

Where a subject requires biopsy, as part of any clinical investigative procedures as directed by the treating physician, a sample of the tissue will be sent to GSK where possible. Routine and special histopathological investigations, including histochemical and/or immunohistochemical stains will be performed to assess for amyloid deposits, inflammatory cellular infiltrates including multinucleated giant cells and macrophages as well as for markers of any parenchymal tissue disruption.

## **7.7. Immunogenicity**

### **7.7.1. Anti-GSK2398852 antibodies (ADA)**

Blood samples for determination of anti-GSK2398852 antibodies will be taken from all subjects in this study as a safety measurement at the time-points specified in the Time and Events Tables (Section 7.1). Timing of the assessments may be adjusted based on emerging data.

Samples will be analysed for the presence of anti-GSK2398852 antibodies using an analytically validated screening assay. If sera contain anti-GSK2398852 antibodies in the screening assay, they will be further analysed for specificity and titres of antibodies. Samples will be retained for further characterisation of neutralising activity if required and reported separately. The immunogenicity assessment report will include the incidence and titres of anti-GSK2398852 binding antibodies.

### **7.7.2. Immune complexes**

4mL blood samples for determination of SAP/anti-SAP mAb immune complexes will be taken as a safety measurement at the time-points specified in the Time & Events tables (Section 7.1) and Table 8. Timing of the assessments may be adjusted based on emerging data.

### **7.7.3. Auto-antibodies**

3mL blood samples for determination of antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-double strand-DNA antibody (refer to [Table 8](#))

## **7.8. Efficacy**

### **7.8.1. Six Minute Walk Test**

The 6-Minute Walk Test (6MWT) assessment will be conducted according to the American Thoracic Society guidelines (in accordance with local standard operating procedures).

### **7.8.2. Safety/exploratory Biomarkers**

Some of the samples taken primarily for assessment of safety, such as proteinuria, and some safety/ exploratory biomarkers, such as NT-proBNP, may also provide evidence of efficacy.

## **7.9. Health Outcomes**

### **7.9.1. MOS 36-item short-form health survey (MOS SF-36)**

The MOS SF-36 has 36 questions. All questions are scored using normative based scoring. Software is available that assists in the scoring of the MOS SF-36 (QualityMetric Health Outcomes Scoring Software 2.0, [Saris-Baglama](#), 2007), and details on scoring can be found in the SF-36v2 user manual.

### **7.9.2. Kansas City Cardiomyopathy Questionnaire (KCCQ)**

The Kansas City Cardiomyopathy Questionnaire is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.

### **7.9.3. European Organisation for Research and Treatment of Cancer (EORTC)**

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30) is a questionnaire developed to assess the quality of life of cancer patients and consists of 30 questions. Subjects in Groups 2 and 3 only will complete this questionnaire.

#### **7.9.4. Dermatology Quality of Life Index (DLQI)**

The dermatology quality of life index is a simple 10 item validated questionnaire that has been used to assess the impact of skin diseases on patient quality of life. It will be administered to subjects in the study who develop dermatological toxicity.

#### **7.9.5. Questionnaire Administration**

Subjects will complete the questionnaires at the time-points specified in the Time and Events Tables,

The Investigator or designee will ask the subject to complete the questionnaire during the clinical visit separately from the medical history and the standard AE and concomitant medication questions.

Questionnaires should be completed in a quiet place (preferably the same place each time, if possible) and at as consistent a time during the study visits as possible. To avoid biasing responses, subjects should not be told the results of diagnostic tests prior to completing the questionnaire. Regardless of when the questionnaire is completed, the subject should be given adequate time to complete all items. No stated or implied time limit for completing the questionnaire items will be given.

The subject should be asked to complete the questionnaire completely and accurately. If the subject requests help or clarification of any question, he should be asked to read the instructions again and to give the best answer possible to each question. Subjects should be encouraged to report their own experiences and opinions. The investigator will not provide the subject with an answer to any question nor interpret any portion of the question.

#### **7.10. Exit Interview**

Exit interviews will be conducted after the 8 week follow-up or Early Withdrawal Visit and over the telephone, in a subset of subjects only, to explore subjects' experience with study treatment. Exit interviews are qualitative interviews conducted with study subjects to capture subject experiences in drug development on completion of participation in a clinical study. Interview questions are designed to fully assess a subject's experience with a study medication and study requirements and are administered in a semi-structured format over the telephone by a trained interviewer independent of study sites and sponsor. Subject feedback will be captured in a data collection sheet as well as being audio-taped for subsequent transcription and qualitative analysis and reported separately. The Exit interview technique and questions will be described in the SRM.

## 7.11. Genetics

If the patient provides additional informed consent, genetic research aimed at understanding variability in patients' response to GSK2398852 & GSK2315698 (or other therapies that subjects may receive while participating in the clinical study) with regard to safety, pharmacokinetics, and efficacy may be undertaken on a genetic sample collected at Baseline. Information regarding the genetic research is included in [Section 12.4](#). Participation in the genetic research is voluntary and refusal to participate will not affect the subject's eligibility to participate in the main study.

The IEC and, where required, the applicable Regulatory Authority must approve the genetic assessments before these can be conducted. The approval(s) must be in writing and will clearly specify approval of the genetic assessments (i.e., approval of [Section 12.4](#)). In some cases, approval of the genetic assessments can occur after approval is obtained for the rest of the study. If so, the written approval will clearly indicate that approval of the genetic assessments is being deferred and in most cases, the study, except for genetic assessments, can be initiated. When genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, the genetic assessments will not be conducted.

Information regarding genetic research is included in [Appendix 4 Section 12.4](#).

## **8. DATA MANAGEMENT**

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug
- Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 will be used
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy



## **9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES**

### **9.1. Hypotheses**

No formal statistical tests are planned in this study.

### **9.2. Sample Size Considerations**

#### **9.2.1. Sample Size Assumptions**

The planned sample size is based on feasibility and the level of precision the study would provide around the estimated change in structural cardiac MRI measure LV mass, used to assess cardiac amyloid load and estimated adverse event rates.

Assuming a standard deviation of 20g for the change in LV mass, the half width for the 95% confidence interval (CI) around the estimated change in LV mass at 8-week follow-up based on the observed data would be  $\pm 14$ g. For example, the 95% CI around an observed change in LV mass of 70g at final follow-up would be (56, 84), i.e. a lower limit of more than 50g.

Based on a sample size of 10 per study group and various observed adverse event rates, [Table 7](#) below presents the following:

- i) 95% credible intervals for the adverse event rate
- ii) probability of a true adverse event rate  $> 10\%$ ,  $30\%$  or  $50\%$ ,

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

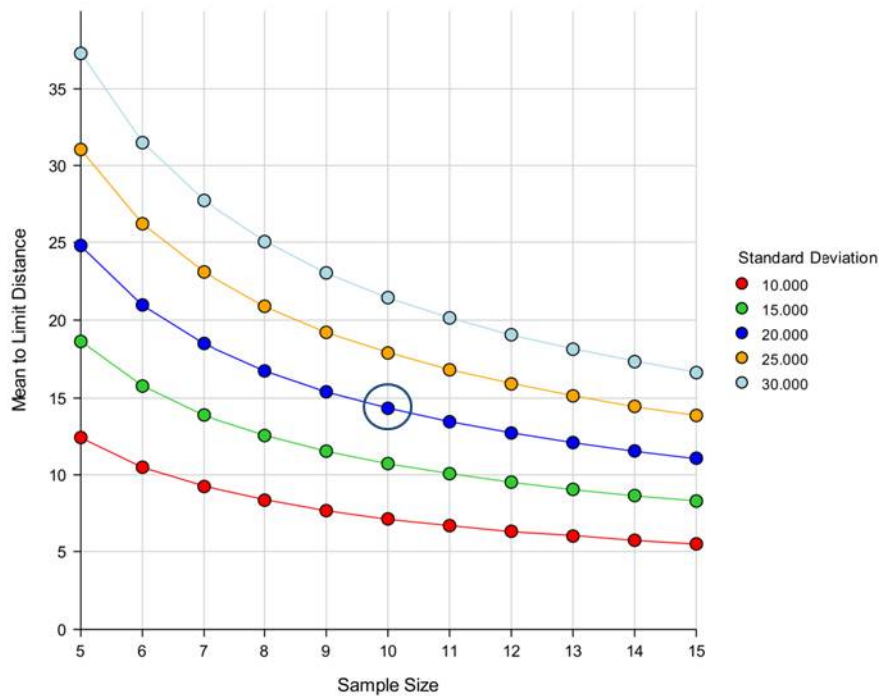
**Table 7      95% credible intervals for adverse event rates and probabilities of adverse event rates > x%**

N	Observed number of subjects experiencing AE	Observed rate	Lower 95% Credible Interval Limit	Upper 95% Credible Interval Limit	Prob. of true AE rate > x%, given observed data		
					> 10%	> 30%	> 50%
10	0/10	0.00	0.00	0.18	0.09	0.00	0.00
10	1/10	0.10	0.01	0.37	0.51	0.06	0.00
10	2/10	0.20	0.04	0.50	0.83	0.24	0.02
10	3/10	0.30	0.09	0.60	0.96	0.50	0.10
10	4/10	0.40	0.15	0.70	0.99	0.75	0.26
10	5/10	0.50	0.22	0.78	1.00	0.91	0.50
10	6/10	0.60	0.30	0.85	1.00	0.98	0.74
10	7/10	0.70	0.40	0.91	1.00	1.00	0.90
10	8/10	0.80	0.50	0.96	1.00	1.00	0.98
10	9/10	0.90	0.63	0.99	1.00	1.00	1.00
10	10/10	1.00	0.82	1.00	1.00	1.00	1.00

### 9.2.2. Sample Size Sensitivity

Figure 5 provides an assessment of the sensitivity of the sample size to differing assumptions around the standard deviation for the change in LV mass.

**Figure 5      Sensitivity of the Sample Size - LVmass**



Note: 'Mean to limit distance' = 95% Confidence Interval half width

### **9.2.3. Sample Size Re-estimation or Adjustment**

The sample size will be re-assessed based on the emerging data. The sample size in one or more groups may be adjusted if, for example, the observed variability is larger than that assumed at the study design stage for changes in LV mass.

## **9.3. Data Analysis Considerations**

### **9.3.1. Analysis Populations**

The ‘Safety Population’ is defined as subjects who receive at least one dose of study medication. This population will be used for the summary and analysis of all data including safety, efficacy, pharmacodynamic and pharmacokinetic data.

### **9.3.2. Interim Analysis**

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

Study specific decisions will be supported by the periodic review of study data, as described in Section 10.8.2. The first review will take place once 5 subjects have completed at least 3 courses of Anti-SAP treatment. Outcomes from the periodic data reviews may include:

- Regulatory interactions and initiation of recruitment in to Group 3
- Triggering of phase III planning and related regulatory interactions
- Sample size re-estimation/adjustment (see Section 9.2.3)
- Adjustment of the schedule and timing of assessments
- Confirmed continuation of the study.

A further interim analysis will be conducted once at least 10 subjects per group have completed their 8-week follow-up visit. Further details will be provided in the Reporting and Analysis Plan regarding key deliverables for this interim.

The final analyses will be conducted once all subjects have completed their 12-month follow-up visit.

## **9.4. Key Elements of Analysis Plan**

### **9.4.1. Primary Analyses**

#### **LV mass**

Analyses detailed below will be performed on data from each study group separately.

Individual subject profiles over time for LV mass will be plotted using historical pre-trial standard of care subject data, where available, and within-study data from the same subject pre and post Anti-SAP treatment. Absolute values and changes from baseline in LV mass will also be summarized over time.

The longitudinal profile of LV mass post Anti-SAP treatment will be analyzed using a Bayesian linear mixed model (LMM). The intention is to also include two sources of historical MRI data in the model from one participating site that will be informative of the standard of care LV mass profile over time:

1. Pre-trial MRI data for subjects enrolling in the study, collected as part of their medical history, where available
2. Repeat historical MRI data for subjects not enrolled in the study (2 to 3 scans per subject).

For subjects who prematurely discontinue treatment, follow-up MRI scans at 8 weeks, 6 months and 12 months post last dose will be performed where possible. All retrieved LV mass data post treatment-discontinuation will be incorporated directly within the model. This will be achieved in two ways: (i) fitting a LMM following a Pattern Mixture Model (PMM) framework, uniquely identifying patterns of treatment discontinuation; and (ii) fitting a LMM to all data ignoring whether subjects prematurely discontinued Anti-SAP treatment.

Any missing data will be imputed assuming a Missing Not at Random mechanism with the historical MRI data acting as reference.

Posterior distributions at time points of interest post Anti-SAP treatment (e.g. after 3 doses, at 8-week follow-up) will be presented graphically. Probability statements around the magnitude of LV mass and/or the reduction in LV mass post Anti-SAP treatment at selected time points will also be presented. Similarly, posterior distributions and probability statements will be presented for standard of care.

Further details will be provided in the reporting and analysis plan.

#### **Safety**

Safety data (e.g. AEs, vital signs, haematology, biochemistry, urinalysis, ECGs, Holter, rash) will be summarized by study group in tabular and/or graphical format. Posterior probabilities of a true adverse event rate being > 10%, > 30% and >50% will be presented for specific AEs (e.g. rash, anti-SAP mAb infusion-related reactions, cardiac AEs),

derived within a Bayesian framework with a neutral non-informative conjugate Beta(1/3,1/3) prior distribution.

Further details will be provided in the Reporting and Analysis Plan.

#### **9.4.2. Secondary Analyses**

For both compounds (GSK2315698 and GSK2398852), plasma concentration-time data will be listed and summarised, and pharmacokinetic parameters of GSK2398852 will be calculated using non-compartmental methods with WinNonlin, version 6 or higher.

Individual profiles over time and summary tables will be presented for circulating PD markers of interest, e.g. IL6, IL8, IL10, CRP, SAA, C3, C4 and CH50.

Functional CMR and ECHO measures (eg stroke volume, left ventricular ejection fraction, end diastolic volume etc) will be analysed as described for LV mass, as data permit.

Further details of the secondary, exploratory and long term follow-up analyses will be specified in the reporting and analysis plan.

## **10. STUDY GOVERNANCE CONSIDERATIONS**

### **10.1. Posting of Information on Publicly Available Clinical Trial Registers**

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

### **10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

### **10.3. Quality Control (Study Monitoring)**

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

### **10.4. Quality Assurance**

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

### **10.5. Study and Site Closure**

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

#### **10.6. Records Retention**

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

#### **10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the



opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

## **10.8. Periodic Meeting with Investigators**

### **10.8.1. Individual Subject Review**

Prior to administration of the next Anti-SAP treatment in each subject, there will be a review of the available data by:

1. the Principal Investigator (or appropriate designee) having consulted with local haematologist, cardiologist, radiologist (CMR / ECHO analyst), and / or dermatologist regarding any findings or concerns, additional attendees will be invited as required
2. GSK team including Medical Monitor, GSK Study Team Leader, additional attendees will be invited as required

The purpose of this review is to consider:

- whether it is appropriate to continue with Anti-SAP treatment in that subject based on a benefit / risk assessment, and
- the dose level for anti-SAP mAb

The review will be a holistic review of the case, but the following will be considered specifically:

- Adverse events
- Whether the subject has experienced a rash
- Cardiac safety including outpatient ECG recording and ECHO/CMR
- Biochemistry, haematology, and urinalysis

### 10.8.2. Periodic Study Review

Patients with systemic amyloidosis are complex and their treatment highly individualized. In a rare disease the precise characteristics of the patient must be taken into account when assessing safety. In addition to meetings of the GSK Safety Review team, meetings will be held with Investigators to conduct periodic holistic evaluation of the safety profile.

These meetings will include the following individuals:

- Investigator from each study site
- Relevant functional experts (e.g. cardiologist, haematologist, dermatologist)
- GSK medical monitor, statistician, study team leader, clinical safety representative

External experts may also be invited.

These meetings will make recommendations on the following based on the review:

- Whether the schedule and timing of assessments are appropriate based on the observed safety profile
- Whether sufficient information is available to start recruitment of Group 3

The Sponsor will be responsible for the final decision on the schedule of assessments and identifying the trigger point for recruitment into Group 3. Recruitment into Group 3 will not start until a review of available safety information has been conducted by regulatory agency.

Scheduled review meetings will be held:

1. After 5 subjects have completed at least 3 treatment sessions
2. After 5 subjects have completed 6 treatment sessions (or 8-week follow-up)

Additional review meetings will be scheduled based on on-going data.

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## 12. APPENDICES

### 12.1. Appendix 1 – Abbreviations and Trademarks

#### Abbreviations

6MWT	6 minute walk test
AA	Amyloid A
ANA	antinuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
AE	Adverse Event
AFib	fibrinogen A alpha chain amyloidosis
AL	immunoglobulin light chain amyloidosis
ALT	alanine transaminase
AApoAI	apolipoprotein A-I amyloidosis
ATTR-CM	transthyretin amyloid cardiomyopathy
AUC	area under the concentration-time profile
BIB	Bioanalysis, Immunogenicity & Biomarkers
BSA	Body surface area
CABG	coronary artery bypass grafting
CI	confidence interval
C <sub>max</sub>	maximum concentration
CMR	cardiac MRI
CPHPC	carboxy pyrrolidine hexanoyl pyrrolidine carboxylate
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	creatinine clearance
CRF	case report form
CRP	c reactive protein
cTnT	cardiac troponin T
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CyBorD	cyclophosphamide, bortezomib, dexamethasone
DCE	dynamic contrast enhanced
DLQI	Dermatology Quality of Life Index
DPD/ <sup>99m</sup> Tc-DPD	<sup>99m</sup> Technetium-dicarboxypropane diphosphonate
ECG	electrocardiogram
ECHO	echocardiography
ECV	extracellular volume
EDTA	Ethylenediaminetetraacetic acid
EDV	end diastolic volume
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay

EORTC QLQ C30	The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EOSI	event of specialist interest
FAC	familial amyloid cardiomyopathy
FDA	food & drug administration
FIH	first in human
FRP	female of reproductive potential (FRP)
FLC	free light-chain
FSH	follicle stimulating hormone
GBCA	gadolinium based contrast agent
Gd	gadolinium
GFR	Glomerular filtration rate
GLP	good laboratory practice
GLS	Global longitudinal strain
GSK	GlaxoSmithKline
hCG	human chorionic gonadotrophin
HPLC-MS	hplc-mass spectrometry
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
ICD	implantable cardiac defibrillator
IMiD	immunomodulatory drug
IND	investigational new drug
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
IV	intravenous
IVIVT	In Vitro In Vivo Translation
L	litre
LCV	leucocytoclastic vasculitis
LGE	late gadolinium enhancement
LMM	linear mixed model
LVAD	left ventricular assist device
LV	left ventricular
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease (equation)
mg	milligram
MGC	multinucleated giant cells
MHRA	Medicines and Healthcare products Regulatory Agency
mL	millilitre
MRI	magnetic resonance imaging
MSDS	Material Safety Data Sheets
ms	millisecond
NT pro-BNP	N-terminal pro b-type Natriuretic Peptide
NYHA class	New York heart association class
od	once daily
PD	pharmacodynamic
PET	Positron emission tomography

PI	Principal Investigator
PIH	Post-inflammatory hyperpigmentation
PK	pharmacokinetic
PK/PD	pharmacokinetics/pharmacodynamics
PMM	Pattern Mixture Model
PPM	permanent pacemaker
PYP/ <sup>99m</sup> Tc-PYP	<sup>99m</sup> Tc-pyrophosphate
QTc	interval from the Q wave on the ECG to point T
QTcF	QTc using Fredericia's formula
RAP	Reporting and Analysis Plan
SAA	serum amyloid A protein
SAE	severe adverse events
SAP	serum amyloid p component
SC	subcutaneous
SRM	study reference manual
SV	stroke volume
TIA	transient ischemic attack
tmax	the time associated with Cmax
TTR	transthyretin
TTS	Study Specific Technical Agreement/Memo
ULN	upper limit of normal
Vd	volume of distribution
VGPR	very good partial response
VT	Ventricular tachycardia

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## 12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

### Liver chemistry stopping criteria and required follow-up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
<b>ALT-absolute</b>	<p>ALT<math>\geq</math>3xULN</p> <p>If ALT<math>\geq</math>3xULN <b>AND</b> bilirubin<sup>1,2</sup> <math>\geq</math> 2xULN (&gt;35% direct bilirubin)</p> <p><b>Or,</b></p> <p><b>INR &gt;1.5 without warfarin anti-coagulation</b></p> <p><b>= Report as an SAE</b></p> <p>See additional Actions and Follow Up Assessments listed below</p>
Required Actions and Follow up Assessments following Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>• <b>Immediately</b> discontinue study treatment</li> <li>• Report the event to GSK <b>within 24 hours</b></li> <li>• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE<sup>2</sup></li> <li>• Perform liver event follow up assessments</li> <li>• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see <b>MONITORING</b> below)</li> <li>• <b>Do not restart / re-challenge</b> subject with study treatment unless allowed per protocol and GSK Medical Governance approval <b>is granted</b></li> <li>• If restart/rechallenge <b>not allowed per protocol or not granted</b>, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments</li> </ul>	<ul style="list-style-type: none"> <li>• Viral hepatitis serology<sup>3</sup></li> <li>• Blood sample for pharmacokinetic (PK) analysis, obtained within 5 days after last dose (mAb or CPHPC) of last dose<sup>4</sup></li> <li>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>• Fractionate bilirubin, if total bilirubin<math>\geq</math>2xULN</li> <li>• Obtain complete blood count with differential to assess eosinophilia</li> <li>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</li> <li>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies,</li> </ul>



<p><b>MONITORING:</b></p> <p><b><u>If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR &gt;1.5:</u></b></p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24 hrs</b></li> <li>Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline</li> <li>A specialist or hepatology consultation is recommended</li> </ul> <p><b><u>If ALT ≥ 3xULN AND bilirubin &lt; 2xULN and INR ≤ 1.5:</u></b></p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24-72 hrs</b></li> <li>Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</li> </ul>	<p>other over the counter medications.</p> <ul style="list-style-type: none"> <li>Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b><u>If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR &gt;1.5:</u></b></p> <ul style="list-style-type: none"> <li>Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).</li> <li>Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).</li> <li>Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and / or liver biopsy to evaluate liver disease; complete Liver Imaging and / or Liver Biopsy CRF forms.</li> </ul>
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1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

## References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

## **12.3. Appendix 3: Guidance on the Clinical Management of Rash Associated with Anti-SAP mAb**

### **12.3.1. Background**

In the FIH study, anti-SAP mAb administration, at doses  $\geq 600\text{mg}$  were commonly associated with the onset of a rash within the first 3 days of completion of anti-SAP mAb dosing. The pathogenesis of the rash is not fully understood but the available evidence indicates that it is related to the peak plasma concentration of anti-SAP mAb.

The clinical presentation of rashes showed significant variability with respect to the body surface area (BSA) affected and the clinical characteristics of the skin lesions.

In the FIH study, the clinical appearances of the skin rashes have included, but are not restricted to, maculopapular exanthema, urticarial and targetoid lesions.

No patients in the FIH study had any clinical evidence of either mucosal or systemic / organ involvement.

Paraffin embedded H&E staining of two separate skin biopsies from two different AL amyloidosis subjects in the FIH study have been obtained. The first subject received a total dose of anti-SAP mAb of 600mg on their first treatment. Their skin biopsy showed an active leucocytoclastic vasculitis (LCV) with migration of circulating neutrophils into the dermal small vessel wall and extravascular tissues with morphological evidence of apoptosis. There was no evidence of fibrinoid change or necrosis and there was also very little red cell extravasation with very few eosinophils present. The second subject received a total dose of anti-SAP mAb of 1000mg on their second treatment session. This biopsy showed basket-weave keratosis with epidermal thinning, mild diffuse spongiosis with focal vacuolar-interface change, and a mild to moderately dense superficial and mid perivascular predominantly lymphocytic inflammatory cell infiltrate with neutrophils and neutrophilic debris. No definitive conclusion was reached by the reporting dermatopathologist for this skin biopsy sample, but the described morphological changes could be consistent with a lymphocytic vasculitis/LCV.

While not definitive these changes are consistent with anti-SAP mAb mediated activation of the complement pathway leading to neutrophilic inflammation. Such a pathophysiological process is consistent with the observed onset of the rash at the peak concentration of anti-SAP mAb and that the most severe case was associated with the highest measured concentrations of mAb.

Alternative explanations have also been considered.

SAP is also present in microfibrillar mantle of elastic fibres throughout the body and also in the lamina rara interna of the glomerulus basement membrane (GBM). Binding of anti-SAP mAb to SAP in these locations could lead to local inflammation. It is possible this process could be confined to the skin, but widespread organ toxicity would also be expected and this has not been observed to date.

Amyloid deposits are also present in the skin and the rash could represent the therapeutic removal of cutaneous amyloid deposits. Removal of amyloid in other organs has not been associated with persistent inflammation and the limited biopsy evidence is also not consistent with this process.

### 12.3.2. Investigation of rash

Rash is an event of special interest (EOSI) and will undergo comprehensive assessment as outlined in [Table 8](#). The assessments performed may be refined as data emerges.

**Table 8 Investigation of rash**

Investigation	Timing/Procedure	Proposed tests
EOSI form	Rash onset and at least every 12 hours until resolution or study investigator satisfied that clinically stable	Formal questionnaire to record rash progression/resolution including patient assessment of symptoms Includes assessment of systemic involvement
Photographs	Rash onset and during evolution	Photographs from all sites will be reviewed centrally.
Skin biopsy (3-4mm punch)	Biopsy at rash onset may also include an unaffected area for comparison. To be taken as soon as possible after rash onset Consider repeat biopsy if rash worsens Follow-up biopsy from a rash affected region when active lesions fully clinically resolved Up to 10 subjects (5 ATTR patients, 5 AL patients) who consent to this procedure, will be invited to have a baseline (pre treatment) biopsy to provide a comparison  In the event of recurrent clinically similar rash in the same subject repeat biopsy may be omitted	Biopsies will be processed as detailed in the SRM Biopsies will be examined for: Light microscopy Congo Red staining and examination under polarised light for amyloid  SAP Immunohistochemistry for cell activation and differentiation markers Immunoglobulins and complement factors  <b>This list is not exhaustive and may be modified based on observations</b>

Investigation	Timing/Procedure	Proposed tests
Blood samples	Paired with each skin biopsy	<p>Multiplex ELISA for blood cytokines, CRP, SAA, detection of circulating mAb-SAP immune complexes using C1q assays</p> <p>Fluid phase complement markers: e.g. C3dg / total C3 ratio, C3a, C5a, C4a &amp; C5b-C9 (TCC)</p> <p>ANA; ANCA; anti-DS-DNA antibody</p> <p>RNA transcriptomic research</p> <p>Blood renal and liver function tests (if not already assessed per routine schedule)</p> <p><b>This list is not exhaustive and may be modified based on observations</b></p>
Urinalysis	Rash onset and evolution	<p>Assessment of urine sediment for evidence of glomerulonephritis</p> <p>Protein excretion</p>

### 12.3.3. Management of Rash

Rash will be graded using the following criteria based on symptoms and the body surface area (BSA) affected [Table 9].

**Table 9 Grading criteria for rash**

Rash Grade	Distribution/Symptoms	Action
1	<10% BSA AND asymptomatic	Dermatology review <sup>c</sup> before patient discharge if rash persists ≥7 days post-mAb dose
2	10-30% BSA and/or mild symptoms <sup>a</sup>	Dermatology review <sup>c</sup> before patient discharge if rash persists ≥7 days post-mAb dose
3	>30% BSA and/or moderate/severe symptoms <sup>a</sup>	Local dermatology review <sup>c</sup> to be performed as soon as possible after rash onset, but must be performed within 72 hours
4	Any rash with mucosal or systemic involvement <sup>b</sup>	<p>Immediate dermatology review</p> <p>Withdraw from study treatment.</p> <p>See specific advice Section <a href="#">12.3.4</a></p>

a. Symptoms include: pain, itch and burning

b. E.g. evidence of renal involvement

c. In addition, at the discretion of the Investigator or designee a telemedicine review of rash photos and general rash management advice from remote dermatologist may be requested

Dermatological review should also be sought if a persistent rash worsens.

Symptomatic management of mild/moderate rash should be under the direction of the Investigator with expert dermatological advice as appropriate. Initial management of rashes could include, but is not restricted to, use of emollients, topical corticosteroids and antihistamines.

#### 12.3.3.1. Modification of anti-SAP mAb dose based on rash

In the event that rash appears following the first day's infusion of anti-SAP mAb the following algorithm should be followed [Figure 6].

**Figure 6 Intra-dosing Management Plan for Rash**

Day 1	Day 2	Day 3 (prior to dosing)		Day 3
Administer first portion of anti-SAP mAb dose e.g. 600 mg	Assess for Rash		No rash attributable to anti-SAP mAb	Proceed with dosing second portion of anti-SAP mAb dose (e.g. 600 mg)
			Rash attributable to anti-SAP mAb	Do NOT administer anti-SAP mAb

The decision whether to proceed with further Anti-SAP treatments and the dose level for anti-SAP mAb will be based on the severity and persistence of any rash observed.

**Figure 7 Dosing algorithm for Anti-SAP mAb according to severity of rash**

Maximum grade of rash			
1	2	3	4
<b>All subjects to be reviewed prior to each Anti-SAP treatment.</b>			
<p>If rash persistent then review weekly for resolution of rash.</p> <p>Next Anti-SAP treatment can be administered once rash resolved.</p> <p>Anti-SAP mAb dose level same as previously administered</p> <p>If rash not resolved by 8 weeks post last mAb dose withdraw from study</p>	<p>If rash persistent then review weekly for resolution of rash.</p> <p>Next Anti-SAP treatment can be administered once rash resolved but at reduced dose</p> <p>If rash not resolved by 8 weeks post last mAb dose withdraw from study treatment</p> <p>Reduce dose by 300 mg from previous dose. Dose levels = 900 mg, 600 mg, 300 mg</p> <p><b>Note:</b> If a dose reduction is required following Session 1, then the Session 2 mAb dose level will be 300mg.</p> <p>If grade 2 or 3 rash observed at 300 mg dose level withdraw from study treatment</p>	<p>Follow emergency management plan</p> <p>Withdraw from study</p>	

When a dose reduction is warranted the dose of anti-SAP mAb to be administered on subsequent treatment session should be modified as outlined in Section 6.2

#### **12.3.4. Emergency management of rash with systemic /mucosal involvement**

Severe (Grade 4) rash, with systemic or mucosal involvement is a medical emergency.

An immediate consultation for consideration of transfer of care to high dependency or intensive care unit should also be undertaken.

Immediate expert dermatology review should be undertaken.

The subject should be withdrawn from the study and not receive any further anti-SAP mAb treatment however CPHPC should continue to be administered to Day 11 whenever feasible.

The GSK medical monitor should be contacted as soon as possible.

The management is largely supportive and should be directed by local expert advice.

At this time there is insufficient information to recommend specific treatment but corticosteroids are commonly administered for severe rash with systemic/ mucosal involvement.

#### **12.3.5. Post-Inflammatory Hyperpigmentation (PIH)**

PIH is a recognised chronic complication of acute skin inflammation, and can take weeks to months to completely resolve dependent upon the skin layer which is principally involved. PIH will be reported separately from rash

## 12.4. Appendix 4: Genetic Research

### Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic aetiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

### Genetic Research Objectives and Analyses

- The objectives of the genetic research are to investigate the relationship between genetic variants and: Response to anti-SAP treatment, including any regimens under investigation in this study or any concomitant medicines. Response includes pharmacokinetics, efficacy and safety/tolerability (e.g. skin rash)
- Susceptibility, severity and progression of cardiac amyloidosis and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (e.g. whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

### Study Population

Any subject who is enrolled in the study can participate in genetic research.

### Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been

identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

### **Informed Consent**

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

### **Subject Withdrawal from Study**

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.



Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

### **Screen and Baseline Failures**

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

### **Provision of Study Results and Confidentiality of Subject's Genetic Data**

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

### **References**

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33:467-486.

## 12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

### 12.5.1. Definition of Adverse Events

#### Adverse Event Definition:

- An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

#### Events meeting AE definition include:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).
- Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

#### Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's

**Events NOT meeting definition of an AE include:**

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**12.5.2. Definition of Serious Adverse Events**

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

**Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:**

**a. Results in death****b. Is life-threatening**

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

**c. Requires hospitalization or prolongation of existing hospitalization**

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in disability/incapacity**

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct

normal life functions.
<ul style="list-style-type: none"> <li>This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption</li> </ul>
<b>e. Is a congenital anomaly/birth defect</b>
<b>f. Other situations:</b> <ul style="list-style-type: none"> <li>Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.</li> <li>Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse</li> </ul>
<b>g. Is associated with liver injury <u>and</u> impaired liver function defined as:</b> <ul style="list-style-type: none"> <li>ALT <math>\geq</math> 3xULN and total bilirubin* <math>\geq</math> 2xULN (&gt;35% direct), <b>or</b></li> <li>ALT <math>\geq</math> 3xULN and INR** <math>&gt;</math> 1.5.</li> </ul> <p>* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT <math>\geq</math> 3xULN and total bilirubin <math>\geq</math> 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>
<b>h. Grade 4 rash</b>
<ul style="list-style-type: none"> <li>Refer to <a href="#">Appendix 2</a> for the required liver chemistry follow-up instructions</li> </ul>

### 12.5.3. Definition of Cardiovascular Events

<b>Cardiovascular Events (CV) Definition:</b>
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:
<ul style="list-style-type: none"> <li>Myocardial infarction/unstable angina</li> <li>Congestive heart failure</li> </ul>

**Cardiovascular Events (CV) Definition:**

- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

**12.5.4. Recording of AEs and SAEs****AEs and SAE Recording:**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

### 12.5.5. Evaluating AEs and SAEs

#### Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

#### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

### Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

### 12.5.6. Reporting of SAEs to GSK

#### SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and e-mail in portable document format (PDF) to both the primary and secondary medical monitors (details on the medical monitor / sponsor contact information page of this protocol), and also to GSK's case management group mailbox PPD
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the medical monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

## 12.6. Appendix 6: Collection of Pregnancy Information

### 12.6.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [[Hatcher](#), 2011]
4. Injectable progestogen [[Hatcher](#), 2011]
5. Contraceptive vaginal ring [[Hatcher](#), 2011]
6. Percutaneous contraceptive patches [[Hatcher](#), 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [[Hatcher](#), 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

#### **Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable).**

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until [at least five half-lives of study medication OR for a cycle of spermatogenesis following five terminal half-lives] after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
  - Contraceptive subdermal implant
  - Intrauterine device or intrauterine system
  - Combined estrogen and progestogen oral contraceptive [[Hatcher](#), 2011]



- Injectable progestogen [[Hatcher](#), 2011]
- Contraceptive vaginal ring [[Hatcher](#), 2011]
- Percutaneous contraceptive patches [[Hatcher](#), 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

#### **12.6.2. Collection of Pregnancy Information**

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in [Appendix 5](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

#### **Any female subject who becomes pregnant while participating**

- will be withdrawn from the study treatment study

**12.6.3. Pregnancy in female partner of a male study subject**

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

**References**

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20<sup>th</sup> edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

## 12.7. Appendix 7: Reference tables

**Table 10 Haematologic Response to Chemotherapy**

Criteria	Response
Complete Response - CR	Normalization of the free light chain levels and ratio, negative serum and urine immunofixation
Very Good partial Response - VGPR	Reduction in the dFLC to $\leq 40$ mg/L
Partial Response - PR	A greater than 50% reduction in the dFLC
No Response	Less than PR
[Comenzo, 2012]	

**Table 11 Mayo stage and prognosis in AL amyloidosis**

Stage	I	II	IIIa	IIIb
	Both markers below threshold	Either greater than threshold	Both greater than threshold BNP $\leq 8500$ ng/L	Both greater than threshold BNP $> 8500$ ng/L
Survival @24 months	Approx 100%	60%	60%	30%
Proportion of patients	18%	33%	29%	20%

Thresholds for cTnT and NT-proBNP are  $< 0.035$   $\mu\text{g/L}$  and  $< 332$  ng/L, respectively [Palladini, 2015]

**Equation 1 4-variable MDRD formula for estimated glomerular filtration rate (eGFR)**

If serum creatinine (SCr) in  $\mu\text{mol/L}$

$$\text{eGFR} = 186.3 \times (\text{SCr}/88.4)^{-1.154} \times (\text{age, y})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

If SCr in mg/dL:

$$\text{eGFR} = 186.3 \times (\text{SCr})^{-1.154} \times (\text{age, y})^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}.$$

Note: ethnic group only has adjustment for African/African American; age is in years

## Classification- for groups

- This table classifies stages of CKD and outlines actions to improve outcomes in each stage
- Stages are defined based on level of kidney function (eGFR)
- "Cut-off" levels between stages are inherently arbitrary BUT staging facilitates application of clinical practice guidelines to the evaluation and management of CKD

Stage	Description	GFR (mL/min/1.73 m <sup>2</sup> )	Action*
	At increased risk	≥60 (with CKD risk factors)	Screening, CKD risk reduction
<b>1</b>	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
<b>2</b>	Kidney damage with mild ↓ GFR	60–89	Estimating progression
<b>3</b>	Moderate ↓ GFR	30–59	Evaluating and treating complications
<b>4</b>	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
<b>5</b>	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Shaded area identifies patients who have chronic kidney disease; unshaded area designates individuals who are at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m<sup>2</sup> for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

\* Includes actions from preceding stages.

Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; CVD, cardiovascular disease

Source: National Kidney Foundation. *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification*. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1) www.kdoqi.org

**Table 12 New York Heart Association (NYHA) Classification**

	Patient Symptoms
<b>I</b>	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
<b>II</b>	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
<b>III</b>	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
<b>IV</b>	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

## References

Comenzo RL, Reece D, Palladini *et al*. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. *Leukemia*. 2012;26(11):2317-25

Palladini G, Sachchithanantham S, Milani P *et al*. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015 30;126(5):612-5

## 12.8. Appendix 8: Protocol Amendments

### Amendment 1

#### Where the Amendment Applies

Throughout the protocol

#### Summary of Amendment Changes

Changes made to reflect regulatory input from the FDA. Other changes made to correct minor errors included in the original version.

#### List of Specific Changes

##### Medical Monitor / Sponsor Information Page

###### RATIONALE FOR CHANGE

Update to Primary Medical Monitor contact details and a change in Secondary Medical Monitor.

###### PREVIOUS TEXT

Primary Medical Monitor	PPD	GlaxoSmithKline Medicines Research & Development, Gunnels Wood Road, Stevenage SG1 2NY United Kingdom
Secondary Medical Monitor		GlaxoSmithKline Clinical Unit Cambridge Addenbrooke's Hospital Box 128, Hills Rd, Cambridge CB2 2GG United Kingdom

###### REVISED TEXT

Primary Medical Monitor	PPD	GlaxoSmithKline Medicines Research & Development, Gunnels Wood Road, Stevenage SG1 2NY United Kingdom
Secondary Medical Monitor		GlaxoSmithKline Clinical Unit Cambridge Addenbrooke's Hospital Box 128, Hills Rd, Cambridge CB2 2GG United Kingdom

### Protocol Synopsis, Objectives and Endpoints

#### RATIONALE FOR CHANGE

Inclusion of objective and endpoint to investigate subject experience of study treatment.

#### REVISED TEXT

<u>To characterise the subject experience of Anti-SAP Treatment regimen</u>	<u>Subject Exit Interviews completed over the telephone after the 8 week follow-up or Early Withdrawal Visit</u>
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### Protocol Synopsis, Treatment Groups and Duration

#### RATIONALE FOR CHANGE

Correction of unit.

#### PREVIOUS TEXT

**Group 3: Newly diagnosed Mayo stage II or IIIa AL amyloidosis patients, and with plasma NT-proBNP levels  $\leq$  8500 ng/mL**

REVISED TEXT

**Group 3: Newly diagnosed Mayo stage II or IIIa AL amyloidosis patients, and with plasma NT-proBNP levels  $\leq$  8500 ng/mL**

### **Protocol Synopsis, Treatment Groups and Duration**

#### **RATIONALE FOR CHANGE**

Clarification that the regulatory agencies will be involved in the decision to start recruitment into Group 3.

#### **PREVIOUS TEXT**

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.

#### **REVISED TEXT**

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.**

### **Protocol Synopsis, Analysis**

#### **RATIONALE FOR CHANGE**

Clarification that regulatory agency interactions may follow a data review.

#### **PREVIOUS TEXT**

Study specific decisions will be supported by the periodic review of study data. The first review will take place once 5 subjects have completed at least 3 courses of Anti-SAP treatment. Outcomes from the periodic data reviews may include:

- Initiation of recruitment in to Group 3

#### **REVISED TEXT**

Study specific decisions will be supported by the periodic review of study data. The first review will take place once 5 subjects have completed at least 3 courses of Anti-SAP treatment. Outcomes from the periodic data reviews may include:

- **Regulatory interactions and** initiation of recruitment in to Group 3

### 3.Objectives and Endpoints

#### RATIONALE FOR CHANGE

Inclusion of objective and endpoint to investigate subject experience of study treatment.

#### PREVIOUS TEXT

None

#### REVISED TEXT

<b><u>To characterise the subject experience of Anti-SAP Treatment regimen</u></b>	<b><u>Subject Exit Interviews completed over the telephone after the 8 week follow-up or Early Withdrawal Visit</u></b>
--	---

### 4.1 Overall Design

#### RATIONALE FOR CHANGE

Inclusion of statement to restrict the number of subjects on active treatment at each site at any given time.

#### PREVIOUS TEXT

Subjects will return to clinic for long term follow-up of safety and functional status (including CMR and ECHO), 6 and 12 months post last anti-SAP mAb treatment.

#### REVISED TEXT

Subjects will return to clinic for long term follow-up of safety and functional status (including CMR and ECHO), 6 and 12 months post last anti-SAP mAb treatment.

**No more than two subjects will be in active treatment (dosing) at each study site at any given time.**



**4.1 Overall Design, Figure 2**

## RATIONALE FOR CHANGE

Increase in the duration of the combined screening and baseline period due to requirement of 2 week cardiac assessment at baseline.

## PREVIOUS TEXT

28 days

## REVISED TEXT

28-~~42~~ days

**4.1 Overall Design, Table 1 (Day 4-11)**

## RATIONALE FOR CHANGE

Removal of allowance to self-administer CPHPC.

## PREVIOUS TEXT

**Inpatient safety follow up**

Administration of CPHPC SC continues until Day 11

[Subjects may be allowed to self administer SC CPHPC as outpatients at investigators' discretion]

## REVISED TEXT

**Inpatient safety follow up**

Administration of CPHPC SC continues until Day 11

~~[Subjects may be allowed to self administer SC CPHPC as outpatients at investigators' discretion]~~

**Protocol Synopsis, Objectives and Endpoints, Table 1 (Day 17)**

## RATIONALE FOR CHANGE

Removal of 1 day window around visit.

## PREVIOUS TEXT

17 ± 1d

REVISED TEXT

17 ±4d

## 4.2 Treatment Groups and Duration

RATIONALE FOR CHANGE

Correction of unit.

PREVIOUS TEXT

**Group 3: Newly diagnosed Mayo stage II or IIIa AL amyloidosis patients** (plasma NT-proBNP levels ≤ 8500 ng/mL)

---

Group 1 and Group 2 will begin recruitment first. Recruitment into Group 3 will start only after data has been reviewed as detailed in Section 10.8.2.

REVISED TEXT

**Group 3: Newly diagnosed Mayo stage II or IIIa AL amyloidosis patients** (plasma NT-proBNP levels ≤ 8500 ng/mL)

---

Group 1 and Group 2 will begin recruitment first. Recruitment into Group 3 will start only after data has been reviewed **and regulatory interaction sought** as detailed in Section 10.8.2.

### 4.5.1 GSK2315698 (CPHPC - Plasma SAP Depleter)

RATIONALE FOR CHANGE

To clarify that the circulating SAP level of 2mg/L from the FIH (SAP115570) study was determined using a Hycult ELISA assay.

PREVIOUS TEXT

In the FIH study (SAP115570), the standard dosing regimen of CPHPC consisted of an IV infusion of 20 mg/hour for 72 hours prior to anti-SAP mAb administration. This regimen was reliably effective in depleting circulating SAP to <2 mg/L. Since there is no precedent for the present treatment, this empirical target SAP concentration was adopted on the basis of evaluation of the potential for formation of harmful circulating immune

complexes and safety evaluation in the FIH study did not identify signals suggestive of adverse effects from residual SAP.

#### REVISED TEXT

In the FIH study (SAP115570), the standard dosing regimen of CPHPC consisted of an IV infusion of 20 mg/hour for 72 hours prior to anti-SAP mAb administration. This regimen was reliably effective in depleting circulating SAP to <2 mg/L (**using Hycult ELISA assay**). Since there is no precedent for the present treatment, this empirical target SAP concentration was adopted on the basis of evaluation of the potential for formation of harmful circulating immune complexes and safety evaluation in the FIH study did not identify signals suggestive of adverse effects from residual SAP.

#### 4.5.2 GSK2398852 (anti-SAP mAb)

##### RATIONALE FOR CHANGE

To reduce the dose given in Session 1 to 600mg. The dose planned for the other sessions (1200mg) remains unchanged.

##### PREVIOUS TEXT

The anti-SAP mAb dose in this study is 1200 mg in each monthly cycle, given as two infusions over 6-8 hour each, on Days 1 and 3. The dose and regimen is based on the results of the FIH study (SAP115570), and has been selected to promote rapid elimination of amyloid deposits whilst minimising adverse effects.

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Although doses up to 2000 mg were well tolerated in those with a large (hepatic) amyloid load, much of the target patient population for this phase 2 study will have a small to moderate amyloid load. The dose response information from the FIH study in those with renal amyloidosis (also a small/moderate load population) show that a dose level of 600 mg is effective in about one third of the subjects treated but at a dose level of 1200 mg the response rate is substantially higher (>80%). It is recognized that while the dose of 1200 mg is associated with a high rate of amyloid clearance, it is also associated with rash which has been severe in one case. At this time the most likely causes of the rash are related to the peak concentration of the anti-SAP mAb. For this reason the anti-SAP mAb dose in this study will be split: administered as two infusions (duration of 6-8hr) of 600 mg on Days 1 and 3. This will have the effect of blunting the maximum concentration while maintaining a moderate concentration in the plasma for longer. This approach may also enhance delivery of anti-SAP mAb to the heart.

The risk of skin rashes will be mitigated by giving the anti-SAP mAb dose in two slowly infused 600 mg portions on days 1 and 3, with availability of a reduced dose schedule according to the safety assessment algorithm in Section 6.2. Emerging results will be reviewed regularly to enable dose reduction if necessary and to select the appropriate starting dose for Group 3.

## REVISED TEXT

The **proposed starting dose level of anti-SAP mAb dose in this study is 600mg given as a divided dose of two infusions of 300 mg over 6-8 hours each on Days 1 and 3. This dose level and regimen is expected to be well tolerated based on previous experience and to be pharmacologically active in a proportion of patients (estimated to be 30% based on previous experience).**

**Dose escalation on subsequent sessions will be considered on a case by case basis based on tolerability and evidence of pharmacodynamic effect. It is proposed that the dose in subsequent treatment sessions will be maximally** 1200 mg ~~in each monthly cycle~~, given as two infusions over 6-8 hours each, on Days 1 and 3. The dose and regimen is based on the results of the FIH study (SAP115570), and has been selected to promote rapid elimination of amyloid deposits whilst minimising adverse effects.

Although doses up to 2000 mg were well tolerated in those with a large (hepatic) amyloid load, much of the target patient population for this phase 2 study will have a small to moderate amyloid load. The dose response information from the FIH study in those with renal amyloidosis (also a small/moderate load population) show that a dose level of 600 mg is effective in about one third of the subjects treated but at a dose level of 1200 mg the response rate is substantially higher (>80%). It is recognized that while the dose of 1200 mg is associated with a high rate of amyloid clearance, it is also associated with rash which has been severe in one case. At this time the most likely causes of the rash are related to the peak concentration of the anti-SAP mAb. For this reason the anti-SAP mAb dose in this study will be split: administered as two infusions (duration of 6-8hr) ~~of 600 mg~~ on Days 1 and 3. This will have the effect of blunting the maximum concentration while maintaining a moderate concentration in the plasma for longer. This approach may also enhance delivery of anti-SAP mAb to the heart.

The risk of skin rashes will be mitigated by giving the anti-SAP mAb dose in two slowly infused ~~600 mg~~ portions on ~~4~~ Days 1 and 3, with availability of a reduced dose schedule according to the safety assessment algorithm in Section 6.2. Emerging results will be reviewed regularly to enable dose reduction if necessary and to select the appropriate starting dose for Group 3.

#### 4.6.1.1 Potential For Cardiotoxicity

##### RATIONALE FOR CHANGE

Clarification that Baseline and Outpatient ECG analysis will be performed using BodyGuardian.

##### PREVIOUS TEXT

The present study design therefore includes comprehensive assessment and monitoring designed specifically to detect and characterize these and any other adverse cardiac effects which may arise. Baseline will include leadless non-implantable ECG analysis,

for example using ZioPatch, to provide the individual's own control profile for any changes following treatment. Monitoring during the study will comprise in-patient telemetry, out-patient leadless ECG analysis (e.g. ZioPatch) between treatment sessions, monthly ECHO & CMR imaging, and serial monitoring of cardiac blood biomarkers. Any adverse effects on cardiac function will thus be detected promptly, enabling swift and appropriate intervention and management.

#### REVISED TEXT

The present study design therefore includes comprehensive assessment and monitoring designed specifically to detect and characterize these and any other adverse cardiac effects which may arise. Baseline will include leadless non-implantable ECG analysis, for example using ~~ZioPatch~~ **BodyGuardian**, to provide the individual's own control profile for any changes following treatment. Monitoring during the study will comprise in-patient telemetry, out-patient leadless ECG analysis (e.g. ~~ZioPatch~~ **BodyGuardian**) between treatment sessions, monthly ECHO & CMR imaging, and serial monitoring of cardiac blood biomarkers. Any adverse effects on cardiac function will thus be detected promptly, enabling swift and appropriate intervention and management.

#### 4.6.1.3 Potential for Circulating Immune Complex Formation

##### RATIONALE FOR CHANGE

To include that anti-SAP immune complex assessments will be performed in the event of a rash.

##### PREVIOUS TEXT

In order to mitigate this potential risk, blood samples for determination of SAP/anti-SAP mAb immune complexes will be taken from all subjects in this study as a safety measurement at the time-points specified in the Time & Events tables (Section 7.1). Timing of the assessments may be adjusted based on emerging data.

##### REVISED TEXT

In order to mitigate this potential risk, blood samples for determination of SAP/anti-SAP mAb immune complexes will be taken from all subjects in this study as a safety measurement at the time-points specified in the Time & Events tables (Section 7.1) **and in the event of a rash**. Timing of the assessments may be adjusted based on emerging data.

#### 4.6.2 Risk Assessment Table, Myocarditis / Cardiac remodelling associated with removal of amyloid

##### RATIONALE FOR CHANGE

Clarification that Baseline and Outpatient ECG analysis will be performed using Body Guardian and correction of assessment timepoints.

##### PREVIOUS TEXT

Non-implantable, ECG recording devices (e.g. ZioPatch) will be used to detect abnormalities in cardiac electrophysiology on discharge from in-patient stay and at 8-week and 6 and 12 month follow-up

##### REVISED TEXT

Non-implantable, ECG recording devices (e.g. ~~ZioPatch~~ **BodyGuardian**) will be used to detect abnormalities in cardiac electrophysiology on discharge from in-patient stay and at 8-week and 6- ~~and 12~~-month follow-up

#### 4.6.2 Risk Assessment Table, Epistaxis

##### RATIONALE FOR CHANGE

Clarification of the clinical mitigation strategy should epistaxis occur.

##### PREVIOUS TEXT

Baseline coagulation and serial blood haematology

Serial coagulation if epistaxis occurs.

##### REVISED TEXT

**Serial blood haematology and b**~~Baseline~~ **and session 1 post dose** coagulation **assessment.** ~~and serial blood haematology~~

Serial coagulation if epistaxis **or other bleeding abnormalities** occurs. **If abnormalities are observed in coagulation tests, additional investigations including platelet function tests may be performed.**

#### 4.6.2 Risk Assessment Table, Cytopenia

##### RATIONALE FOR CHANGE

Removal of Cytopenia risk from the risk assessment table as in vitro data demonstrates that GSK2315698 does not inhibit either Pgp or BCRP up to 300µM.

##### PREVIOUS TEXT

Although no observations in the preclinical and clinical use of GSK2315698, have shown any evidence of it mediating DDI effects, in silico modelling suggests that it could potentially inhibit PGP-1 & BRCP drug efflux transporters, thereby augmenting the cytopenic effects of cyclophosphamide within the CyBorD chemotherapy regimen	Serial blood haematology
--	--------------------------

##### REVISED TEXT

<del>Although no observations in the preclinical and clinical use of GSK2315698, have shown any evidence of it mediating DDI effects, in silico modelling suggests that it could potentially inhibit PGP-1 &amp; BRCP drug efflux transporters, thereby augmenting the cytopenic effects of cyclophosphamide within the CyBorD chemotherapy regimen</del>	Serial blood haematology
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#### 5.1 Inclusion Criteria, Inclusion Criteria for Group 2 and Inclusion Criteria for Group 3 (same wording applies to inclusion criteria for both groups)

##### RATIONALE FOR CHANGE

To provide clarification regarding presence of any mutations in amyloidogenic genes will establish the eligibility criteria for this group. Once there is a positive identification of a mutation in an amyloidogenic gene then patients are not tested for all known mutations.

##### PREVIOUS TEXT

AL amyloidosis confirmed by biopsy with immunohistochemical staining or proteomic identification of AL amyloid fibril type, in subjects with definite monoclonal gammopathy in whom causative mutations of all known relevant amyloidogenic genes have been excluded

## REVISED TEXT

AL amyloidosis confirmed by biopsy with immunohistochemical staining or proteomic identification of AL amyloid fibril type, in subjects with definite monoclonal gammopathy in whom causative mutations of ~~all known relevant~~ amyloidogenic genes have been excluded

**6.2.1 CPHPC dosing regimen according to renal function**

## RATIONALE FOR CHANGE

In SAP115570 (FIH) pharmacokinetic data from blood samples collected on the ninth day after antiSAP mAb administration the PK levels of antiSAP mAb were below the target and therefore dose of CPHPC is not required following the morning dose on Day 11 (ninth day after antiSAP mAb administration). Additional column showing the dose regimen on Day 11 is added to indicate only the morning dose on Day 11 is required.

## PREVIOUS TEXT

Renal Function	IV dose level	SC dose regimen	Time points of SC administration	
eGFR <sup>a</sup> (mL/min/1.73m <sup>2</sup> )			Day 1 <sup>b</sup> 1st mAb dose per treatment session	Subsequent days (Days 2-11)
≥ 64	20mg/hour	60 mg t.i.d	14:00, 22:00	08:00, 14:00, 22:00
≥ 46 and < 64	10mg/hour	60 mg t.i.d	14:00, 22:00	08:00, 14:00, 22:00
≥ 39 and < 46	10mg/hour	60 mg b.i.d	21:00	09:00, 21:00
≥ 33 and < 39	5mg/hour	60 mg b.i.d	21:00	09:00, 21:00
≥ 27 and < 33	5mg/hour	60 mg o.d	-	09:00

## REVISED TEXT

Renal Function	IV dose level	SC dose regimen	Time points of SC administration		
eGFR <sup>a</sup> (mL/min/1.73m <sup>2</sup> )			Day 1 <sup>b</sup> 1st mAb dose per treatment session	Subsequent days (Days 2-140)	<u>Subsequent day (Day 11)</u>
≥ 64	20mg/hour	60 mg t.i.d	14:00, 22:00	08:00, 14:00, 22:00	<u>08:00</u>
≥ 46 and < 64	10mg/hour	60 mg t.i.d	14:00, 22:00	08:00, 14:00, 22:00	<u>08:00</u>
≥ 39 and < 46	10mg/hour	60 mg b.i.d	21:00	09:00, 21:00	<u>09:00</u>
≥ 33 and < 39	5mg/hour	60 mg b.i.d	21:00	09:00, 21:00	<u>09:00</u>
≥ 27 and < 33	5mg/hour	60 mg o.d	-	09:00	<u>09:00</u>



## 6.2.2 Dose-Level reduction Schedule for anti-SAP mAb due to Adverse Events

### RATIONALE FOR CHANGE

To provide clarification of the composition of doses of antiSAP mAb in any dose reduction and information on dose level reduction with the introduction of Session 1 total dose of 600mg.

### PREVIOUS TEXT

Reductions in dose level are at the discretion of the Investigator in consultation with the GSK study team during the dose confirmation meeting, and can be triggered based upon the intensity of the adverse event (AE) which is observed during any treatment session and is reasonably attributable to anti-SAP mAb. (See Figure 4)

- a) First dose reduction will be to 900 mg
- b) Second dose reduction to 600mg
- c) Third dose reduction to 300mg

**No further dose modifications will be permitted below the 300mg dose level.**

### REVISED TEXT

Reductions in dose level are at the discretion of the Investigator in consultation with the GSK study team during the dose confirmation meeting, and can be triggered based upon the intensity of the adverse event (AE) which is observed during any treatment session and is reasonably attributable to anti-SAP mAb. (See Figure 4). **The recommended dose reduction scheme is provided in Figure 4 although greater than 300 mg reductions would be allowed based on clinical tolerability.**

- 1. First dose reduction will be to 900 mg **(300mg on D1, 600mg on D3)**
- 2. Second dose reduction to 600mg **(300mg on D1, 300mg on D3)**
- 3. Third dose reduction to 300mg **(150mg on D1, 150mg on D3)**

**No further dose modifications will be permitted below the 300mg dose level.**

**Note: If a dose reduction is required following Session 1, then the Session 2 mAb dose level will be 300mg ('c' in the above list).**

## Study Treatment, Preparation/Handling/Storage/Accountability

### RATIONALE FOR CHANGE

Removal of text discussing subjects' self-administration of CPHPC as this option is no longer applicable.

## REVISED TEXT

- ~~If required the subjects may self-administer treatment by sub-cutaneous injection of CPHPC if discharged from clinical unit prior to completion of administration. Subjects will receive training on sub-cutaneous injection prior to discharge and will only be discharged if the PI considers they are competent to administer.~~

**6.6 Compliance with Study Treatment Administration**

## RATIONALE FOR CHANGE

Removal of text discussing subjects' self-administration of CPHPC as this option is no longer applicable.

## PREVIOUS TEXT

When subjects are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When subjects self-administer study treatment(s) at home, compliance with CPHPC will be assessed through querying the subject during the site visits and documented in the source documents and CRF. A record of the number of vials/syringes dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

## REVISED TEXT

~~When~~ sSubjects **will be** dosed at the site, ~~they~~ **and** will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

~~When subjects self-administer study treatment(s) at home, compliance with CPHPC will be assessed through querying the subject during the site visits and documented in the source documents and CRF. A record of the number of vials/syringes dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.~~

### 7.1 Time and Events Table, Table 3

#### RATIONALE FOR CHANGE

To include timepoints / clarification not included in the previous version of the protocol, and to include edits made as part of the current amendment

#### REVISED TEXT

- Outpatient visit added at Session 1, 'Day 24'
- Haematology/Clinical Chemistry/Urinalysis added at all Sessions 'Day-2 to 11'
- 24hr Urine collection for protein and creatinine added at 6 month Follow-up visit
- Inclusion of an Exit interview at 8 week Follow-up visit
- Edit to Footnote '1' to state screening to take place within **42** days of start of treatment
- Edit to Footnote '7' to include that out-patient cardiac recording will be for approximately 2 weeks at both the 8 week and 6 month follow-up timepoints in addition to baseline
- Addition of Footnote '13' (For subjects with a GFR <40ml/min/1.73m<sup>2</sup>, MRI will be performed at the scheduled times but without contrast)
- Addition of Footnote '14' (Subjects are allowed to be admitted on **Day** -3 to allow for pre-dose assessments to be performed)
- Addition of lines for 'Concomitant therapy' and Adverse event review'

### 7.1 Time and Events Table, Table 4

#### RATIONALE FOR CHANGE

To include timepoints / clarification not included in the previous version of the protocol, and to include edits made as part of the current amendment

#### REVISED TEXT

- Edit to Footnote 3 to replace SAP levels being 'below 2mg/L' with being 'below target'
- Addition of Footnote '12' to state that 'Morning dose only to be administered (see Table 2)' on Day 11
- Addition of Footnote '13' (Subjects are allowed to be admitted on Day -3 to allow for pre-dose assessments to be performed)

### 7.1 Time and Events Table, Table 5

#### RATIONALE FOR CHANGE

To include timepoints / clarification not included in the previous version of the protocol, and to include edits made as part of the current amendment

## REVISED TEXT

- Addition of 'of that day' to Footnote '5' to clarify reference of blood sampling times
- Addition of Footnote '8' (To include clotting tests for Session 1 only – see Table 6)

**7.4.7.2 Cardiac Recording**

## RATIONALE FOR CHANGE

Ziopatch device will not be used in this study. Text is amended to provide the example of 'BodyGuardian' may be used as a cardiac recording device, and that baseline assessment of cardiac recording will be up to 2 weeks.

## PREVIOUS TEXT

The type of device will be at the discretion of the Study site and might include, but is not restricted to, use of a ZioPatch or Cardio-Net device.

The recording will be analysed prior to the next anti-SAP treatment and the analysis reviewed by the Investigator.

Following confirmation of eligibility, a baseline assessment for two weeks will be performed to provide baseline data. Whenever feasible the same device as that used at baseline will be used for subsequent measures.

## REVISED TEXT

The type of device will be at the discretion of the Study site and might include, but is not restricted to, use of a ~~ZioPatch~~ **BodyGuardian** or Cardio-Net device.

The recording will be analysed prior to the next anti-SAP treatment and the analysis reviewed by the Investigator.

Following confirmation of eligibility, a baseline assessment for **up to** two weeks will be performed to provide baseline data. Whenever feasible the same device as that used at baseline will be used for subsequent measures.

**7.4.8 Clinical Safety Laboratory Assessments**

## RATIONALE FOR CHANGE

To provide clarification of how central and local laboratories will be used in the study

## PREVIOUS TEXT

Study-required laboratory assessments will be performed by a central laboratory. Where applicable some laboratory assessments will be performed by a local laboratory. The results of each test must be entered into the CRF.

## REVISED TEXT

Study-required **clinical safety** laboratory assessments will be performed by a ~~central~~ **local** laboratory. **All other** ~~Where applicable some~~ laboratory assessments will be performed by a ~~local~~ **central** laboratory. The results of each test must be entered into the CRF.

**7.4.8 Protocol Required Safety Laboratory Assessments (Table 6)**

## RATIONALE FOR CHANGE

To include PT and APTT on Session 1, Day 2 in order to assess clotting function. To include clotting tests and, if required platelet function tests as investigation of adverse bleeding events.

## REVISED TEXT

<b><u>Further Tests (Session 1, Day 2 only)</u></b>	<ul style="list-style-type: none"> <li>• <b><u>Clotting tests – PT and APTT</u></b></li> </ul>
<b><u>Investigation of adverse bleeding event</u></b>	<ul style="list-style-type: none"> <li>• <b><u>Clotting tests – PT and APTT</u></b></li> <li>• <b><u>Platelet function tests (at discretion of Investigator or designee)</u></b></li> </ul>

**7.5.1 Blood Sample Collection**

## RATIONALE FOR CHANGE

Correction of individual blood sample collection volumes. Total maximum blood volume collected per session remains unchanged.

## PREVIOUS TEXT

3mL of blood will be collected into ethylenediaminetetraacetic acid (EDTA) tubes.

## REVISED TEXT

~~3mL~~ **2ml** of blood will be collected into ethylenediaminetetraacetic acid (EDTA) tubes.

### 7.6.1 Pharmacodynamic markers in blood

#### RATIONALE FOR CHANGE

Correction of individual blood sample collection volumes. Total maximum blood volume collected per session remains unchanged.

#### PREVIOUS TEXT

A 3mL blood sample will be collected at the time points as per Section 7.1, Time and Events Tables

#### REVISED TEXT

A ~~3mL~~ **4mL** blood sample will be collected at the time points as per Section 7.1, Time and Events Tables

### 7.6.3.2 RNA Transcriptome Research

#### RATIONALE FOR CHANGE

Correction of individual blood sample collection volumes. Total maximum blood volume collected per session remains unchanged.

#### PREVIOUS TEXT

A 0.5mL blood sample will be collected and the same samples may also be used to confirm findings by application of alternative technologies

#### REVISED TEXT

A ~~0.5mL~~ **2.5mL** blood sample will be collected and the same samples may also be used to confirm findings by application of alternative technologies

### 7.7.2 Immune complexes

#### RATIONALE FOR CHANGE

Correction of individual blood sample collection volumes. Total maximum blood volume collected per session remains unchanged.

#### PREVIOUS TEXT

0.5mL blood samples for determination of SAP/anti-SAP mAb immune complexes will be taken as a safety measurement at the time-points specified in the Time & Events tables

(Section 7.1) and Table 8. Timing of the assessments may be adjusted based on emerging data.

REVISED TEXT

~~0.5~~ **4**mL blood samples for determination of SAP/anti-SAP mAb immune complexes will be taken as a safety measurement at the time-points specified in the Time & Events tables (Section 7.1) and Table 8. Timing of the assessments may be adjusted based on emerging data.

### 7.10 Exit Interview

RATIONALE FOR CHANGE

Exit Interviews are added to better understand the patient perspective of systemic amyloidosis, to characterize patient experience and treatment benefit with Anti-SAP treatment, and to better understand patient involvement in the clinical trial. The output of this research will be used to understand the impact of the treatment as well as inform the design and endpoints for future clinical studies from the patient perspective.

REVISED TEXT

### 7.10 Exit Interview

**Exit interviews will be conducted after the 8 week follow-up or Early Withdrawal Visit and over the telephone, in a subset of subjects only, to explore subjects' experience with study treatment. Exit interviews are qualitative interviews conducted with study subjects to capture subject experiences in drug development on completion of participation in a clinical study. Interview questions are designed to fully assess a subject's experience with a study medication and study requirements and are administered in a semi-structured format over the telephone by a trained interviewer independent of study sites and sponsor. Subject feedback will be captured in a data collection sheet as well as being audio-taped for subsequent transcription and qualitative analysis and reported separately. The Exit interview technique and questions will be described in the SRM.**

### 9.3.2 Interim Analysis

RATIONALE FOR CHANGE

Clarification that regulatory agency interactions may follow a data review.

PREVIOUS TEXT

- Initiation of recruitment in to Group 3

## REVISED TEXT

- **Regulatory interactions and** initiation of recruitment in to Group 3

**10.8.1 Individual Subject Review**

## RATIONALE FOR CHANGE

To state that a benefit / risk assessment will make up part of the individual subject review

## PREVIOUS TEXT

The purpose of this review is to consider:

- whether it is appropriate to continue with Anti-SAP treatment in that subject, and
- the dose level for anti-SAP mAb

## REVISED TEXT

The purpose of this review is to consider:

- whether it is appropriate to continue with Anti-SAP treatment in that subject **based on a benefit / risk assessment**, and
- the dose level for anti-SAP mAb

**10.8.2 Periodic Study Review**

## RATIONALE FOR CHANGE

To include a statement that regulatory agency review of safety information will be conducted prior to commencement of recruitment into Group 3

## PREVIOUS TEXT

- Whether the schedule and timing of assessments are appropriate based on the observed safety profile
- Whether sufficient information is available to start recruitment of Group 3
- The Sponsor will be responsible for the final decision on the schedule of assessments and trigger point for recruitment into Group 3



## REVISED TEXT

- Whether the schedule and timing of assessments are appropriate based on the observed safety profile
- Whether sufficient information is available to start recruitment of Group 3

**The Sponsor will be responsible for the final decision on the schedule of assessments and identifying the trigger point for recruitment into Group 3. Recruitment into Group 3 will not start until a review of available safety information has been conducted by regulatory agency.** ~~The Sponsor will be responsible for the final decision on the schedule of assessments and trigger point for recruitment into Group 3~~

## Trademark Information

## RATIONALE FOR CHANGE

To update the trademark part of the protocol to accurately reflect changes made in the current amendment.

## PREVIOUS TEXT

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
NONE	Cardio-Net
	Chiron RIBA
	SAS
	WinNonlin
	ZioPatch

## REVISED TEXT

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
NONE	Cardio-Net
	Chiron RIBA
	SAS
	WinNonlin
	<del>ZioPatch</del> <b><u>BodyGuardian</u></b>

**Appendix 3, Investigation of Rash, Table 3 (skin biopsies)**

## RATIONALE FOR CHANGE

To provide clarification that from the 10 subjects who provide a baseline biopsy, 5 of these will be ATTR patients and the other 5 will be AL patients

## PREVIOUS TEXT

Up to 10 subjects will be invited to have a baseline (pre treatment) biopsy to provide a comparison

## REVISED TEXT

Up to 10 subjects **(5 ATTR patients, 5 AL patients) who consent to this procedure,** will be invited to have a baseline (pre treatment) biopsy to provide a comparison

**Appendix 3, Investigation of Rash, Table 3 (Blood samples)**

## RATIONALE FOR CHANGE

Correction of typographical error and inclusion of test not listed in previous version of protocol

## PREVIOUS TEXT

Paired with each skin biopsy	<p>Multiplex ELISA for blood cytokines, CRP, SAA, detection of circulating mAb-SAP immune complexes using C1q assays</p> <p>Fluid phase complement markers: C3dg / total C3 ratio, C3a, C5a, C4a &amp; C5b-C9 (TCC)</p> <p>ANA; ANCA; anti-DS-DNA antibody</p> <p>Blood renal and liver function tests (if not already assessed per routine schedule)</p> <p><b>This list is not exhaustive and may be modified based on observations</b></p>
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## REVISED TEXT

Paired with each skin biopsy	<p>Multiplex ELISA for blood cytokines, CRP, SAA, detection of circulating mAb-SAP immune complexes using C1q assays</p> <p>Fluid phase complement markers: <u>e.g.</u> C3dg / total C3 ratio, C3a, C5a, C4a &amp; C5b-C9 (TCC)</p> <p>ANA; ANCA; anti-DS-DNA antibody</p> <p><b><u>RNA transcriptomic research</u></b></p> <p>Blood renal and liver function tests (if not already assessed per routine schedule)</p> <p><b>This list is not exhaustive and may be modified based on observations</b></p>
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**Appendix 3, Figure 7**

## RATIONALE FOR CHANGE

Inclusion of text regarding dose reduction following Session 1

## PREVIOUS TEXT

Maximum grade of rash			
1	2	3	4
<b>All subjects to be reviewed prior to each Anti-SAP treatment.</b>			
<p>If rash persistent then review weekly for resolution of rash.</p> <p>Next Anti-SAP treatment can be administered once rash resolved.</p> <p>Anti-SAP mAb dose level same as previously administered</p> <p>If rash not resolved by 8 weeks post last mAb dose withdraw from study</p>	<p>If rash persistent then review weekly for resolution of rash.</p> <p>Next Anti-SAP treatment can be administered once rash resolved but at reduced dose</p> <p>If rash not resolved by 8 weeks post last mAb dose withdraw from study treatment</p> <p>Reduce dose by 300 mg from previous dose. Dose levels = 900 mg, 600 mg, 300 mg</p> <p>If grade 2 or 3 rash observed at 300 mg dose level withdraw from study treatment</p>	<p>Follow emergency management plan</p> <p>Withdraw from study</p>	

## REVISED TEXT

Maximum grade of rash			
1	2	3	4
<b>All subjects to be reviewed prior to each Anti-SAP treatment.</b>			
<p>If rash persistent then review weekly for resolution of rash.</p> <p>Next Anti-SAP treatment</p>	<p>If rash persistent then review weekly for resolution of rash.</p> <p>Next Anti-SAP treatment can be administered once rash</p>	<p>Follow emergency management plan</p> <p>Withdraw from study</p>	

<p>can be administered once rash resolved.</p> <p>Anti-SAP mAb dose level same as previously administered</p> <p>If rash not resolved by 8 weeks post last mAb dose withdraw from study</p>	<p>resolved but at reduced dose</p> <p>If rash not resolved by 8 weeks post last mAb dose withdraw from study treatment</p> <p>Reduce dose by 300 mg from previous dose. Dose levels = 900 mg, 600 mg, 300 mg</p> <p><b><u>Note: If a dose reduction is required following Session 1, then the Session 2 mAb dose level will be 300mg.</u></b></p> <p>If grade 2 or 3 rash observed at 300 mg dose level withdraw from study treatment</p>	
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## Appendix 5, Reporting of SAEs to GSK

### RATIONALE FOR CHANGE

Clarification of the process by which sites should inform GSK of SAE should the electronic data collection tool be unavailable

### PREVIOUS TEXT

- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the medical monitor

### REVISED TEXT

- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and ~~fax it to the medical monitor~~ **e-mail in portable document format (PDF) to both the primary and secondary medical monitors (details on the medical monitor / sponsor contact information page of this protocol), and also to GSK's case management group mailbox**

PPD

## Section 11, References

### RATIONALE FOR CHANGE

Inclusion of Reference

### REVISED TEXT

Saris-Baglana. User's Manual for the SF-36v2 Health Survey, Second Edition, 2007, Chapter 7, pages 81-84.

## Amendment 2

### Where the Amendment Applies

Global

### Summary of Amendment Changes

Regulatory input from the FDA on clarifying requirements for recruitment.

Define plasma SAP depletion target level of <3 mg/L.

Inclusion criterion for LVmass updated for Groups 2 and 3 to reflect the AL patient population

Reflect regulatory safety update information for Gadolinium contrast agents.

Dermatology review timings adjusted for grade 3 rash incidence.

Other changes made for clarity and to correct minor typographical errors.

### List of Specific Changes

#### 4.1 Overall Design

##### RATIONALE FOR CHANGE

FDA feedback has clarified the intention is to limit enrolment to 2 subjects at each site per month.

##### PREVIOUS TEXT

No more than two subjects will be in active treatment (dosing) at each study site at any given time.

##### REVISED TEXT

No more than two subjects will be in ~~active treatment~~ **session 1 (up to Day 24)** ~~(dosing)~~ at each study site at any given time.

#### 4.5.1 GSK2315698 (CPHPC - Plasma SAP Depleter)

##### RATIONALE FOR CHANGE

The antiSAP mAb interferes with the Hycult SAP ELISA assay that was used in previous clinical studies at GSK and so that assay cannot be used in this study once the antiSAP mAb has been administered. An alternative Meso Scale Discovery (MSD) immunoassay for the measurement of SAP has been developed by GSK. The target concentration of SAP measured by the Hycult assay was <2 mg/L before administration of anti-SAP mAb. Based on the re-calibration the equivalent target using the MSD assay is <3 mg/L. This is

considered to provide clinical comparability with the target applied in a previous study [SAP115570] which was well tolerated in human subjects in that study

*also*

Correction of typographical error.

#### PREVIOUS TEXT

This regimen was reliably effective in depleting circulating SAP to <2 mg/L (using Hycult ELISA assay).

*also*

Blood SAP concentration will be checked after 24 hours of administration of CPHPC to confirm administration of anti-SAP mAb on the next day to.

#### REVISED TEXT

This regimen was reliably effective in depleting circulating SAP to <2 mg/L (using a Hycult ELISA assay). **The current study is using a MSD assay and due to difference in SAP concentration scale between the assay types, a SAP concentration of <3 mg/L will be the target plasma SAP depletion level in this study).**

*also*

Blood SAP concentration will be checked after 24 hours of administration of CPHPC to confirm administration of anti-SAP mAb on the next day to.

#### 4.6.2 Risk Assessment Table (CMR Contrast Agent - gadolinium)

##### RATIONALE FOR CHANGE

MHRA have issued restrictions on gadolinium-containing contrast agents due to the association of higher retention of gadolinium in the brain with linear gadolinium-containing contrast agents. Section 7.6.2.1. details that the macrocyclic agents gadoteric acid, gadoteridol, and gadobutrol are to be used in this study, these accepted agents are added to the mitigation strategy for risk in the table in Section 4.6.2. for clarity.

## PREVIOUS TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>CMR Contrast Agent - gadolinium (Gd)</b>		
Delayed excretion and tissue accumulation of gadolinium contrast agent after repeated contrast CMR scans	<p>Gadolinium is mostly excreted in the urine and this is impaired in subjects with reduced renal function. Patients with systemic AL amyloidosis very often have renal amyloid and impaired renal function while cardiac ATTR patients are all elderly and therefore may also have non-amyloid chronic kidney disease. All these individuals are therefore at increased risk of Gd accumulation.</p> <p>FDA have issued an alert for tissue accumulation of Gd in organs including the brain following its repeated use, including some patients with normal renal function, although no new neurological complications have been reported to date</p>	<p>Exclusion of patients with GFR &lt; 40 mL/min</p> <p>GFR will be checked prior to each Gd contrast CMR and if GFR is &lt;40mL/min then CMR without Gd contrast will be performed</p> <p>Gd contrast CMR will be performed at five scheduled visits over the 18 month study period</p> <p>Other CMR scans will be without Gd contrast</p>

## REVISED TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>CMR Contrast Agent - gadolinium (Gd)</b>		
Delayed excretion and tissue accumulation of gadolinium contrast agent after repeated contrast CMR scans	<p>Gadolinium is mostly excreted in the urine and this is impaired in subjects with reduced renal function. Patients with systemic AL amyloidosis very often have renal amyloid and impaired renal function while cardiac ATTR patients are all elderly and therefore may also have non-amyloid chronic kidney disease. All these individuals are therefore at increased risk of Gd accumulation.</p> <p>FDA <b>and MHRA</b> have issued an alert for tissue accumulation of Gd in organs including the brain following its repeated use, including some patients with normal renal function, although no new neurological complications have been reported to date</p>	<p>Exclusion of patients with GFR &lt; 40 mLs/min</p> <p>GFR will be checked prior to each Gd contrast CMR and if GFR is &lt;40mL/min then CMR without Gd contrast will be performed</p> <p>Gd contrast CMR will be performed at five scheduled visits over the 18 month study period</p> <p>Other CMR scans will be without Gd contrast</p> <p><b><u>Gd contrast agents for this study are gadoteric acid, gadoteridol, and gadobutrol</u></b></p>



## 5.1 Inclusion Criteria

### RATIONALE FOR CHANGE

In contrast to ATTR patients, an LVmass measure on CMR of >200g is markedly less common in cardiac AL patients and would therefore impede recruitment. Review of historical data indicates that the LVmass for these patients is generally lower than that for ATTR patients. The new LVmass inclusion criterion for AL patients in Groups 2 and 3 considers the published literature [Fontana; 2015], and does not impact the sample size assumptions made in Section 9.2.1.

### PREVIOUS TEXT

OTHER
<ol style="list-style-type: none"> <li>4. Late-Gadolinium enhancement (LGE) on CMR indicative of cardiac amyloidosis</li> <li>5. LVmass on CMR &gt; 200 g</li> </ol>

### REVISED TEXT

OTHER
<ol style="list-style-type: none"> <li>4. Late-Gadolinium enhancement (LGE) on CMR indicative of cardiac amyloidosis</li> <li><del>5. LVmass on CMR &gt; 200 g</del></li> </ol>

*and subsequent re-numbering of list*

### Inclusion Criteria for Group 1

[1] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
<b>6. <u>LVmass on CMR &gt; 200 g</u></b>

*and subsequent re-numbering of list*

### Inclusion Criteria for Group 2

[1] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
<b>11. <u>LV mass on CMR &gt; 150 g</u></b>

*and subsequent re-numbering of list*

### Inclusion Criteria for Group 3

[1] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
--

<b>15. <u>LV mass on CMR &gt; 150 g</u></b>
---

*and subsequent re-numbering of list*

### 5.5 Subject Withdrawal Procedures

#### RATIONALE FOR CHANGE

Inclusion of section to detail procedures to follow should a subject be withdrawn from the study after enrolment

#### REVISED TEXT

**Subjects withdrawn following one or more administrations of mAb should follow the procedures at the 8 week follow-up visit shown in the Time and Events Table.**

**Subjects withdrawn following administration of CPHPC but no administration of anti SAP mAb should follow the procedures at the 8 week follow-up visit shown in the Time and Events Table, with the exception of: Blood sampling for anti-SAP mAb, Cardiac MRI, ECHO, <sup>99m</sup>TC-DPD / PYP scans (Group 1 only), SAP Scan (Groups 2 & 3, UK only) or out-patient cardiac monitoring.**

### 6.2 Table 2 CPHPC dosing regimen according to renal function

#### RATIONALE FOR CHANGE

Additional text in Footnote to clarify CPHPC dosing requirements should a change in eGFR occur during a treatment session.

#### PREVIOUS TEXT

eGFR determined by MDRD must be used to define CPHPC dose based on renal function.

#### REVISED TEXT

eGFR determined by MDRD must be used to define CPHPC dose based on renal function. **The most recent eGFR value available at the time of the pharmacy prescription being prepared will be used to determine the CPHPC dosing requirement for the treatment session. Should subsequent eGFR results within that treatment session show a change in eGFR, the CPHPC dosing requirement will not be altered as a result. Changes to eGFR which the Investigator considers to be a safety concern should be discussed with the Medical Monitor.**

## 6.8 Treatment after the End of the Study

### RATIONALE FOR CHANGE

Correction of typographical error

### PREVIOUS TEXT

Given the lack information about the safety and efficacy of Anti-SAP treatment in AL and ATTR-CM, treatment will not be provided after the end of the study. This may be reviewed once more information is available

### REVISED TEXT

Given the lack of information about the safety and efficacy of Anti-SAP treatment in AL and ATTR-CM, treatment will not be provided after the end of the study. This may be reviewed once more information is available.

## 6.10.1 Permitted Medications and Non-Drug Therapies

### RATIONALE FOR CHANGE

Addition of text to allow for administration of prophylactic treatments.

### REVISED TEXT

#### **Prophylactic treatments for rash**

**If a rash and associated symptoms (e.g. pruritus) are experienced by a subject at a treatment session, during subsequent treatment sessions prophylactic treatment (any first and / or second generation H<sub>1</sub> antihistamine) are permitted at discretion of Investigator or designee.**

## 7.1 Time and Events Table, Table 3 Overview of all groups

### RATIONALE FOR CHANGE

Addition in clarification in footnote regarding physical examinations

*also*

Addition of clarification in footnote regarding 24hr urine collection timepoints.

### PREVIOUS TEXT

Full examination at screening only, brief examination at all other time-points.

*also*

24hr collection - 3.5ml serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples.

REVISED TEXT

**Complete** Full examination at screening only, brief examination at all other time-points.  
**Weight will be recorded at Baseline, D17 and D24. Abdominal girth will be recorded at Baseline.**

*also*

24hr collection - 3.5ml serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples. **Day indicated in Table represents the end of the 24hr collection period.**

## **7.1 Time and Events Table, Table 4**

RATIONALE FOR CHANGE

Alteration to how Lead II telemetry is displayed in the table

*also*

Extension of D-1 biopsy to include D-2

*also*

Addition of footnote relating to Brief Physical Examination to include weight and girth measurements during in patient stay.

*also*

Addition of Footnote 14 regarding physical examinations

PREVIOUS TEXT

24h collection - 3.5mL serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples.

REVISED TEXT

24h collection - 3.5mL serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry

samples. Day 6 represents the start of the collection period, Day 11 represents the end of the collection period. See Table 5 for details of Day 1-3.

*also*

Weight should be recorded on D-2, D5, D8 and D11. Abdominal girth should be recorded on D-2 and D11.

## 7.1 Time and Events Table, Table 5

### RATIONALE FOR CHANGE

Alteration to how D2 times are represented in the table

*also*

Alteration to how Lead II telemetry is displayed in the table

*also*

Changes to footnote to clarify 24hr urine collection periods

*also*

Addition of footnote to clarify early assessment timings

### PREVIOUS TEXT

24h collection - 3.5mL serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples.

### REVISED TEXT

24h collection - 3.5mL serum biochemistry sample to be taken for creatinine measurements at time points where there are no corresponding clinical chemistry samples. Day indicated in the Table represents the start (pre-dose) of the 24hr collection period.

*also*

Time shown to indicate early in the day only – not a specific time. The collection of these should be timed with other pre-dose sample collection in order to minimise inconvenience and needle-sticks for the subjects.

### 7.4.3 Physical Exams

#### RATIONALE FOR CHANGE

Additional assessments included during brief physical examination

#### PREVIOUS TEXT

- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

#### REVISED TEXT

- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). **Weight and girth measurements will also be included at times stated in the Time and Events Table.**

### 7.4.8 Clinical Safety Laboratory Assessments

#### RATIONALE FOR CHANGE

Clarification that Troponin measurements include those for High Sensitivity

#### PREVIOUS TEXT

- Troponin-T

#### REVISED TEXT

- Troponin-T **(including High Sensitivity)**

## 11 References

Addition of Fontana, M (2015) reference to support LV mass historical data

### 12.3.3 Management of Rash (Table 9, Rash Grade 3)

#### RATIONALE FOR CHANGE

Skin rashes to date have been reported as mild adverse events where the highest reported grade has been a grade 2 rash in one Group 1 subject; this was promptly resolved with the administration of oral steroids.

This prompt steroid sensitivity of the rash in the Group 1 subject is clinically typical for any urticarial vasculitis rash caused by an early leucocytoclastic mechanism, and is consistent with the prompt rash resolution seen with the administration of oral steroids in

a cardiac AL amyloidosis subject treated with GSK2398852 in the first-in-human study (GSK study 115570).

On the emerging phase 2 study rash background, an advisory therapeutic algorithm for the management of skin rashes – which includes the use of steroids (either as ointments / creams / oral) and anti-histamines - has been developed. Detailed in the study reference manual (SRM).

Given the consistent pathological results of an early leucocytoclastic vasculitis on all skin biopsies, and the known steroid responsiveness of this type of skin vasculitis), relaxation of the timeframe for dermatologist 'face to face' review for grade 3 rash from 'within 24 hours of rash onset' to 'within 72 hours' is considered to be acceptable from a safety perspective. The availability of telemedicine review of rash photographs and general rash management advice from external, remote dermatologist is added for sites to use at the discretion of the Investigator or designee.

PREVIOUS TEXT

**Table 9 Grading criteria for rash**

<b>Rash Grade</b>	<b>Distribution/Symptoms</b>		<b>Action</b>
1	<10% BSA AND asymptomatic		Dermatology review before patient discharge if rash persists $\geq 7$ days post-mAb dose
2	10-30% BSA and/or mild symptoms <sup>a</sup>		Dermatology review before patient discharge if rash persists $\geq 7$ days post-mAb dose
3	>30% BSA and/or moderate/severe symptoms <sup>a</sup>		Dermatology review within 24 hours
4	Any rash with mucosal or systemic involvement <sup>b</sup>		Immediate dermatology review Withdraw from study treatment. See specific advice Section 12.3.4

a.

b. Symptoms include: pain, itch and burning

c. E.g. evidence of renal involvement

REVISED TEXT

**Table 9      Grading criteria for rash**

<b>Rash Grade</b>	<b>Distribution/Symptoms</b>	<b>Action</b>
1	<10% BSA AND asymptomatic	Dermatology <b><u>review<sup>c</sup></u></b> before patient discharge if rash persists $\geq 7$ days post-mAb dose
2	10-30% BSA and/or mild symptoms <sup>a</sup>	Dermatology <b><u>review<sup>c</sup></u></b> before patient discharge if rash persists $\geq 7$ days post-mAb dose
3	>30% BSA and/or moderate/severe symptoms <sup>a</sup>	<b><u>Local</u></b> dermatology <b><u>review<sup>c</sup> to be performed as soon as possible after rash onset, but must be performed within 72 hours</u></b>
4	Any rash with mucosal or systemic involvement <sup>b</sup>	Immediate dermatology review Withdraw from study treatment. See specific advice Section 12.3.4

a. Symptoms include: pain, itch and burning

b. E.g. evidence of renal involvement

c. **In addition, at the discretion of the Investigator or designee a telemedicine review of rash photos and general rash management advice from remote dermatologist may be requested**