TITLE PAGE

Protocol Title: An Adaptive, Open-Label Study to Evaluate the Biodistribution of ^{89}Zirconium-labelled GSK2398852 in the Heart and Other Organs of Patients with Transthyretin Cardiomyopathy (ATTR-CM) using Positron Emission Tomography (PET) Imaging

Protocol Number: 204512

Short Title: Biodistribution of ^{89}Zirconium-labelled GSK2398852 using PET Imaging

Compound Numbers:	GSK2315698 + GSK2398852+ Radiolabelled ^{89}Zr-GSK2398852

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1. SYNOPSIS

Protocol Title: An Adaptive, Open-Label Study to Evaluate the Biodistribution of ^{89}Zirconium-labelled GSK2398852 in the Heart and Other Organs of Patients with Transthyretin Cardiomyopathy (ATTR-CM) using Positron Emission Tomography (PET) Imaging

Short Title: Biodistribution of ^{89}Zirconium-labelled GSK2398852 using PET Imaging

Rationale:

The principal aim of this PET imaging study is to investigate the cardiac uptake of ^{89}Zr-GSK2398852 in patients with transthyretin amyloidosis restrictive cardiomyopathy (ATTR-CM), and its biodistribution to other organs. This study constitutes an adjunct study to the Phase 2 trial to evaluate the therapeutic efficacy of anti-serum amyloid P component (anti-SAP) treatment (GSK Study Number 201464). This PET study will enhance the development of Anti-SAP treatment by providing direct in vivo evaluation of anti-SAP monoclonal antibody (mAb) myocardial tissue uptake.

This adaptive, dose-ranging study of the distribution of ^{89}Zr-GSK2398852 in both cardiac and non-cardiac organs/tissues will strengthen the understanding of the therapeutic mAb biodistribution and provide further insight to optimize this investigational Anti-SAP therapeutic approach.

NOMENCLATURE:

In this document:

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

Primary and Secondary Objectives and Endpoints:

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

Overall Design:

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

Each dosing session will include:

- Administration of anti-SAP treatment consisting of:
    - CPHPC administered via intravenous (IV) infusion for at least 48 hours, followed by
    - Unlabelled anti-SAP mAb together with ^{89}Zr-GSK2398852 via two separate intravenous infusions, and
    - CPHPC administered via subcutaneous (SC) injections for at least 9 days.
- Up to three PET scans at varying intervals after ^{89}Zr-GSK2398852 administration.
- An inpatient stay of up to 11 days, followed by an additional week of outpatient cardiac monitoring.

At a single suitable time point, depending on technical and logistic aspects, the subject will undergo one additional PET scan with the administration of Carbon-11 Pittsburgh Compound B (PiB), a tracer known to bind to amyloid, for the characterization of the regional amyloid burden in the heart, and up to two further PET scans with the administration of Oxygen-15 labelled water (WAT) for the characterization of the regional blood flow in the heart.

This study has an adaptive study design in order to identify the conditions and dose of anti-SAP mAb which provide optimal assessment of cardiac update. As the name suggests, systemic amyloidosis is associated with amyloid deposits in multiple organs. The delivery of monoclonal antibodies to individual organs depends on the blood flow and nature of the endothelium. Because the amount of tracer ^{89}Zr-GSK2398852 is small relative to total amyloid load, if given alone it would distribute to the best-perfused organs with discontinuous endothelia. For this reason, the radiolabelled tracer will be co-administered with unlabelled anti-SAP mAb so that distribution will better reflect the situation when therapeutic doses are administered.

During each dosing session, subjects will receive a TMD of anti-SAP mAb ≤500 mg. The dose will vary between subjects and dosing sessions, and will be contingent on both the PET imaging and ^{89}Zr-GSK2398852 PK findings from the 1st dosing session, or the findings from previous subjects.

Number of Subjects:

Sufficient subjects will be screened such that up to six subjects complete the study.

Treatment Groups and Duration:

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

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

All subjects will receive IV CPHPC prior to anti-SAP mAb and SC CPHPC post anti-SAP mAb. Unlabelled anti-SAP mAb will be administered at varying doses throughout the study. The radioactivity dose of ^{89}Zr-GSK2398852 will be the same in each dosing session for all subjects throughout the study.

The TMD of anti-SAP mAb administered per subject per dosing session in this study is determined by the mass dose of *unlabelled* anti-SAP mAb plus 10 mg associated with ^{89}Zr-GSK2398852.

The GSK study team including the Medical Monitor will confirm the unlabelled anti-SAP mAb dose for each subject prior to administration.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Part A and Part B Overview

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

Table 2 Overview All Groups

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

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

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

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

Footnotes:

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

Table 3 Allowable Assessment/Visit Windows

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

Table 4 Unlabelled anti-SAP mAb PK Sampling (Dosing Sessions 1 and 2)

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

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

Table 5 ^{89}Zr-GSK2398852 Radio-PK Sampling (Dosing Sessions 1 and 2)

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

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

3. INTRODUCTION

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].

Serum amyloid P component (SAP) is a normal, circulating, constitutive plasma glycoprotein which is invariably present in human amyloid deposits of all types.

Anti-SAP treatment is in development for systemic amyloidosis. Anti-SAP treatment consists of an obligate combination of Carboxy pyrrolidine hexanoyl pyrrolidine carboxylate (CPHPC, miridesap) a small molecule depletor of plasma SAP and an anti-SAP humanized immunoglobulin G1 (IgG1) mAb (dezamizumab). Depletion of circulating SAP by CPHPC [Pepys 2002] enables the administration of anti-SAP antibodies which bind to SAP on amyloid deposits, opsonizing them for macrophage giant cell mediated clearance.

Myocardial amyloid deposition in *transthyretin* amyloidosis (ATTR) causes restrictive cardiomyopathy (ATTR-CM) leading to heart failure 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 improve cardiac function, reduce symptoms and prolong survival in patients with ATTR amyloidosis, as well as in other types of systemic amyloidosis (e.g. amyloid Light-chain [AL] amyloidosis) where the heart is also frequently involved.

NOMENCLATURE:

In this document:

- GSK2315698 (miridesap) is referred to as **CPHPC**.
- GSK2398852 (dezamizumab) is referred to as **unlabelled anti-SAP mAb**.
- ^{89}Zirconium-desferrioxamine (Df) labelled anti-SAP mAb is referred to as **^{89}Zr-GSK2398852**.
- The administration of CPHPC and anti-SAP mAb is referred to as **Anti-SAP treatment**.
- **Total Mass Dose (TMD) of anti-SAP mAb =** unlabelled anti-SAP mAb + ^{89}Zr-GSK2398852.

3.1. Study Rationale

The principal aim of this study is to investigate the cardiac uptake of ^{89}Zr-GSK2398852 in patients with ATTR-CM, and its biodistribution to other organs.

The cardiac endothelium is continuous and although the heart is well perfused, regional variations occur especially in cardiac amyloidosis. The anti-SAP mAb is expected to reach cardiac amyloid but the pharmacokinetics and proportion reaching the heart relative to other organs is unknown. This study will augment the interpretation of the ongoing phase 2 therapeutic trial by providing important information on the relative uptake of a radiolabelled tracer dose of ^{89}Zr-GSK2398852.

The uptake ^{89}Zr-GSK2398852 data will be contextualised by Carbon-11 PiB, a tracer known to bind to amyloid, for the characterization of the regional amyloid burden in the heart, and up to two further PET scans with the administration of WAT for the characterization of the regional blood flow in the heart.

As the name suggests, systemic amyloidosis is associated with amyloid deposits in multiple organs. The delivery of monoclonal antibodies to individual organs depends on the blood flow and nature of the endothelium. Because the amount of tracer ^{89}Zr-GSK2398852 is small relative to total amyloid load, if given alone it would distribute to the best perfused organs with discontinuous endothelia. For this reason, the radiolabelled tracer will be co-administered with unlabelled anti-SAP mAb so that distribution will better reflect the situation when therapeutic doses are administered.

3.2. Background

Involvement of the heart is the most important determinant of patient survival in the two commonest types of systemic amyloidosis: ATTR amyloidosis and AL amyloidosis. Deposition of both TTR and AL amyloid in the heart leads to restrictive cardiomyopathy which predominantly causes heart failure with preserved ejection fraction (HFpEF). The natural history of amyloid deposition within the heart involves early deposition in the subendocardium (causing a high incidence of arrhythmias) followed by asymmetrical deposition of amyloid within the myocardium mainly affecting the interventricular septum and free left ventricular wall.

As part of Anti-SAP treatment in systemic amyloidosis, CPHPC is administered first intravenously (and then subcutaneously during and after anti-SAP mAb administration) to deplete and maintain circulating plasma SAP levels to target. This enables the safe administration of anti-SAP mAb to target amyloid-involved organs without the systemic formation of large amounts of circulating SAP / anti-SAP mAb immune complexes. The anti-SAP mAb can then reach and bind to residual SAP in the amyloid deposits and trigger the normal opsonophagocytic processes for removal of amyloid deposits from the extracellular space through the formation of multinucleated giant cells.

As proof of pharmacology, GSK has shown in a first-in-human (FIH) study (SAP115570) that Anti-SAP treatment can promote the clearance of amyloid deposits from extra-cardiac tissues (e.g. liver and kidney) with an acceptable safety profile (Please see Investigator's Brochure (IB) GlaxoSmithKline Document Number 2012N141587_06 and Richards 2015).

3.2.1. Preliminary Evidence of Anti SAP Therapeutic Effect & Safety in Cardiac Amyloidosis

A total of twenty-three patients with systemic amyloidosis received Anti-SAP treatment in the FIH study (SAP115570). Six of these subjects had cardiac amyloidosis: three ATTR-CM subjects and three AL amyloidosis subjects.

Two subjects received 3 treatment sessions (session 1: 600 mg GSK2398852 and session 2 and 3: 1200 mg GSK2398852); the remainder received a single Anti-SAP treatment session (dose of GSK2398852 ranged from 600 to 1200 mg). Of the 2 subjects who received more than one Anti-SAP treatment session, cardiac magnetic resonance (CMR) imaging in one subject showed a reduction in LVmass that was outside the variability associated with the test and is, therefore, considered preliminary evidence of the potential to remove cardiac amyloid (refer to IB: GlaxoSmithKline Document Number 2012N141587_06).

None of the other subjects with cardiac amyloidosis had any detectable signals of amyloid removal on CMR imaging, however several did show a transient rise in NT-proBNP which may represent engagement of the target mechanism in the heart (refer to IB: GlaxoSmithKline Document Number 2012N141587_06).

Importantly, no cardiac adverse events were observed in the First in Human (FIH) study (SAP115570) in any of these subjects. Overall, the adverse event profile of anti-SAP mAb in subjects with cardiac amyloidosis was no different to those subjects with only abdominal organ involvement in the FIH study.

A Phase 2 trial (Study Number 201464) evaluating the effect of Anti-SAP therapy in ATTR-CM and cardiac AL amyloidosis has commenced in the United Kingdom, and has received Food and Drug Administration (FDA) approval in the United States. The Phase 2 study is using serial CMR imaging to evaluate the potential markers of cardiac amyloid removal effect of up to six sessions of Anti-SAP treatment.

3.2.2. Radiolabelled Anti-SAP mAb: 89Zr-GSK2398852

PET has been selected as the imaging modality for this because it provides sufficiently high spatial resolution (about 6 mm) and a high sensitivity and ability for accurate quantitation of radioactivity concentration throughout the body.

There are several positron emitting radionuclides which are used for human PET studies, but for a study like the one proposed here, the half-life of the radionuclide is a key selection factor. ^{15}O (2 minutes), ^{11}C (20 minutes), ^{68}Ga (68 minutes), and ^{18}F (2 hours) are frequently used in PET, but these short half-lives would not allow recording of biodistribution of labelled antibodies with plasma elimination half-lives of multiple hours to days and very slow anticipated penetration to the extracellular space. ^{89}Zr with a half-life of 3.2 days is suited for such studies since it allows a more comprehensive evaluation of tissue biodistribution of the radiolabelled antibody for longer than two days.

A further advantage of ^{89}Zr is that generic labelling methods have been developed whereby antibodies can be labelled in a standardized procedure and with the binding and

distribution properties retained [Dijkers 2009, Perk 2010, Gaykema 2013, Menke-van der Houven van Oordt CW 2015, Pendit-Taskar 2014, Pendit-Taskar 2015, Laforest 2016].

GSK2398852 (anti-SAP mAb) has been conjugated to ^{89}Zirconium (Zr) using a non-cleavable linker (See Supplement to Investigator Brochure for GSK2398852 + GSK2315698, GlaxoSmith Kline Document Number 2017N343159_00).

In vitro experiments have shown that the binding affinity of the Fab domain of ^{89}Zr-GSK2398852 for SAP is similar to unlabelled anti-SAP mAb which has been therapeutically used in combination with CPHPC in the FIH study (SAP115570). In contrast, the Fc domain of ^{89}Zr-GSK2398852 has been shown in vitro to have an approximate 30% reduction in C1q binding which could lead to a potential reduction in immunological effector function. Thus the small dose of ^{89}Zr-GSK2398852 (10 mg) is unlikely to substantially contribute pharmacology whether beneficial or adverse.

The local vascular distribution, tissue permeability, and PK profile of ^{89}Zr-GSK2398852 in the myocardium of ATTR-CM patients is predicted to be dependent upon five factors:

1. Vascular distribution of the antibody to the heart is principally via epicardial coronary arteries. The plasma PK profile of anti-SAP mAb may be altered by the presence of variable amounts of amyloid (decorated with SAP) in other organs.
2. Intra-myocardial, locoregional, distribution of ^{89}Zr-GSK2398852 is dependent on myocardial microvessel capillary endothelium patency. The capillary endothelium may be altered (impaired) in areas of amyloid deposition as compared to regions unaffected by amyloid deposition.
3. The rate of extravasation across the myocardial microvessel endothelium is expected to be governed partly by paracellular convection of fluid and possibly by transcellular transport via neonatal Fc receptor (FcRn) receptors. In a first order description, the bulk flow is assumed to be proportional to the blood flow. In areas of amyloid deposition, there is likely to be a reduction of tissue blood flow, with potentially small areas of ischemia.
4. ^{89}Zr-GSK2398852 is expected to bind to SAP on amyloid accessible in the interstitium. The rate and duration of this bound antibody is dependent upon binding affinity and dissociation rate and the available concentration and its time course in the interstitium.

The factors above indicate a complex chain of events mediating the resulting PET signal in the heart. The study has an adaptive iterative design to allow for use of prior data to inform future doses of unlabelled mAb and the timing of assessments.

3.3. Cardiac Amyloidosis Imaging

3.3.1. ^{89}Zr-GSK2398852 PET Imaging

PET allows an accurate assessment of radioactivity distribution in the body after the administration of the radioactivity tracer.

Each PET sequence is anticipated to last 60-90 minutes and will have up to 3 scans per dosing session. All PET scans are expected to be performed within 5 days of ^{89}Zr-GSK2398852 administration.

From the time of tracer administration multiple blood samples are taken for the measurement of radioactivity concentration in whole blood and plasma. These data will be used in relation to the tissue uptake.

The images can be visually inspected but more important is that selected areas in the images will be used for quantitative evaluation of radioactivity concentration and further used for the modelling.

3.3.2. Additional PET Imaging Procedures

Whenever possible, the following baseline PET procedures should be performed after a subject has passed other eligibility requirements.

3.3.2.1. PiB PET Imaging: Cardiac Amyloid Burden

The PET tracer Carbon-11 PiB has been used extensively for the characterization of amyloid load in patients with Alzheimer's disease but also in a number of publications for amyloid burden in the heart [Pilebro 2016, Antoni 2013]. This type of study has shown excellent visualization and quantitative values which identifies amyloid-loaded hearts as compared to hearts without amyloid. The studies have also identified differences in the anatomical location of the amyloid deposits, information which can be of great importance for the interpretation of the ^{89}Zr-GSK2398852 distribution in the heart.

If logistically possible, this PiB PET procedure will be introduced at a time point which is suitable in relation to technical aspects such as availability of cyclotron and radiochemistry or logistical aspects related to patient handling. It includes a single IV bolus administration of the tracer followed by about 30 minutes scanning over the heart.

3.3.2.2. ^{15}O-labelled Water PET Imaging: Myocardial Blood Flow

15-Oxygen-labelled water (WAT) has been used extensively in PET studies for the characterization and quantitative evaluation of regional tissue blood flow [Antoni 2013, Dorbala 2014]. Such or similar studies have demonstrated marked and regionally different reductions in the blood flow in the heart of patients with systemic amyloidosis. This is additional information which can be important for the interpretation of the signal in the ^{89}Zr-GSK2398852 study.

This PET procedure may be introduced at up to two time points which are suitable in relation to technical aspects such as availability of cyclotron and radiochemistry or logistical aspects related the patient handling.

The procedure includes the bolus administration of WAT followed by scanning across the heart for a few minutes.

3.3.3. Cardiac Magnetic Resonance (CMR) Imaging

CMR methods precisely and specifically quantify the left ventricle (LV) mass and the cardiac 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 ATTR-CM [Martinez-Naharro 2017].

However, the specificity of ECV as a measure of amyloid involvement in myocardial tissue remains to be determined. In this study, contrast-enhanced CMR will be used to determine the amyloid load and myocardial perfusion in ATTR-CM patients at baseline. Baseline CMR will also enable exploratory investigations to co-localise regions of ^{89}Zr-GSK2398852 cardiac uptake on PET imaging with anatomical sites of TTR amyloid deposition within the myocardium, as well as potentially loco-regional intramyocardial perfusion parameters since myocardial blood flow is expected to be an important determinant of ^{89}Zr-GSK2398852 myocardial uptake and distribution.

Whenever possible, the baseline contrast-enhanced CMR should be performed after a subject has passed other eligibility requirements.

3.4. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Anti-SAP treatment may be found in the Investigator's Brochure.

Summaries of the pre-clinical and clinical studies conducted with CPHPC alone and with CPHPC + anti-SAP mAb are presented in the Investigator's Brochure [GlaxoSmithKline Document Number 2012N141587_06].

3.4.1. Risk Assessment for Anti-SAP mAb

Given that the administered dose of ^{89}Zr-GSK2398852 per anti-SAP dosing session will be low (10 mg), the principal risks associated with anti-SAP mAb in this PET study are likely to be associated with the administration of unlabelled anti-SAP mAb.

At this time, there are two main identified risks for administration of unlabelled anti-SAP mAb in this PET study, based on observations in the FIH study: **i)** skin rash (Section 3.4.1.1); **ii)** anti-SAP mAb infusion-related reactions (IRR).

3.4.1.1. Rashes

Many subjects who received 582 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 distribution, severity and persistence; all but one of these rashes, were self-limiting. Skin biopsy in two other affected AL amyloidosis patients demonstrated pathological changes consistent with an early leukocytoclastic vasculitis (LCV).

The pathophysiological mechanism for these rashes is not known to date 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. The potential mechanisms will be thoroughly investigated in the ongoing Phase 2 study (Study Number 201464).

GSK will also inform the study site as to the emerging immuno-toxicological / skin pathological findings from the Anti-SAP Phase 2 study since this might assist the evaluation and management of any rashes which are observed during this PET imaging study.

See Section 3.4.3 for risk mitigation strategy.

3.4.1.2. Potential for mAb Infusion-Related Reactions (IRR)

Most subjects receiving more than 200 mg of anti-SAP mAb in the FIH study experienced infusion-related reactions varying in type 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 hydrocortisone and chlorphenamine.

See Section 3.4.3 for risk mitigation strategy.

3.4.1.3. Potential for Cardiotoxicity

Cardiac amyloidosis (ATTR & AL) patients have been dosed in the FIH study. This was associated with an overall acceptable safety profile.

Since the minimum effective dose for anti-SAP mAb dependent amyloid removal in the heart of ATTR-CM patients has not yet been established, and because there is a known high background incidence of arrhythmias in this patient population, there remains the theoretical potential for engagement of complement and macrophage mechanisms within the myocardium of subjects receiving anti-SAP mAb TMD up to and including ≤500 mg. Therefore, this yields a potential risk of cardiotoxicity through disturbance of electrophysiology and / or myocardial contractility, or perfusion.

See Section 3.4.3 for risk mitigation strategy.

3.4.2. Radiation exposure

The study will involve radiation exposure from up to 2 separate administrations of ^{89}Zr labelled anti-SAP (^{89}Zr-GSK2398852) to patients, each associated with 3 low-dose whole-body CT imaging scans, plus potential PET procedures with PiB and WAT.

In oncology ^{89}Zr-labelled mAb studies, a minimum administration of 37 MBq is regarded as adequate for good image quality. In some studies, this administration has been repeated up to 3 times. Some of the studies have been associated with other PET studies, notably Fludeoxyglucose (FDG). The studies conducted in the United States (US) have

typically been associated with much higher administrated doses such as 185 MBq [Pendit-Taskar 2014, Ulaner 2016].

The prognosis of ATTR-CM is similar to that of metastatic cancers, in that the life expectancy is less than 4 years from diagnosis, and the older age at presentation for wild-type ATTR (median 75 years), means that the subjects can be exposed to higher levels of radiation without significantly increasing the risk of developing secondary tumors [Shuryak 2010].

Based on the above information and rationales, the proposed ^{89}Zr-GSK2398852 dose is approximately 37 MBq for each administration, 2 dosing sessions per subject, with a total of approximately 74 MBq. The mean effective dose for ^{89}Zr-mAb PET study was reported to be 0.53 mSv/MBq [Börjesson 2009], hence 37 MBq of ^{89}Zr-GSK3128349 in this study would provide approximately 19.61 mSv (37 MBq x 0.53 mSv/MBq) of exposure, which together with the low-dose CT scans (0.5 mSv/CT scan x 3 CT scans) yield approximately 21.11 mSv. The single PiB procedure including its CT component is expected to add 1.5 mSv, and the two WAT procedures to add a total of 1 mSv in radiation exposure.

Total radiation dose exposure per subject is therefore expected to be a maximum of up to 44.7 mSv. With some residual radioactivity in the injection syringe and considering radioactive decay till time of injection, we will aim to be below 44 mSv across the study. Reference Appendix 9 for additional information.

3.4.3. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2398852; anti-SAP mAb]		
Acute onset rash within first 7 days of infusing anti-SAP mAb	Many patients who received 582 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. Skin biopsy in one AL amyloidosis patient who had a diffuse maculopapular / urticarial rash after being administered 600 mg anti-SAP mAb on the first treatment session was reported as a LCV. In this biopsy sample, there was no demonstrable deposition of immunoglobulins, complement, immune complexes, or amyloid in the tissues. A second AL amyloidosis patient with improving liver load (after 1st treatment session) had a diffuse rash after receiving 1000 mg anti-SAP mAb on the 2nd treatment session. The dermato-pathological changes on this subject's skin biopsy was consistent with a lymphocytic / leucocytoclastic vasculitis.	**Administration of TMDs ≤500 mg per dosing session** Dermatological (skin) monitoring Prompt clinical dermatology review dependent on the presenting Grade, persistence and overall temporal evolution of the rash (see Section 12.7) Use of topical or systemic anti-inflammatory medications, including but not restricted to corticosteroids and anti-histamines, at the discretion of Investigator, designee, or dermatologist (as necessary) Subjects will be withdrawn from the study after the 1st dosing session if a rash has not completely resolved by the scheduled time of the 2nd dosing session, or if the rash has been designated as >Grade 2 following session 1 (see Section 8.1.7)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Post-inflammatory hyperpigmentation (PIH)	Some FIH study patients who repeatedly experienced acute rashes with repeat anti-SAP mAb dosing ≥582 mg developed variable PIH. PIH is benign but may only resolve completely 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.	**Anti-SAP mAb TMD ≤500 mg per dosing session to mitigate risk of acute rashes** All subjects who develop PIH will be monitored clinically Dermatology review for all PIH occurrences
Infusion Reactions	Most subjects receiving more than 200 mg of anti-SAP antibody in the FIH study experienced infusion 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 hydrocortisone and chlorphenamine.	**Unlabelled anti-SAP mAb will be given as a single infusion slowly over at least 6 hours where the intended mass dose per dosing session will be >200 mg range.** **(i.e. TMD range: 200 mg < TMD ≤500 mg)** Interrupting the infusion and/or reducing the rate of administration of each mAb infusion Hydrocortisone premedication Antihistamine premedication Careful monitoring of blood pressure, and appropriate clinical management if required (e.g. fluid balance and urine output with immediate access to IV fluids). Use of anti-emetics for nausea & vomiting
Myocarditis	The intended and desired pharmacodynamics (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	**Administration of anti-SAP mAb TMD during each session which will be up to approximately 12-fold lower than anti-SAP mAb doses administered to cardiac amyloidosis subjects in the FIH study (SAP115570)**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	deposits in the heart, activation of complement and attraction of macrophage infiltration and fusogenic activation to form multinucleate giant cells (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.	(i.e. 80 mg ≤TMD ≤500 mg per dosing session) Comprehensive inpatient cardiac monitoring comprising: Serial heart rate and blood pressure measurement Continuous inpatient telemetry during and after each anti-SAP treatment session Serial 12-lead ECG recording Serial inpatient evaluations of cardiac troponin T and NT-proBNP 2D-ECHO will be performed at Screening to provide reference cardiac functional data in the event of cardiac adverse event(s) during the study which might perturb cardiac function. Non-implantable cardiac monitoring devices (e.g. BodyGuardian) will be used to evaluate the background electrophysiology of subjects at Screening. The same monitoring device will be used for at least 7 consecutive days after in-patent discharge to detect potential later-onset cardiac electrophysiology changes associated with administration of an anti-SAP mAb TMD.
Investigational Product (IP) [GSK2315698 - CPHPC]		
Epistaxis	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. No causal relationship to Anti-SAP treatment has been	Serial haemoglobin & platelet monitoring, and Screening coagulation test. These investigations may be repeated if an epistasis event occurs.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	identified at this time.	Serial heart rate and blood pressure measurement
CMR Contrast Agent - gadolinium (Gd)		
Delayed excretion and tissue accumulation of gadolinium contrast after CMR scan	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. 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	Gd-contrast CMR will be only performed once during the study, at Screening Exclusion of patients with eGFR <50 mL/min eGFR will be checked prior to Gd-contrast CMR
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 estimated glomerular filtration rate (eGFR) <50 mL/min (see exclusion criteria) Monitoring of serum creatinine before and after administration of Gd contrast agent. Dermatological inspection for rashes.
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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Procedural risks		
Subjects exposed to ionising radiation as a consequence of participation in this study (e.g. ^{89}Zr-GSK2398852 imaging).	Ionising radiation exposure from PET scanning comes from the administered radioligand and CT examination. The total radiation burden per subject is calculated as 21.1 mSv per ^{89}Zr-GSK2398852 scan session; and the single PiB and two WAT scans together 2.5 mSv; up to total 44.7 mSv for all PET scans and this corresponds to a lifetime risk of a fatal malignancy of about 1 in 600 [ICRP 2007]. Subjects who participate will receive a radiation exposure up to a maximum of 44.7 mSv across two separate dosing sessions. The ceiling radiation exposure of 44.7 mSv is judged as safe to the individual, and justified on a trial basis due to the clinically severe and life-limiting nature of ATTR cardiomyopathy, and the importance to the study objectives of optimising the signal-noise ratio from the myocardium during each PET scan	The study has been designed to keep the radiation dose as low as reasonably practicable (ALARP) whilst obtaining images of sufficient quality to meet the objectives. **Subjects <65 years of age will not be eligible** The study will exclude women of childbearing potential. Subjects who have been exposed to ionising radiation in excess of 10 mSv above background over the previous three-year period as a result of occupational exposure to radiation or as a result of research studies are excluded. Clinically justified (therapeutic or diagnostic) exposures are not included in the exposure calculation. Subjects are asked about any occupational exposure or previous participation in research studies at screening so that dose estimates can be obtained where necessary.

3.4.4. Benefit Assessment

The purpose of this study is to provide an assessment of the myocardial uptake of anti-SAP mAb using a radiotracer technique. Unlabelled anti-SAP mAb is also given because the ratio of tracer to total body amyloid is low. In order to minimise the risk of dose-dependent adverse effects the maximum total dose of anti-SAP mAb has been capped at 500 mg. In the first in human study the lowest dose associated with objective evidence of amyloid removal (in the liver) was 246 mg in a single subject. Thus the doses of anti-SAP mAb given in this study have the potential to pharmacologically active and to trigger amyloid removal however they are low and are not expected to result in therapeutic removal. Thus participants in this study are not expected to derive direct therapeutic benefit but the information from this and the ongoing phase 2 study will be combined to inform rational dose selection for future development.

3.4.5. Overall Benefit:Risk Conclusion

Although ATTR-CM subjects recruited into this PET study are unlikely to derive any overall therapeutic benefit from Anti-SAP treatment, their participation in this PET study will however help the overall development of Anti-SAP treatment for cardiac amyloidosis.

The total radiation exposure (up to a maximum of 44.7 mSv) per subject ensures optimal myocardial signal-to-noise ratio per PET scan and is considered justified given the limited survival from diagnosis of ATTR-CM patients.

The dose of anti-SAP mAb in this study will be adjusted to optimise information on myocardial uptake but is set at a level that, based on previous clinical experience, is likely to be well tolerated

Therefore, overall the ^{89}Zr-GSK2398852 PET imaging study is justified given the safety mitigation strategies in place for each subject during the study.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Assessment of ^{89}Zr-GSK2398852 cardiac uptake as evaluated by PET imaging at different mass doses	Standardized Uptake Values (SUV) [i.e. Radioactivity concentrations] in focal anatomical locations within the heart, as well as SUV of the whole heart at different time points after ^{89}Zr-GSK2398852 administration and at different anti-SAP mAb TMDs.
Secondary	
Assessment of ^{89}Zr-GSK2398852 biodistribution in non-cardiac tissues and organs	Focal and total radioactivity uptake (including, but not limited to SUV) in different tissues

Objectives	Endpoints
	(including potentially at those peripheral tissue sites where transthyretin amyloidosis (TTR) amyloid deposition can be clinically occult) at different time points and after different TMDs.
Characterisation of the plasma pharmacokinetics of total mAb (unlabelled GSK2398852 and ^{89}Zr-GSK2398852)	Descriptive PK parameters, including the maximum concentration in plasma (C_{max}), the time associated with C_{max} (T_{max}), clearance, terminal half-life (T½) and the area under the concentration-time profile (AUC).
Characterisation of the plasma pharmacokinetics of radioactivity (^{89}Zr-GSK2398852 radio-PK)	Descriptive PK parameters including the Cmax, Tmax, T½ and AUC based on scintillation counter.
Safety & tolerability of Anti-SAP treatment including administration of ^{89}Zr-GSK2398852	All AEs including the incidence and grading of skin rashes, cardiac adverse events and infusion-related reactions, as well as other AEs utilizing standard pharmacovigilance practices. Absolute changes in safety lab parameters, including cardiac troponin and NT-proBNP. Other safety information, including ECG, inpatient and outpatient cardiac telemetry, vital signs, and physical exam data.
Exploratory	
Correlation of regional pattern of ^{89}Zr-GSK2398852 uptake in the heart with the pattern of amyloid load by PiB scan and blood flow by WAT scan or MRI signal pattern	Maps of regional PET signals or MRI signals over the myocardium will be visually compared and scored. Regional derived PET and MRI parameters correlated within and across ATTR-CM patients.
Assess feasibility of patients to operate remote data collection equipment. This may include ECGs, vital signs, and streaming video device.	Number of “virtual visits” and number of additional remote assessments collected.

5. STUDY DESIGN

5.1. Overall Design

This is an open-label, non-randomised ^{89}Zr-GSK2398852 PET imaging study in clinically stable patients with cardiac dysfunction caused by ATTR-CM. A screening visit and baseline assessments will be conducted prior to the first dosing session. Subjects will participate in up to two Anti-SAP dosing sessions in combination with ^{89}Zr-

GSK2398852 over approximately a two-month interval with at least 4 weeks between each ^{89}Zr-GSK2398852 dose.

At a suitable time point, depending on technical and logistic aspects, each subject will undergo one PET scan with the administration of PiB for the characterization of the regional amyloid burden in the heart and up to two PET scans with the administration of WAT for the characterization of the regional blood flow in the heart.

5.2. Part A and Part B

The study will be divided into two parts. Part A will complete up to 3 subjects who participate in up to two anti-SAP dosing sessions. The first two subjects in Part A will have up to three ^{89}Zr PET scans, while the remaining subject will undergo up to two ^{89}Zr PET scans.

Part B will complete up to three subjects who participate in only one anti-SAP dosing session. Subjects will undergo up to two ^{89}Zr PET scans.

Part B will be triggered by the sponsor in consultation with the Principal Investigator. This will be based on data obtained in Part A, which includes but is not restricted to equivocal myocardial uptake of ^{89}Zr-GSK2398852 in all subjects treated in Part A. This decision will also be contingent based on emerging data from the concurrent Phase 2 trial (Study Number 201464).

Should Part B not be triggered, then the study will conclude with Part A.

5.3. Study Schematic

A single dosing session in this study constitutes treatment with CPHPC, TMD administration of anti-SAP mAb consisting of in vivo mixing of a single infusion of unlabelled anti-SAP mAb and a separate infusion of ^{89}Zr-GSK2398852 via a different peripheral venous line, and up to 3 serial PET scanning procedures after administration of ^{89}Zr-GSK2398852 (Figure 1).

Figure 1 Study Schematic – Part A

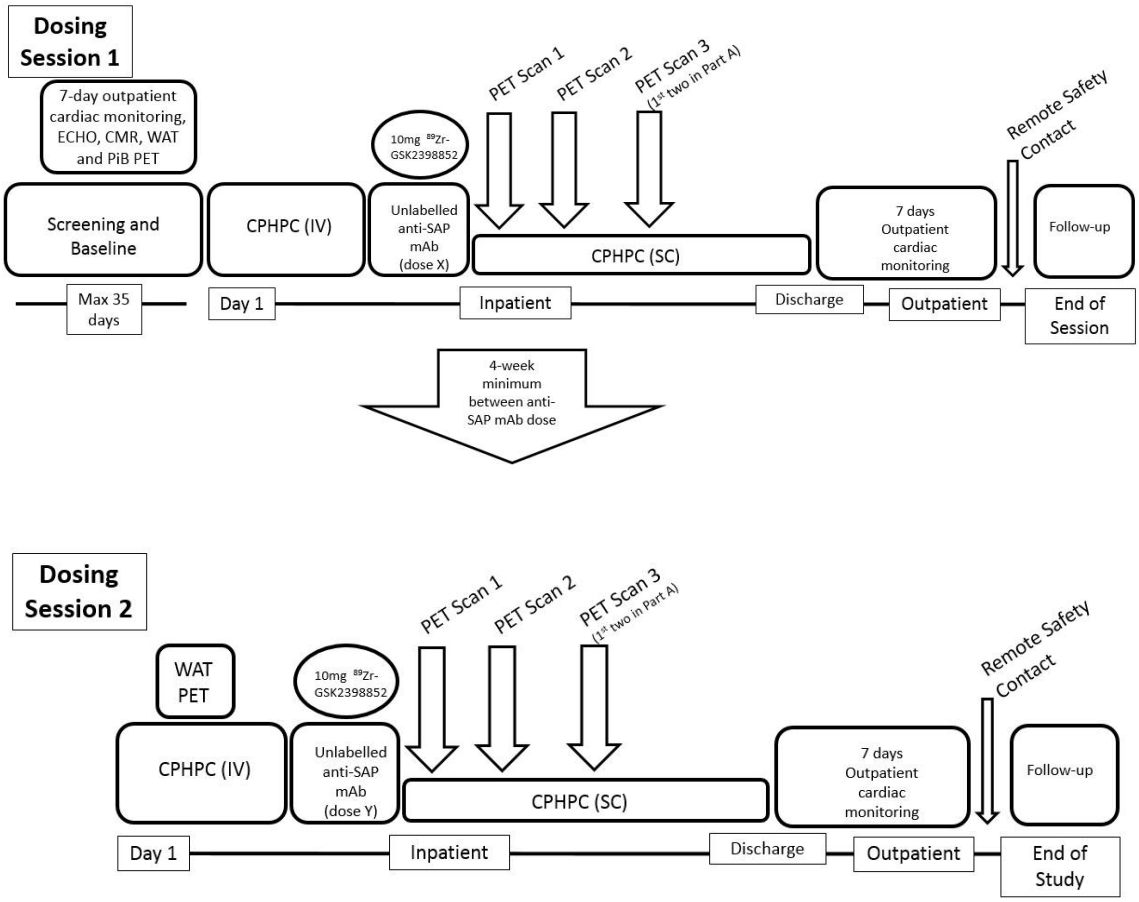
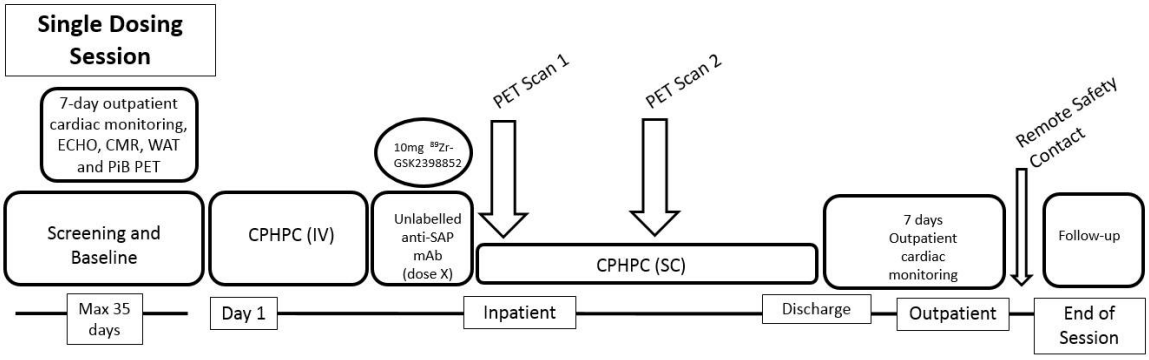


Figure 2 Study Schematic – Part B



See Section 9.3.4 for details about cardiac safety monitoring during and after Anti-SAP & ^{89}Zr-GSK2398852 dosing

5.3.1. Timing of ^{89}Zr-GSK2398852 PET scans

Up to three serial ^{89}Zr-GSK2398852 PET scans will be performed during each dosing session.

For the 1st subject in Part A, PET scans for each dosing session will be performed at the following times in relation to administration of the ^{89}Zr-GSK2398852 infusion on Day 3:

1st PET scan: Day 3 → 5 ± 2 hours from the end of ^{89}Zr-GSK2398852 infusion

2nd PET scan: Day 4 → 24 ± 4 hours from the end of ^{89}Zr-GSK2398852 infusion

3rd PET scan: Day 6 → 72 ± 6 hours from the end of ^{89}Zr-GSK2398852 infusion

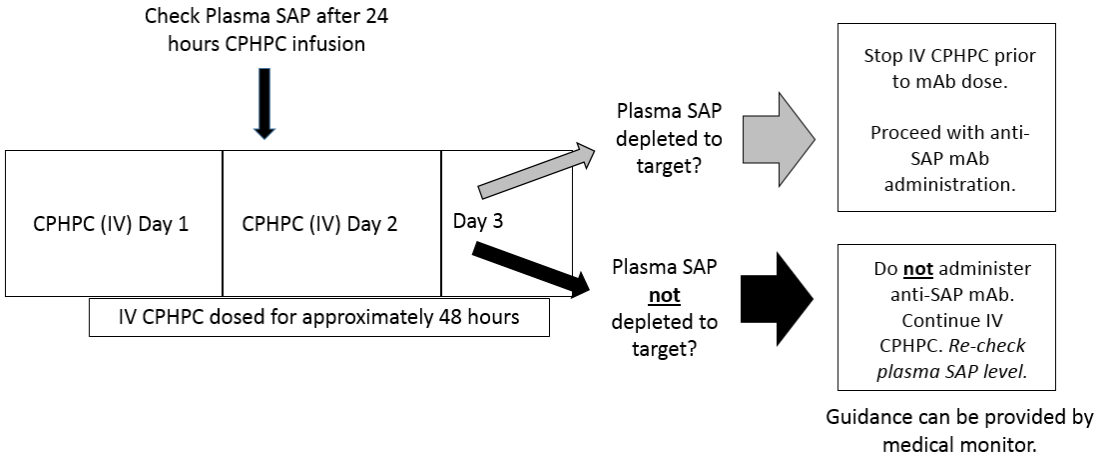
For subsequent subjects in Part A and Part B, the timing and number of the PET scans may be varied after the 1st subject in Part A has completed both dosing sessions based on emerging SUV & radiolabel PK data. This information will be communicated to the site in a file note prior to the start of each subsequent dosing session.

Further details on PET procedures and analyses are given in the Imaging Acquisition and Analysis Manual.

5.4. Administration of CPHPC

Subjects will begin IV CPHPC infusion on Day 1 and continue the infusion for a minimum of approximately 48 hours until Day 3. The infusion will be stopped prior to the anti-SAP mAb infusion. It is critical that the subject's plasma SAP level is below the target prior to beginning the anti-SAP mAb infusion.

Figure 3 IV CPHPC Infusion Schematic



SC CPHPC injections will be administered thrice daily, with the first SC CPHPC dose administered approximately 5 hours after the end of the IV CPHPC infusion. It is possible this may overlap with anti-SAP mAb administration.

It is important that the SC CPHPC doses are administered after the administration of anti-SAP mAb to ensure circulating SAP remains low to prevent the formation of large amounts of anti-SAP mAb / SAP immune complex formation, even if the subject withdraws from the study.

If a subject is unable to tolerate SC CPHPC injections, the investigator should consider administration of CPHPC via an IV infusion.

If anti-SAP mAb dosing is delayed (e.g. due to PET scanner availability or delay in ^{89}Zr-GSK2398852 transport), the subject may continue IV CPHPC infusion for an additional day. Should this occur, an additional plasma SAP specimen should be collected, and the result confirmed to be below target prior to administering anti-SAP mAb, in effect repeating all Day 2 procedures. This should only be done if logistics permit and PET camera availability is confirmed.

Should the delay be any longer than 1 day, IV CPHPC administration will be stopped, and subject may be invited to return at a later date to re-start the dosing session. The Medical Monitor should be notified in such instances.

5.5. Plasma SAP Target

Plasma SAP concentration must be below target prior to administering anti-SAP mAb. If plasma SAP levels are not below target then continue CPHPC IV and do not administer anti-SAP mAb. This test may be repeated if required (Section 9.5.1).

5.6. Administration of ^{89}Zr-GSK2398852 in relation to administration of unlabelled anti-SAP mAb

For each TMD, ^{89}Zr-GSK2398852 and anti-SAP mAb will be mixed in vivo via two separate peripheral venous lines.

For TMDs ≤200 mg: For the first patient in Part A Dosing Session 1, ^{89}Zr-GSK2398852 will be administered simultaneously with unlabelled anti-SAP mAb, over 1 hour, such that both infusions finish at the same time. For subsequent patients, based on emerging data, ^{89}Zr-GSK2398852 may be initiated at any time during the unlabelled anti-SAP mAb infusion or after the unlabelled anti-SAP mAb infusion has completed. The exact timing of infusions will be communicated to the site in a file note.

For total anti-SAP mAb mass doses >200 mg (range: 200 < TMD ≤500 mg): Refer to Table 6. The exact timing of infusions will be communicated to the site in a file note.

Table 6 Proposed Duration and Timing of anti-SAP mAb and ^{89}Zr-GSK2398852 administration

Total Mass Doses of anti-SAP mAb	Proposed Duration of Unlabelled anti-SAP mAb Infusions	Planned Timing of ^{89}Zr-GSK2398852 Administration in Relation to Unlabelled anti-SAP mAb Infusion[1, 2]
80 – 200 mg	1 Hour	**Simultaneous administration:** *Both* infusions administered over 1 hour & finishing at approximately the same time[3]
200 mg < Total Mass Dose ≤500 mg	6 Hours	**Co-administration:** ^{89}Zr-GSK2398852 administered over 1 hour, commencing any time after start of unlabelled anti-SAP mAb, including after its completion

[1]If a subject experiences infusion reaction, dosing may be paused and resumed at investigator discretion.
[2]Unlabelled anti-SAP mAb and ^{89}Zr-GSK2398852 will be administered via two separate peripheral venous lines
[3]After the first subject, there is an option (based on emerging data) that administration of ^{89}Zr-GSK2398852 may be initiated at any time during the infusion or after the unlabelled anti-SAP mAb infusion has completed.

Table 7 Anti-SAP Treatment Dosing Sessions 1 and 2

Dosing Sessions 1 and 2						
Day	**Day 1 & 2**	**Day 3**	**Up to Day 11**	**Day 11-18**	**Day 20 ± 1d**	**Day 26 ± 2d**
Setting	Inpatient			Outpatient		
Activity	**Plasma SAP depletion** Administration of IV CPHPC for approximately 48 hours Plasma SAP concentration confirmed before anti-SAP mAb infusion.	**Administration of anti-SAP mAb and ^{89}Zr-GSK2398852** Each infusion of unlabelled anti-SAP mAb either over 1 hour or 6 hours dependent on unlabelled mass doses CPHPC continues SC. Subjects closely monitored.	**Inpatient safety follow up** Administration of CPHPC SC continues until up to Day 11 Subject discharged to home.	Outpatient Cardiac monitoring (approximately 1 week after discharge)	Outpatient contact assessment with preliminary review of Remote Cardiac Telemetry device data feedback to subject (if available).	**Safety follow up**
					If possible, subject will have option to conduct Day 20 and Day 26 visits via telephone or video link using study-approved device. Optional remote ECG and vital signs collection device may be used.	

5.7. Number of Subjects

Sufficient ATTR-CM subjects will be screened such that 3 subjects complete at least one Dosing Session in both Part A and Part B (3 subjects in each part).

If a subject prematurely discontinues the study, additional replacement subject(s) may be recruited at the discretion of the Sponsor in consultation with the Investigator.

5.8. Treatment Groups and Duration

The treatment group will consist of ATTR-CM subjects: Wild-type & mutant genotypes primarily associated with familial amyloidotic cardiomyopathy (FAC).

The length of time between dosing sessions should be no less than 4 weeks. This is calculated as 4 weeks from administration of anti-SAP mAb.

Participation will last approximately 2-4 months, depending the subject's participation in Part A or Part B, and length of time between dosing sessions.

5.9. Length of Time Between Dosing Sessions

There must be a minimum of 4 weeks between each dose of anti-SAP mAb, to allow for plasma SAP levels to return to baseline.

5.10. Periodic Meeting with Investigators

5.10.1. Individual Subject Safety Review

Prior to beginning the next dosing session in each subject, there will be a review of the available data by:

1. Principal Investigator (or appropriate designee) having consulted with local cardiologist, and / or any other appropriate clinical colleague (e.g. dermatologist) regarding any findings or concerns; additional attendees will be invited as required.

2. GSK team including Medical Monitor, GSK Safety Representative, GSK Study Team Leader, additional attendees will be invited as required.

The purpose of this review is to consider whether it is appropriate to administer a second dose to confirm the unlabelled anti-SAP mAb dose. The review will be a holistic review of the case, but the following safety parameters will be considered specifically:

- Adverse events
- Whether the subject has experienced a rash
- Cardiac safety, including outpatient cardiac monitoring recording and cardiac biomarkers
- Biochemistry & Haematology
- When imaging and PK data are available, these will be reviewed to consider potential need to change imaging and PK time points.

5.11. Subject and Study Completion

A subject is considered to have completed the study if he/she has completed all planned dosing sessions, including the follow-up visit.

A Subject in Part A who participates in only one dosing session, and complete the final follow-up visit, may also be considered to have completed the study.

The end of the study is defined as the date of the last visit of the last subject in the study.

5.12. Scientific Rationale for Study Design

5.12.1. Justification for the administration of CPHPC & unlabelled anti-SAP mAb

5.12.1.1. CPHPC

Pharmacologically, IV CPHPC is a highly predictable drug as demonstrated in FIH study (SAP115570) where all systemic amyloidosis subjects attained plasma SAP depletion below the specified target level.

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 both effective and consistently predictable in depleting circulating SAP to <2 mg/L (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 formation of potentially harmful (i.e. high titres of) circulating immune complexes. Safety evaluation in the FIH study did not identify any signals suggestive of adverse effects from residual plasma SAP, such as clinical manifestations of systemic/organ vasculitis.

CPHPC is predominantly cleared from the plasma by the kidneys and excreted in the urine. CPHPC doses will therefore be adjusted (see Section 7.2.1, Table 8) based on individual renal function as measured by 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.

Subjects with overall low amyloid load, such as ATTR-CM patients in this study, are likely to deplete their plasma SAP level to target within 48 hours of administration of IV CPHPC. The first plasma SAP concentration will be checked after 24 hours of administration of IV CPHPC to confirm whether the anti-SAP mAb and ^{89}Zr-GSK2398852 can be administered at approximately 48 hours after initiation of IV CPHPC.

The total duration of administration of maintenance SC CPHPC in this study will be 8 days (i.e. last dose per session on Day 11), and is in line with the schedule of administration in the Phase 2 study (201464).

5.12.1.2. Unlabelled Anti-SAP mAb

The dose level of unlabelled anti-SAP mAb in each dosing session will be selected to ensure the TMD will not exceed 500 mg

Given that SAP is known to be constitutively present in normal tissues and that TTR amyloid deposits might also be present in a clinically occult manner within peripheral

soft tissues, skeletal muscle, and nerve fibre sheaths of ATTR-CM subjects, unlabelled anti-SAP mAb will be administered during each dosing session in order to 'block' the extra-cardiac SAP in tissues. This will enable sufficient ^{89}Zr-GSK2398852 in the systemic circulation to be distributed to SAP-containing amyloid deposits within the heart rather than being distributed to well vascularised extra-cardiac tissue sites (e.g. liver and skin) where circulating ^{89}Zr-GSK2398852 could potentially be more accessible to tissue-bound SAP.

The rationale to start with a relatively low mass dose of unlabelled anti-SAP mAb in the first ATTR CM subject (e.g. 70 mg) is that a higher mass dose of unlabelled mAb could potentially be distributed to the myocardium, such that the binding of ^{89}Zr-GSK2398852 to cardiac amyloid deposits could be attenuated, therefore leading to a lower probability of detecting a PET imaging signal indicative of cardiac tissue uptake of ^{89}Zr-GSK2398852.

Due to the complex relationship between allowing better “targeting” to cardiac amyloid at lower doses and potential attenuation of SAP-amyloid binding at higher doses, we suggest that up to two different mass doses are evaluated in each individual ATTR-CM subject from the perspective of both the (radiolabel) PK profile of ^{89}Zr-GSK2398852 and the cardiac SUV/ extra-cardiac SUV ratio determined by the final PET scan per dosing session.

By comparing the ^{89}Zr-GSK2398852 uptake within the same patient, we expect to significantly reduce the variability which could come from very different amyloid load in different subjects. Furthermore, the design includes the potential to have different TMDs in different patients and to guide the selection of the dose of unlabelled anti-SAP mAb adaptively by review of results from previous subjects.

5.13. Study Overview of Anti-SAP Treatment and ^{89}Zr-GSK2398852

5.13.1. Unlabelled anti-SAP mAb Dose Selection

The study aims to identify the dose range leading to “optimal” ^{89}Zr-mAb radiotracer uptake in the heart.

It is anticipated that at very low doses of unlabelled anti-SAP mAb, the clearance of radio-labelled PK may be fast and the expected slow penetration from plasma to heart muscle interstitium may therefore lead to a low uptake of ^{89}Zr-GSK2398852 in heart tissue. This may give a low radioactivity signal in the heart impairing the possibility to obtain a good measurement.

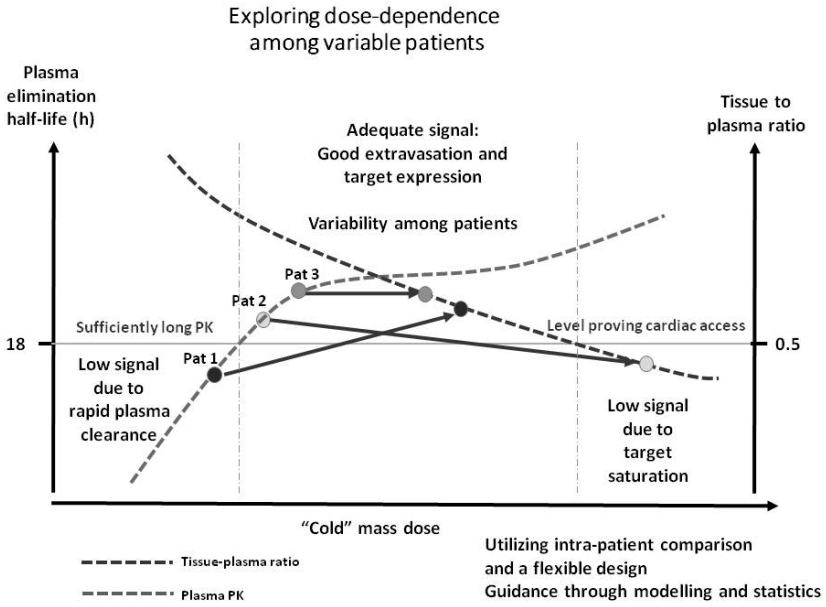
On the other hand, a low unlabelled anti-SAP mAb dose may be beneficial to the binding of ^{89}Zr-GSK2398852 to amyloid-SAP complexes in the myocardium because of lack of competition with binding of radiolabelled compound from a possible excess of unlabelled mAb within the interstitial space.

At higher TMDs of anti-SAP mAb, the plasma clearance of ^{89}Zr-GSK2398852 is expected to be slower, facilitating an increased uptake in the tissue interstitium, while at

the same time this may be associated with an increased risk of unlabelled anti-SAP mAb competing with binding of the radiolabelled mAb.

The search for "optimal dose" needs to consider an expected inter-subject variability in the read-out due to biological factors (Figure 4**)**.

Figure 4 Examples of inter- and intra-subject relationships between tissue / plasma SUV ratio across a range of unlabelled ("cold") anti-SAP mAb mass doses



In order to increase the probability of obtaining data which provides a good cardiac signal we propose the following concept:

- The first subject in Part A, Dosing Session 1 is investigated with the TMD 80 mg (70 mg unlabelled anti-SAP mAb *plus* 10 mg ^{89}Zr-GSK2398852). The 80 mg dose is selected because this is the lowest dose in which we have previous adequate human PK data, and these data indicate a terminal elimination half-life in the range of 15 hours. This relatively short plasma residence may hamper the cardiac uptake but is still predicted to have a potential for adequate cardiac signal.
    - The TMD for this subject's Dosing Session 2 will be determined by the central study team based on data from Dosing Session 1. This will be communicated to the clinical site by filenote prior to Dosing Session 2.
- Subsequent subjects will receive up to two doses, selected based on the following criteria:
    - The combined and individual doses should be below the highest single dose which in the therapeutic trials has been found to be safe

- Up to 6 fully evaluated subjects will be included (N=3 in Part A, and N=3 in Part B)
- Doses in subsequent subjects will be selected based on previous subject's data and decided upon by the project team with advice from the GSK statistician and modeler
- The guiding principle is to have as many subjects as possible having at least one mass dose which is within a perceived "optimal" mass dose range.

5.13.2. Justification of serial PET scanning per Anti-SAP session

The time course of the radiolabel mAb PK profile, and the temporal pattern of ^{89}Zr-GSK2398852 uptake in the myocardium are the two key parameters guiding anti-SAP mAb TMD selection in this PET study.

A total of up to 3 serial ^{89}Zr-GSK2398852 PET scanning procedures will be performed per dosing session. The scanning times will be predefined only for the first patient, but may be different for the following patients, guided by previous results.

In Part A, the first two subjects will have 3 PET scans per dosing session. The first two scans in these two subjects will be performed over approximately the first 24 hours after ^{89}Zr-GSK2398852 administration. The third scan will be performed at a later time (timing to be determined from emerging data during the initial part of the study).

After the first two subjects have completed Part A, the subsequent subjects are planned to undergo only two PET scans, the timing of which will be determined by emerging data.

Up to 3 PET scans per dosing session in Part A are justified after administration of ^{89}Zr-GSK2398852 because the timing of each of these three scanning procedures is a reflection of the predicted time-related whole body biodistribution of ^{89}Zr-GSK2398852. That is, a later PET scan performed at approximately 72 hours after administration of ^{89}Zr-GSK2398852 is more likely to detect myocardial tissue specific uptake compared to PET scans performed at earlier time points which are more likely to detect ^{89}Zr-GSK2398852 within the blood pool of the cardiac chambers.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

Age

1. Subject must be 65 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Subject and Disease Characteristics

2. Subjects with a diagnosis of ATTR-CM

    a. Wild-type ATTR status must be confirmed by genotyping AND have one of the following:

        i. 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

        OR

        ii. Scintigraphy Technetium-99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) with confirmed myocardial uptake.

    b. Hereditary ATTR amyloidosis (e.g. TTR Val30Met) should have a known amyloidogenic TTR mutation demonstrated by genotyping AND is recognised to be primarily associated with cardiomyopathy AND one of the following:

        i. 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.

        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.

        OR

        ii. Scintigraphy: ^{99m}Tc-DPD with confirmed myocardial uptake.

Sex

3. Both male and female subjects are eligible to participate.

    a. Male subjects:

    A male subject must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 3 months after the last scan and refrain from donating sperm during this period.

    b. Female subjects:

    A female subject is eligible to participate if she is not of childbearing potential as defined in Appendix 5.

Informed Consent

4. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other

5. New York Heart Association (NYHA) up to class 3; subjects should be clinically stable for at least 3 months preceding to Screening.

6.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Cardiomyopathy primarily caused by non-amyloid diseases (e.g. ischemic heart disease; valvular heart disease).
2. Interval from the Q wave on the ECG to point T using Fredericia's formula (QTcF) >500 msec.
3. Sustained (at a rate of ≥120 beats per min for ≥30 seconds), or symptomatic monomorphic ventricular tachycardia (VT), or rapid polymorphic VT, at screening/baseline cardiac monitoring.
4. Systolic blood pressure ≤100 mm/Hg based on triplicate readings at screening.
5. Unstable heart failure defined as emergency hospitalization for worsening, or decompensated heart failure, or syncopal episode within 1 month of screening.
6. Implantable cardiac defibrillator (ICD) or permanent pacemaker (PPM) at screening.
7. Estimated Glomerular filtration rate (eGFR) at Screening <50 mL/min calculated using modification of diet in renal disease (MDRD).
8. Any active and persistent dermatological condition, which in the opinion of the Investigator and Medical Monitor would preclude safe participation.
9. History of allogeneic stem cell transplantation, prior solid organ transplant, or anticipated to undergo solid organ transplantation, or left ventricular assist device (LVAD) implantation.
10. 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.
    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.
11. Acute coronary syndrome, or any form of coronary revascularization procedure (including coronary artery bypass grafting [CABG]), within 6 months of screening.
12. Symptomatic, clinically significant autonomic neuropathy which the Principal Investigator (PI) feels will preclude administration of study treatment.
13. Uncontrolled hypertension during Screening.

14. Alanine transaminase (ALT) >3x upper limit of normal (ULN) OR bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
15. Peripheral oedema at Screening that in the opinion of the PI or designee might prevent adequate absorption of subcutaneously administered CPHPC.
16. Presence of any co-morbid (e.g. steroid refractory rheumatoid arthritis), or an uncontrolled medical condition (e.g. diabetes mellitus), which in the opinion of the investigator would increase the potential risk to the subject. *Investigator should liaise with the Medical Monitor where there is uncertainty as to the eligibility of a patient.*
17. 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.
18. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
19. Inability to comprehend and / or understand the study patient information sheet, and / or unwillingness or inability to follow the procedures outlined in the protocol.

ATTR-CM Specific Criteria

20. Has any of the following:
    a. Fulfilment of diagnostic criteria for AL amyloidosis
    b. Fulfilment of diagnostic criteria for amyloid A (AA) or non-TTR hereditary amyloidosis
21. ATTR Disease Load:
    c. Histologically proven or clinically suspected gastrointestinal TTR amyloidosis
    d. Diffuse skeletal muscle uptake of 99m(Tc)-DPD on Single-photon emission computed tomography (SPECT) imaging (where available)
    e. Peripheral neuropathy causing more than mild morbidity (e.g. walking disability; neuropathic pain affecting activities of daily living)
    f. Proven or clinically suspected intracranial TTR involvement including ophthalmological disease
22. 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

Prior/Concomitant Therapy

23. Participation in a separate clinical trial involving CPHPC within 3 months of screening

24. Any prohibited concomitant medication as per Section 7.7.2 within referenced timeframe

Prior/Concurrent Clinical Study Experience

25. 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.

Diagnostic assessments for PET & Cardiac Magnetic Resonance (CMR) Scanning

26. Orthopnoea of sufficient severity to preclude supine scanning as determined at screening
27. Inability to fit inside scanner due to body size (girth)
28. History of claustrophobia
29. Contraindication to MRI contrast agents
30. Contraindication for MRI scanning (as assessed by local MRI safety questionnaire), which includes but is not limited to:

    a. Intracranial aneurysm clips (except Sugita) or other metallic objects
    b. Intra-orbital metal fragments that have not been removed
    c. Pacemakers or other implanted cardiac rhythm management/monitoring devices and non-MR conditional heart valves
    d. Inner ear implants

Other Exclusions

31. Donation of blood or blood products in excess of 500 mL within 84 days of screening
32. Poor or unsuitable venous access

6.3. Lifestyle Restrictions

The following restrictions apply:

6.3.1. Caffeine, Alcohol, and Tobacco

- Subjects will abstain from caffeine (e.g. tea, coffee, cola, chocolate) from Day 1 until final PET scan of dosing session, and 24 hours prior to any imaging scan.
- During each dosing session, subjects will abstain from alcohol for 24 hours prior to any imaging scan and for 24 hours prior to and during inpatient stays.
- Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted 24 hours prior to any imaging scan or PK sample. Subjects will be required to adhere to clinical unit policy on tobacco/nicotine use.

6.3.2. Activity

Subjects will abstain from strenuous exercise for at least 24 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watching television, reading).

6.3.3. In-person Social Interaction

Following administration of ^{89}Zr-GSK2398852, subjects will be advised to maintain a safe distance from young children and pregnant women consistent with local radiation safety guidelines. The clinical site should adhere to local hospital policy regarding in-person social interaction.

6.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

7. TREATMENTS

Study treatment is defined as any investigational treatments intended to be administered to a study subject according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	**GSK2315698 (CPHPC)**	**GSK2398852 (unlabelled anti-SAP mAb)**	**^{89}Zr-GSK2398852 (^{89}Zr-Df-labelled anti-SAP mAb)**
Dosage formulation:	GSK2315698 Solution for Subcutaneous Injection or Intravenous Infusion, 200 mg/mL	GSK2398852 Concentrate for Solution for Infusion, 100 mg/mL	Solution containing 10 mg ^{89}Zr-GSK2398852 for Infusion, 10 mg/10mL or 10 mg/20mL

Study Treatment Name:	**GSK2315698 (CPHPC)**	**GSK2398852 (unlabelled anti-SAP mAb)**	**^{89}Zr-GSK2398852 (^{89}Zr-Df-labelled anti-SAP mAb)**
Unit dose strength(s)/ Dosage level(s):	200 mg/mL provided as 2 mL solution per vial Dosage levels: variable dependent on renal function	100 mg/mL provided as 1 mL solution per vial. Variable total mass doses of anti-SAP mAb not exceeding 500 mg per dosing session	37 MBq ^{89}Zr-GSK2398852 associated with a mass of 10 mg GSK2398852
Route of Administration	Intravenous infusion usually for approximately 48 hours but up to 72 hours Subcutaneous injection up to 3x daily for up to 8 days after unlabelled anti-SAP mAb dose per dosing session	Intravenous infusion of variable duration.	Refer to Table 6
Dosing instructions:	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	Study medication will be diluted in 0.9% w/v sodium chloride and administered by intravenous infusion by study personnel following specified regimens	To be administered via separate intravenous cannula. Refer to Table 6 See local Standard operating procedure (SOP) to protect from ionising radiation
Packaging and Labelling	Study Treatment will be provided in Type 1 clear glass vials sealed with grey polymer coated rubber stoppers that meet extractable criteria for sterile dosage forms. A silver aluminium overseal is placed over each vial and crimped. Each vial will be labelled as required per country requirement.	Study Treatment will be provided in glass vials. Each vial will be labelled as required per country requirement.	Study Treatment will be provided in glass vials. Each vial will be labelled as required per country requirement.

Study Treatment Name:	GSK2315698 (CPHPC)	GSK2398852 (unlabelled anti-SAP mAb)	^{89}Zr-GSK2398852 (^{89}Zr-Df-labelled anti-SAP mAb)
Manufacturer	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]	VU University Medical Center Radiology & Nuclear Medicine

Anti-SAP mAb must not be administered until plasma SAP level has reached target. See Section 5.5.

See Section 5.4, Section 5.5, and Section 5.13 for additional dosing information.

7.2. Dose Modification

7.2.1. CPHPC dosing regimen according to renal function

Table 8 CPHPC dosing regimen according to renal function

Renal Function eGFR[a] (mL/min/1.73 m^2)	IV dose level	SC dose regimen
≥64	20 mg/hour	60 mg t.i.d
≥46 and< 64[b]	10 mg/hour	60 mg t.i.d
<46	Consult Medical Monitor	Consult Medical Monitor

a. eGFR determined by MDRD (Modification of Diet in Renal Disease) must be used to define CPHPC dose based on renal function
b. Note renal withdrawal criteria in Section 8.1.3
t.i.d. = three times daily, approximately 8 hours apart.

7.2.2. CPHPC Route of Administration Change

If the subject is unable to tolerate SC CPHPC injections post anti-SAP mAb infusion, in order to continue CPHPC, the investigator may switch the route of administration from SC injection to IV infusion. The Medical Monitor should be consulted in this instance.

7.3. Method of Treatment Assignment

Subjects will be identified by a unique subject number at screening that will remain consistent for the duration of the study. Upon completion of screening subjects will will commence study treatments as described in Section 7. There will be no control group in this study.

The study has a non-randomised design. However, for internal study reporting, subjects will be assigned randomisation numbers for database/programming purposes, e.g. to flag screened subjects who commence study treatment and therefore are to be included in the All-Treated Population (see Section 10.3.1).

7.4. Blinding

This is a non-randomised open-label study. All investigators and GSK Study Team members, have direct access to the subject's individual study treatment and dosing schedules for each constituent drug.

Analyses for PET imaging data per subject will not be blinded.

7.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of GSK2398852, ^{89}Zr-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.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. 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 labeled storage conditions with access limited to the investigator and authorized site staff.
3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

- 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.
- A Material Safety Data Sheet (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.

7.6. Treatment Compliance

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 treatments 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.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

Subjects usual medication can be continued during this study with the exception of those listed in Section 7.7.2.

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Pre-medication prior to unlabelled 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 unlabelled anti-SAP mAb. Additional administrations of either or both medications are permitted at discretion of Investigator or designee if symptoms require this.

Given that the infusion of ^{89}Zr-GSK2388852 will commence during or shortly after the infusion of the unlabelled anti-SAP mAb infusion, administration of a separate premedication schedule is not required before the radiolabelled mAb infusion commences.

7.7.2. Prohibited Medications and Non-Drug Therapies

The following restrictions apply from pre-screening up to the final visit.

Table 9 Restricted Medications

Medication	Pre-screen restriction
Tafamidis, diflunisal, tauroursodeoxycholic acid (TUDCA)	Initiation of, or change of dose, within 28 days
Green tea extract	Initiation of, or change of dose, within 28 days
Silencing therapies (e.g. small interfering ribonucleic acid [siRNA]) for ATTR protein synthesis	3 months
Disease-modifying drug for any type of autoimmune disease, including but not restricted to, methotrexate, cyclophosphamide, or anti-cytokine antibodies (e.g. anti tumor necrosis factor (TNF)-α monoclonal antibody)	At any time
Antibody therapy for amyloidosis treatment	At any time

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

7.8. 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 ATTR-CM, treatment will not be provided after the end of the study. This may be reviewed once more information is available.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Discontinuation for failure to deplete plasma SAP levels with IV CPHPC

Subjects will be withdrawn from the study if they are unable to deplete plasma SAP levels to target (Section 5.4 and Section 5.5).

8.1.2. Adverse Event Discontinuation Criteria

Subjects with any adverse event(s) (e.g. skin rash) that have arisen during the 1st dosing session and is potentially attributable to administration of any component of Anti-SAP treatment or ^{89}Zr-GSK2398852, and that has not completely resolved by the time the 2nd dosing session is expected to commence, will be withdrawn from the study.

8.1.3. Renal Function Discontinuation Criteria

Subjects will not receive anti-SAP mAb if

- The eGFR calculated by the MDRD equation has reduced to <40 mL/min/1.73m^2 after Screening,

  or

- There has been a reduction in eGFR from baseline by >50%.

If the eGFR falls to between 40 – 50 during the trial, the subject can continue participation at the investigator/designee's discretion.

Dose adjustment of IV and / or SC CPHPC may be necessary for subjects with reduced eGFR at baseline, before administration of anti-SAP mAb in the 2nd dosing session, or at any time during the study; refer to Section 7.2.1 and Table 8 for CPHPC renal dosing regimen.

8.1.4. Cardiovascular Safety Discontinuation Criteria

8.1.4.1. 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 (≥ 120 beats/min for ≥ 30 seconds), or development of new rapid polymorphic VT, or new ventricular fibrillation (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 either prophylaxis or treatment with a permanent cardiac pacemaker, or ICD

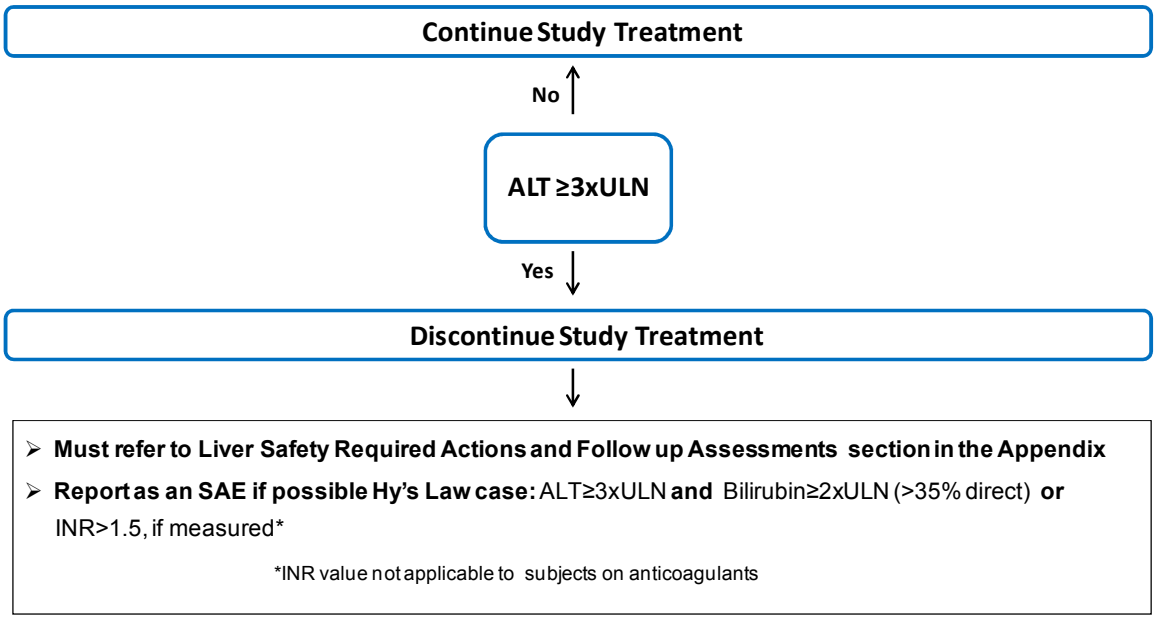
8.1.5. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology.

Discontinuation of study treatment for abnormal liver tests is required when:

- a subject meets one of the conditions outlined in the algorithm (Figure 5)
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the subject.

Figure 5 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.6. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- 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.

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

1. QTc ≥530 msec, irrespective of bundle branch block status

or,

2. Increase from baseline: change in QTc >60 msec

8.1.7. Dermatological Toxicity Stopping Criteria

8.1.7.1. Individual subject dermatological stopping criteria

A subject who meets any criterion below will be withdrawn from further treatment sessions:

- Any skin rash >Grade 2
- Any grade of skin rash which has not completely resolved before dosing session 2
- Peripheral oedema which is deemed by the Investigator to be affecting the systemic absorption of SC CPHPC (i.e. CPHPC administration should continue by IV infusion to Day 11)
- Skin toxicity of any grade which is refractory to dermatological treatment
- Clinical evidence of skin necrosis, irrespective of 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)

8.1.8. 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 Grade 4 rash (see Appendix 7)

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.

See the SoA for data to be collected at the time of treatment discontinuation (i.e. all follow-up procedures).

8.1.9. Rechallenge

8.1.9.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Withdrawal of study treatment does not necessarily require withdrawal from study.
- Refer to Day 26 assessments in the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Whenever possible, subjects should complete SC CPHPC maintenance following administration of anti-SAP mAb to prevent circulating anti-SAP mAb / SAP immune complexes.

8.3. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and 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.
- Before a 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, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the study (see Section 8).

9.1.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs will be collected from the signing of the ICF until the final visit at the time points specified in the SoA (Section 2).
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- 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 to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.1.2. Method of Detecting AEs and SAEs

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

9.1.3. 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 will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.1.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the case report

form (CRF) will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.1.6. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after baseline and until 3 months after last PET scan.

If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

For this study, any dose of CPHPC, unlabelled anti-SAP mAb, or ^{89}Zr-GSK2398852 greater than the intended dose within the scheduled dosing period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

9.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight 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).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.2. Vital Signs

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

9.3.3. Electrocardiograms

- Single or triplicate 12-lead ECGs will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF or QTc corrected by Bazett's formula (QTcB) intervals. Refer to Section 8.1.4 for QTc withdrawal criteria and additional readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- 12-lead ECGs should be measured in a semi-supine position after approximately 5 minutes of rest.

9.3.4. Cardiac Safety Monitoring

9.3.4.1. Electrophysiology

Given that cardiac amyloidosis patients have a high background incidence of arrhythmias [Boldrini 2013, Barbhaiya 2016], ATTR-CM subjects in this PET study will have a thorough evaluation of their background disposition to arrhythmias by performing electrophysiological cardiac monitoring at Screening and at Baseline. During each dosing session, continuous in-patient cardiac telemetry will be performed up to Day 11 (see Figure 6, below).

Screening: 7-day outpatient electrophysiological cardiac monitoring using an appropriate non-implantable recording device (e.g. BodyGuardian) – this will evaluate the arrhythmic background of eligible ATTR-CM patients such that false positive attribution of arrhythmias to anti-SAP mAb TMDs will be minimized.

Inpatient Lead II Cardiac Telemetry: Continuous telemetry will be performed to detect any arrhythmias which are proximate to the administration of Anti-SAP treatment

and ^{89}Zr-GSK2398852 in ATTR-CM patients including worsening of known patient-specific arrhythmias from Screening and / or Baseline assessments. This should be continued until remote continuous cardiac monitoring is initiated.

At investigator discretion, in consultation with the Medical Monitor, Inpatient Lead II Cardiac Telemetry can be substituted to the BodyGuardian device.

Outpatient Remote Continuous Cardiac Monitoring: Monitoring will be performed using a non-implantable remote cardiac telemetry device. This device will be started before discharge.

Review of Remote Cardiac Telemetry: Outpatient electrophysiological data should be downloaded and reviewed by a cardiologist at the local study site *no longer than 48 hours* after the 1-week recording period has completed. Therefore, the preliminary report from 7-day outpatient cardiac monitoring should be available for the investigator or designee to discuss with the subject during their remote consultation "visit".

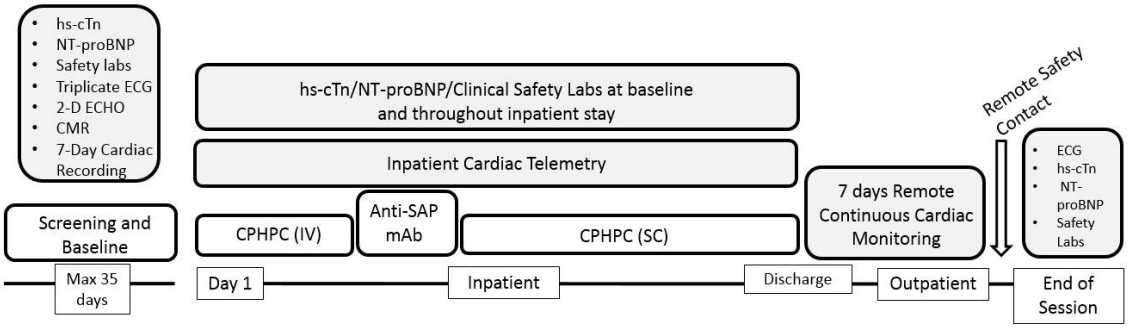
All electrophysiological data, including inpatient telemetry, should be reviewed in comparison to Screening data after the 1st dosing session.

In the event of a cardiac AE, the investigator or designee should compare and contrast the emergent cardiac electrophysiological data with the Screening data as early as possible, and consult with the Medical Monitor as deemed necessary by the emergent clinical safety issues.

Optional Monitoring: Inpatient and / or outpatient electrophysiological cardiac monitoring can continue / reinitiated at the discretion of the Investigator or designee based on emerging cardiac safety data within a given ATTR-CM subject, and / or based on emerging collective study population data.

Based on emerging cardiac safety data, optional inpatient and / or outpatient cardiac monitoring can be continued for as long as deemed clinically necessary by the investigator or designee in consultation with the Medical Monitor.

Figure 6 Cardiac Safety Monitoring at Screening & during each dosing session



If remote cardiac monitoring uses BodyGuardian device: A separate "critical alert" arrhythmia protocol will be provided to the monitoring centre and study site. This will

include, for example, bradycardic and ventricular tachycardic event notification requirements.

9.3.4.2. High Sensitivity Cardiac Troponin (hs-cTn) Monitoring after a Cardiac Arrhythmia Event

Given that the background incidence of cardiac arrhythmias in ATTR-CM patients is high, and that some subjects recruited into this study might have elevated troponin levels at baseline, ATTR-CM subjects might be particularly susceptible to myocardial ischemia as a result of either a disease or anti-SAP mAb-related arrhythmia.

Baseline hs-cTn Evaluation: In the event that an ATTR-CM subject has a clinically concerning cardiac arrhythmic event after administration of Anti-SAP treatment + ^{89}Zr-GSK2398852, a plasma hs-cTn level will always be measured before each administration of Anti-SAP treatment.

Monitoring of hs-cTn after an Arrhythmia Event: A hs-cTn should be evaluated immediately at the time of onset of a cardiac arrhythmia which is deemed by the Investigator to be of clinical concern (see Section 3.4.1.3).

hs-cTn levels should be serially repeated (using the same assay) following local troponin monitoring protocols at the study site, and with advice from a cardiologist at the local study site if this is deemed clinically necessary by the Investigator or designee.

hs-cTn blood sample can also be drawn from an ATTR CM subject, at any time, for the evaluation of other types of cardiac adverse event where there are no associated electrophysiological changes – e.g. electrically silent acute chest pain.

Similarly, NT-proBNP levels can be performed more frequently during in-patient stay or as an out-patient if this is deemed clinically necessary for cardiac safety reasons by the Investigator or designee.

9.3.4.3. Imaging for Investigation of Cardiac Adverse Events

Contrast-enhanced CMR and ECHO methodologies will be detailed in the separate Image Acquisition and Analysis Manual.

A single 2-D Echocardiogram will be performed at baseline for reference, in the event of an adverse cardiac event being detected during the study (e.g. worsening heart failure symptoms or an unexpected large rise in NT-proBNP levels) which in the opinion of the Investigator or designee would require repeat Echocardiogram to re-evaluate cardiac function.

Similarly, repeat CMR(s) can also be performed at any time during the study (to compare against the baseline CMR) to enable a more detailed evaluation of cardiac function.

Furthermore, at the discretion of the investigator / designee in consultation with the Medical Monitor, a repeat CMR can be performed in the unlikely event that there is suspected change in cardiac amyloid load – e.g. in the clinical opinion of the investigator

or designee, an appreciable reduction in NT-proBNP levels from baseline during or after any of the two Anti-SAP dosing sessions.

Wherever feasible, repeat CMR scan(s) should be performed at the local study site preferably using the same MRI scanner and IV contrast agent as that used at Screening.

9.3.4.4. Insertion of a PPM or ICD for Prophylactic Reasons

Any individual subject who requires insertion of a PPM or ICD for prophylactic reasons during the study will be withdrawn and replaced with a new ATTR-CM subject.

All subjects who have a PPM or ICD inserted should be followed-up by their local cardiologist.

9.3.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

9.3.6. Additional Outpatient Safety Assessments (“Virtual Visit”)

Depending on the availability of technology, subjects may be invited to perform additional remote safety assessments on an outpatient basis. At a maximum, this would include remote ECG collection, remote vital signs collection, and the opportunity to conduct the Remote Safety Assessment (Day 20) and Day 26 visit via video link. Training on the use of this technology would be completed prior to discharge from the clinical unit, and would be optional.

Experience with these technologies will enable the study team to understand the feasibility of incorporating remote safety assessment in future amyloidosis protocols, with the goal to reduce the in-person visit burden on subjects living with chronic disease.

9.4. Pharmacokinetics

9.4.1. GSK2398852

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK2398852 as specified in the SoA. The concentration will be the total of both radio-labelled and unlabelled mAb. The number of blood samples and sampling times for GSK2398852 may be modified during the study. Further details on the blood sample processing and their analyses are given in the study reference manual (SRM).

Once the plasma has been analyzed for GSK2398852, any remaining plasma may be stored and may be used in the development and validation of a companion diagnostic assay to measure SAP levels.

9.4.2. Plasma radioactivity

Blood samples will be collected for measurement of radioactivity as specified in the SoA. The radioactivity will reflect the total concentration of ^{89}Zr-GSK2398852 and its radioactive metabolites. The number of blood samples and sampling times may be modified during the study. Further details on the blood sample processing and their analyses are given in the SRM.

9.5. Pharmacodynamics

9.5.1. SAP Concentration

Venous blood samples of approximately 4 mL will be collected for measurement of plasma SAP concentrations as detailed in the SoA. Further details on the blood sampling process and their analyses are given in the SRM.

Plasma SAP levels must reach target prior to administration of anti-SAP mAb. If there is suspicion that CPHPC treatment has been accidentally interrupted, an additional plasma SAP specimen should be collected and tested prior to administering anti-SAP mAb.

- This specimen must have a fast turnaround in order to enable dosing of anti-SAP mAb on the following day.
- Once the plasma has been analysed for SAP, any remaining plasma may be stored and may be used in the development and validation of a companion diagnostic assay to measure SAP levels.

9.6. Imaging

9.6.1. ^{89}Zr-GSK2398852 PET

Subjects will participate in up to two dosing sessions, each associated with the administration of up to 37 MBq ^{89}Zr-GSK2398852 and up to 3 PET scans within approximately 5 days after the administration of radioactivity. The PET scan times for

each of the dosing sessions of the first patient are listed in Section 5.3.1. These times may then be varied for subsequent patients.

For each dosing session, the ^{89}Zr-GSK2398852 (37 MBq radioactivity and a mass dose of 10 mg) will be administered IV in a room separate from the PET camera room. After a defined waiting time (defined by the time of the first PET scan) the patient will be taken to the PET camera room and placed in comfortable position on the PET couch. Arms are stretched over the head.

A low-dose CT scan is made for orientation of the heart and a PET acquisition of 4-5 scans of about 20 minutes is started. This can be associated with cardiac gating if feasible.

Thereafter a whole body (head to upper thighs) low dose CT scan is made for anatomical orientation and for attenuation correction.

Sequential PET acquisitions will be made with about 3-5 minutes per bed position, covering the head to the upper thigh. The duration is of the order of 45 minutes.

The total duration of the scanning procedure is expected to be less than 2 hours.

Further details on scanning procedure are provided in a dedicated Image Acquisition and Analysis Manual.

9.6.2. Cardiac Magnetic Resonance (CMR) Imaging

Subjects will be asked to refrain from alcohol, caffeine, and nicotine on the days of CMR exams. Each baseline enhanced CMR imaging session will take approximately 45-60 minutes, with a maximum scan time inside of the scanner of approximately 90 minutes. If a scanning failure occurs, there will be a minimum of 24 hours prior to rescan.

As far as it is practicable, the local study site will use the same CMR imaging sequences, software acquisition, and contrast agent (i.e. Dotarem^{TM}) that is currently being used in the Phase 2 trial.

Whenever possible, the baseline contrast enhanced MRI scan will be performed after a subject has passed other eligibility requirements.

For each subject, if follow-up CMR examination(s) are clinically indicated for evaluation of potential cardiac adverse event(s) the same scanner as to the one used at the baseline examination should be used wherever feasible. 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 local study site for disease and potential anti-SAP mAb-related clinical abnormalities.

However, image analysis for key CMR parameters which might be determinant for ^{89}Zr-GSK2398852 myocardial uptake (e.g. extracellular volume [ECV] and myocardial perfusion) will be performed by a qualified imaging laboratory.

9.6.3. Access to Historical Patient ATTR-CM Cardiac Imaging

Since it is likely that ATTR-CM subjects on enrolment into this PET study have had previous cardiac imaging, possibly including 2D-ECHO, CMR, bone tracer SPECT, and / or PET imaging (e.g. PiB or WAT), either at diagnosis and / or at follow-up, the images from these investigations and their respective reports should be available to GSK wherever feasible.

Availability of this patient data would enable a more comprehensive evaluation of ^{89}Zr-GSK2398852 cardiac uptake in relation to cardiac amyloid load and myocardial coronary microvessel function.

9.7. Additional Assessments

9.7.1. Access to Diagnostic Patient Cardiac Biopsy Tissue

Where a ATTR-CM subject has had a cardiac (endomyocardial) biopsy, as part of a previous diagnostic workup, a sample of the tissue will be sent to GSK where possible. Routine and special histopathological investigations, including but not restricted to histochemical and / or immunohistochemical stains will be performed to assess for amyloid deposits and SAP levels, respectively.

9.8. Efficacy

9.8.1. Safety/exploratory Biomarkers

In the unlikely event of cardiac amyloid removal triggered by an anti-SAP mAb TMD(s) during this PET study, change in plasma NT-proBNP levels from baseline may provide surrogate biomarker evidence of cardiac amyloid clearance.

However, it is important that any reduction in plasma NT-proBNP levels are evaluated alongside any change in LV mass and / or ECV from any *repeat* CMR imaging which is performed at the local study site.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

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

10.2. Sample Size Considerations

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

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

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

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

10.2.1. Sample Size Re-estimation or Adjustment

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

10.3. Data analysis considerations

Statistical analyses will be performed by, or under the direct auspices of Clinical Statistics, GSK.

10.3.1. Populations for Analyses

For purposes of analysis, the following populations are defined:

- **All Treated Population:** defined as all subjects who receive at least one Anti-SAP treatment including ^{89}Zr-GSK2398852. All safety analyses will be evaluated on this analysis population.
- **The PK Population:** defined as all subjects from the All Treated Population for whom a PK sample is obtained and analysed.

Additional analysis populations may be defined in the Reporting and Analysis Plan (RAP).

10.3.2. Interim Analyses

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

- **In-stream data review(s):** any emergent PET imaging data from the current study will be complementary to the ongoing phase II study (Study Number 201464) and its associated interim(s), as well as the broader Anti-SAP program. In addition, during the current study, changes may be made to a number of design

parameters based on the emerging data, including: (i) intra and inter mass dose levels; and (ii) the timing of PET scan, all based on the accruing data.

- **Interim analysis at the end of Part A:** once the last subject in Part A has completed their final dosing session, a formal review of all available safety data (including AEs, clinical laboratory data, vital signs, ECGs), PK, ECHO/CMR and PET imaging data will be conducted before deciding whether to trigger Part B.

10.3.3. Inter-Subject Reproducibility of ^{89}Zr-GSK2398852 Myocardial Uptake

In any one subject in Part A, where the radiolabel PK and cardiac SUV profile of ^{89}Zr-GSK2398852 is consistent with myocardial uptake during either the 1st or 2nd dosing session (i.e. cardiac / plasma SUV ratio ≥0.5), the reproducibility of this specific unlabelled anti-SAP mAb dose in enabling myocardial uptake of ^{89}Zr-GSK2398852 may be evaluated by treating further subjects with the same unlabelled anti-SAP mAb mass dose. This is an optional evaluation that is at the discretion of the Investigator or designee in consultation with the Medical Monitor (Figure 7, below).

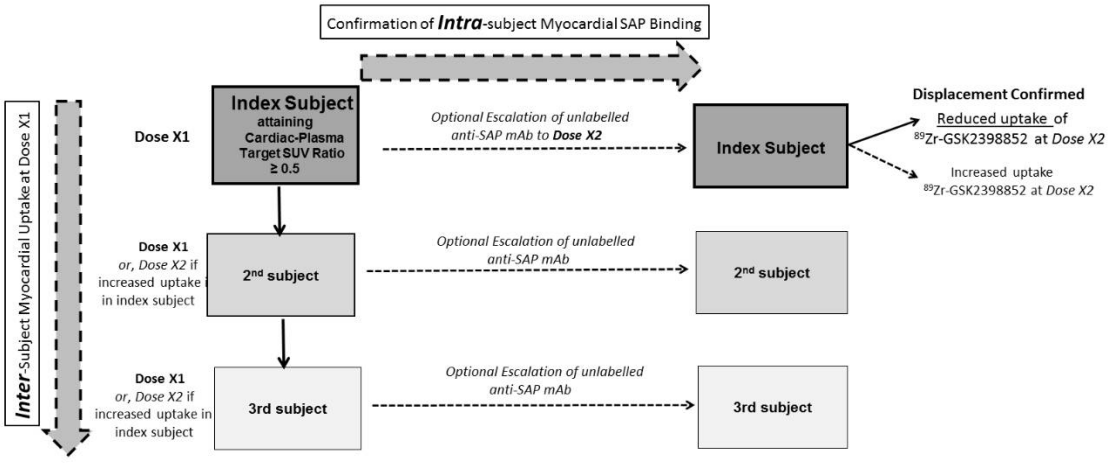
10.3.4. Intra-subject confirmation of ^{89}Zr-GSK2398852 Myocardial SAP Binding

In any one subject in Part A where the radiolabel PK and cardiac SUV profile of ^{89}Zr-GSK2398852 is consistent with myocardial uptake during the 1st dosing session (i.e. cardiac / plasma SUV ratio ≥0.5), ^{89}Zr-GSK2398852 binding to myocardial SAP can be confirmed by performing an ***intra***-subject mAb displacement evaluation.

This will be attained by escalating the unlabelled anti-SAP mAb dose in the same subject on their 2nd dosing session (provided the AE profile from the 1st dosing session is acceptable) to evaluate whether a higher unlabelled anti-SAP mAb mass dose can attenuate the cardiac SUV signal compared to their 1st dosing session; this would be indicative of displacement of ^{89}Zr-GSK2398852 from SAP binding sites on amyloid myocardial deposits.

This is an optional evaluation that is at the discretion of the Investigator or designee in consultation with the Medical Monitor (Figure 7, below).

Figure 7 Optional evaluations of Intra-subject ^{89}Zr-GSK2398852 binding



Reproducibility of myocardial ^{89}Zr-GSK2398852 uptake at a specific unlabelled anti-SAP mAb mass dose between different ATTR-CM subjects (vertical lines), and intra-subject dose escalation to confirm ^{89}Zr-GSK2398852 binding to SAP on amyloid myocardial deposits (horizontal lines).

10.3.5. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

The following is planned for the primary endpoints:

Analysis	Study Objective
Endpoints	• Assessment of ^{89}Zr-GSK2398852 cardiac uptake as evaluated by PET imaging at different unlabelled anti-SAP mAb mass doses
Analysis (Raw Data)	• All data will be listed. • Descriptive statistics, where appropriate, will be calculated for all generated PET imaging endpoints over time grouped by total mass.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

Demographic and baseline characteristics will be summarised.

10.3.6. Pharmacokinetics

Plasma concentrations of GSK2398852, which is the total of both ^{89}Zr-labelled and unlabelled mAb, will be analysed using non-compartmental methods. PK parameters will be summarised by dose with/without treatment period stratification. Dose proportionality will be explored with/without treatment period stratification.

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

The time profile and AUC of the plasma radioactive concentration, resulting from the 10-mg labelled-dose, will be scaled to the TMD and compared to the time profile and AUC of the plasma total mAb concentration.

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

10.3.7. Evaluation of PET images

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

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

Regions of Interest (RoI) are outlined in the images to define radioactivity distribution. All organ and blood analyses are expressed as SUV (Measured radioactivity concentration corrected for radioactive decay and normalized for administered amount of radioactivity per body weight).

These SUV have a few different definitions depending on organ and selection of interesting tissue components:

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

SUVpeak:

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

SUVmean:

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

Total organ radioactivity amount in Regions of Interest (RoI)

SUVtotal_organ:

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

VOLUMEtotal_organ:

Corresponding total volume of the organs above

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

The organs/tissues of interest for analysis include:

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

Where relevant and depending on radioactivity uptake pattern:

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

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

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

Total organ radioactivity amount in Regions of Interest (RoI)

- Heart
- Liver
- Spleen
- One lung
- Both kidneys

Other organs may be included depending on features in the images

The PiB studies, performed only across the heart will be evaluated regionally and as "polar maps" using an extracted parameter called "retention index" which indicates the degree of retention as compared to washout.

The WAT studies will be evaluated regionally with automatic software which generates values and "polar maps" representing absolute blood flow values.

Further details on the analysis of the images are given in the Imaging Acquisition and Analysis Manual.

10.3.7.1. Analysis of PET data

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

It is expected that the tissue-to-plasma ratio of the mAb in the heart will be approximately 0.1-0.2 after equilibration between plasma and tissue interstitium. This is guided by an expected plasma space plus interstitium relative space of 0.1-0.2. Within the blood pool of the heart chambers the ratio is expected to be 0.5 (hematocrit about 0.5). We have placed a limit by which the tissue-to-plasma ratio in the cardiac muscle is indicative of entry to the interstitium and binding to amyloid-SAP complexes at 0.5 in balance between a sufficient increase as compared to passive distribution and avoidance of "spill-over" from cardiac blood pools.

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

10.3.7.2. Storage and potential further analyses of images

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

10.3.8. Safety

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g. laboratory tests, vital signs, ECGs) will be summarised according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a “worst-case” analysis. Complete details of the safety analyses will be provided in the RAP.

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12. APPENDICES

12.1. Appendix 1 Abbreviations and Trademarks

Abbreviations

^{89}Zr-GSK2398852	^{89}-Zirconium-labelled anti-SAP mAb
^{99m}Tc-DPD	Technetium-99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid
AE	Adverse Event
AL	Amyloid Light-chain
ALARP	As Low as Reasonably Practicable
ALT	Alanine transaminase
anti-SAP	anti-Serum Amyloid P component
aPTT	activated partial thromboplastin time
AST	Aspartate transaminase
ATTR-CM	Transthyretin amyloidosis restrictive cardiomyopathy
AUC	Area Under the Curve
Bq	Becquerel
BSA	Body surface area
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Grafting
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimetre
C_{max}	Maximum Concentration
CMR	Cardiac Magnetic Resonance Imaging
CPK	Creatine phosphokinase
Cold anti-SAP mAb	Unlabelled anti-SAP mAb
CONSORT	Consolidated Standards of Reporting Trials
CPHPC	GSK2315698 (Carboxy pyrrolidine hexanoyl pyrrolidine carboxylate)
CRF	Case report form
CRNA	Complementary ribonucleic acid
CSR	Clinical Study Report
CT	Computerised Tomography
CV	Cardiovascular
Df	desferrioxamine
ECG	Electrocardiogram (12-lead)
ECHO	Echocardiogram
ECV	Cardiac Extracellular Volume
eGFR	Estimated Glomerular Filtration Rate
FAC	Familial Amyloidotic Cardiomyopathy
FcRn	neonatal Fc receptor
FDA	Food and Drug administration
FDG	Fludeoxyglucose
FIH	First in Human
FSH	Follicle stimulating hormone
GBM	Glomerulus basement membrane
GCP	Good Clinical Practice
Gd	Gadolinium
GSK	GlaxoSmithKline
GSK2315698	CPHPC (Carboxy pyrrolidine hexanoyl pyrrolidine carboxylate).
GSK2398852	Unlabelled anti-SAP mAb
h	hour
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HFpEF	Heart failure with preserved ejection fraction
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HRT	Hormonal replacement therapy
hs-cTn	High Sensitivity Cardiac Troponin
IB	Investigator's Brochure

ICD	Implantable Cardiac Defibrillator
ICF	Informed Consent Form
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational Medical Product
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRR	Infusion Related Reaction
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
L	Litre
LCV	Leukocytoclastic vasculitis
LDH	Lactate dehydrogenase
LV	Left ventricle
LVAD	Left Ventricular Assist Device
mAb	Monoclonal antibody
MBq	Megabecquerel
MCH	Mean corpuscular hemoglobin
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Mg/dL	Milligram per decilitre
MGC	Multinucleate giant cells
µmol/L	Micromol/litre
mL	Millilitre
mm	Millimetre
mmHg	Millimetre of mercury
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
msec	Millisecond
mSv	Millisievert
NSD	Nephrogenic systemic dermatopathy
NSF	Nephrogenic systemic fibrosis
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
O	Oxygen
PD	Pharmacodynamics
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography and Computed Tomography (combined scan)
PI	Principal Investigator
PiB	Pittsburgh Compound B (binds to amyloid deposit)
PIH	Post-Inflammatory Hyperpigmentation
PK	Pharmacokinetic
PPM	Permanent Pacemaker
PT	Prothrombin time
QTcF	Interval from the Q wave on the ECG to point T using Fredericia's formula
QTcB	QTc corrected by Bazett's formula
RAP	Reporting and Analysis Plan
RoI	Regions of Interest
SAE	Serious Adverse Event
SAP	Serum Amyloid P Component
SC	Subcutaneous
SCr	Serum Creatinine
SD	Starting dose
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
Sec	Seconds
siRNA	Small interfering ribonucleic acid
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SPECT imaging	Single-photon emission computed tomography
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions

SUV	Standardized Uptake Values (Measured radioactivity concentration corrected for radioactive decay and normalized for administered amount of radioactivity per body weight)
T½	Half-life
Tc-DPD	Technetium-99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid
TID	Thrice daily
T_{max}	Time to reach maximum concentration
TMD	Total Mass Dose
TNF	Tumor necrosis factor
TTR	Transthyretin amyloidosis
TTS	Study Specific Technical Agreement/Memo
TUDCA	Tauroursodeoxycholic acid
ULN	Upper Limit of Normal
Unlabelled anti-SAP mAb	GSK2398852
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WAT	15-Oxygen labelled water
WBC	White blood cell
WOCBP	Woman of Childbearing Potential
w/v	Weight by volume
Zr	Zirconium

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
BodyGuardian
Dotarem

12.2. Appendix 2 Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	Albumin
Cardiac Safety	• Troponin-T • NT-proBNP			
Pregnancy testing	• Urine Human chorionic gonadotropin (HCG) (female subjects only)			
Routine Urinalysis	• Specific gravity, pH, glucose, protein, blood, and ketones by dipstick • Urine microscopy may be performed if indicated			
Other Screening Tests	• Clotting tests: prothrombin time (PT) and activated partial thromboplastin time (APTT)			

Laboratory Assessments	Parameters
	• Follicle-stimulating hormone and estradiol (all female subjects only) • Urine alcohol & drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Viral serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) The results of each test must be entered into the CRF.
NOTES : 1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.5 and Appendix 6 All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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).	

12.3. Appendix 3 Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed

consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not

as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• 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 condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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 inpatient hospitalization or prolongation of existing hospitalization

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 outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills 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 persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 events should usually be considered serious.

Examples of such events include 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.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE 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) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GlaxoSmithKline (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 case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs,

symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 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 causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. 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 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool 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, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Email or facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of email or facsimile equipment,

notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Reference Manual.

12.5. Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following from Day 1 until 3 months after last PET scan:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 11 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for up to three months after last scan.
- In addition, male subjects must refrain from donating sperm for duration of study and for 3 months after last scan.

Female subjects

Female subjects of childbearing potential are not eligible to participate.

Table 11 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[a] oral intravaginal transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[a] injectable
Highly Effective Methods That Are User Independent
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] Intrauterine device (IUD) Intrauterine hormone-releasing system (IUS) bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

Pregnancy Testing

- WOCBP are not eligible for the study. However, all women will undergo a negative highly sensitive urine pregnancy test prior to each dosing session.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing will be performed and assayed in a certified laboratory OR by the clinical site using a test kit in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male subject's female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours 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 fetal status (presence or absence of anomalies) or indication for procedure.

Female Subjects who become pregnant

- 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 24 hours 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 subject and neonate, 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 4 While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study treatment or be withdrawn from the study.

12.6. Appendix 6 Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology

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

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) OR INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver chemistry event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (see below). If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and continue subject in the study for any protocol specified follow up assessments
MONITORING:
<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>
• Repeat liver chemistries (include ALT, AST,</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 5 days of last dose of CPHPC or anti-SAP mAb.[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE case report form (CRF)
• Record use of concomitant medications on the concomitant medications CRF page including</td></tr>
</table>

alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 **hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **<u>If</u> ALT≥3xULN <u>AND bilirubin</u> < 2xULN <u>and INR</u> ≤1.5<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24**-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake CRF page **<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James 2009]). **NOTE: not required in China** • 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.

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; HbsAg and Hepatitis B Core Antibody (IgM); Hepatitis complementary ribonucleic acid 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 PK 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, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.7. Appendix 7 Guidance on the Clinical Management of Rash Associated with Anti-SAP mAb

12.7.1. Background

In the FIH study, anti-SAP mAb administration, at doses ≥582 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 600 mg on their first treatment. Their skin biopsy showed an active 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 1000 mg 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 dermato-pathologist for this skin biopsy sample, but the described morphological changes could be consistent with a lymphocytic vasculitis/LCV picture.

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 - which arose after an anti-SAP mAb dose of 1200mg at the 3rd dosing session - was associated with the highest measured plasma concentration of anti-SAP mAb, albeit this subject was concomitantly receiving an immunomodulatory drug.

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.

12.7.2. Management of Rash

Rash will be graded using the following criteria based on symptoms and the body surface area (BSA) affected [Table 12].

Table 12 Grading criteria for rash

Rash Grade	Distribution/Symptoms	Action
1	<10% BSA AND asymptomatic	Dermatology review before patient discharge if rash persists ≥7 days post-mAb dose
2	10-30% BSA and/or mild symptoms[a]	Dermatology review before patient discharge if rash persists ≥7 days post-mAb dose
3	>30% BSA and/or moderate/severe symptoms[a]	Dermatology review within 24 hours
4	Any rash with mucosal or systemic involvement[b]	Immediate dermatology review Withdraw from study treatment. See specific advice Section 12.7.3

a. Symptoms include: pain, itch and burning
b. E.g. evidence of renal involvement

Local dermatological review can be sought at any time during a rash, but should be sought if a rash is deemed to be stable but persistent lasting ≥7 days, or is deemed to be rapidly worsening.

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

12.7.3. 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.

12.7.4. Post-Inflammatory Hyperpigmentation (PIH)

PIH is a recognised chronic complication of acute skin inflammation, and can take weeks to months to completely resolve depending upon the skin layer which is principally involved. PIH is more prevalent in patients with African heritage, such that ATTR CM subjects in this PET study with the mutant *V122I* genotype might be more susceptible to PIH after an acute rash event. The Investigator or designee should report to GSK any PIH events as soon as possible after its onset.

12.8. Appendix 8 Equations and Diagnostic Criteria

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

If serum creatinine (SCr) in µmol/L

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

If SCr in mg/dL:

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

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

Table 13 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

Table 3. Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73 m^2)	Action*
	At increased risk	≥60 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	Estimating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	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^2 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 14 New York Heart Association (NYHA) Classification

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

12.9. Appendix 9 Radiation Dose

Subjects will be exposed to an additional dose of ionising radiation as a consequence of their participation in this study. The ionising radiation exposure from PET/CT scanning comes from two sources. A proportion of the radiation exposure comes from the administered radioligand ^{89}Zr-GSK2398852 and the administration of ^{11}C-PiB and ^{15}O-WAT. The remaining radiation dose comes from low dose CT scans performed in order to correct the PET data for tissue attenuation. If the subject needs to be removed from the scanner and repositioned during the PET scan, then a second low dose CT scan may be performed. The doses chosen for this study aim to deliver a minimal radiation exposure, compatible with a good quality PET and CT signal.

The proposed ^{89}Zr-GSK2398852 radioactivity dose is 37 MBq for each administration, 2 sessions per subject, with total 74 MBq. The mean effective dose for ^{89}Zr-mAb PET study was reported to be 0.53 mSv/MBq [Börjesson 2009], hence 37 MBq of ^{89}Zr-GSK3128349 in this study would provide approximately 19.61 mSv (37 MBq X 0.53 mSv/MBq) of exposure, which together with the low-dose CT scans (0.5 mSv/CT scan X 3 CT scans) yield approximately 21.11 mSv.

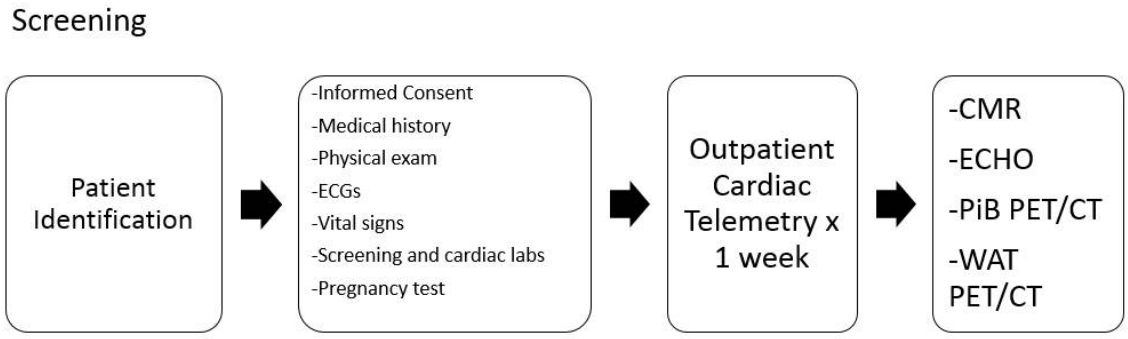
The single PiB study with its associated low dose CT scan is expected to give 1.5 mSv and the WAT scans 0.5 mSv each. (x2 WAT = 1.0 mSv)

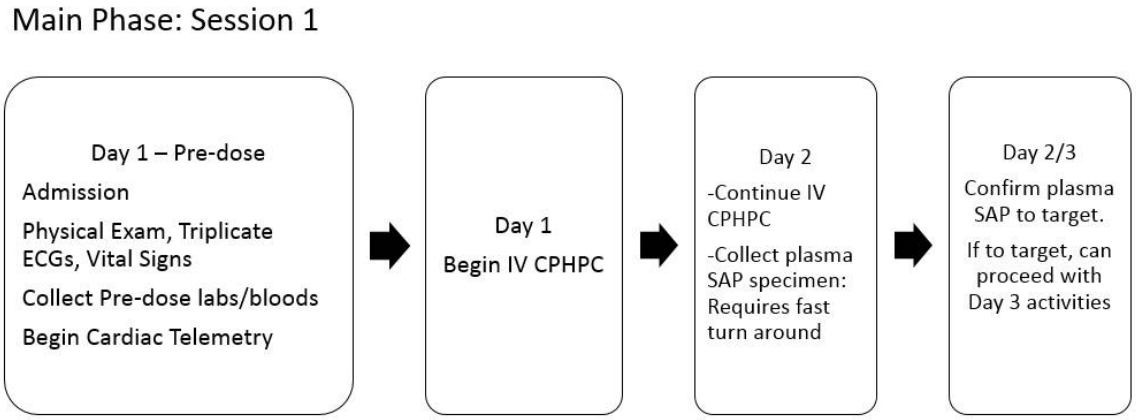
Total radiation dose exposure per subject is therefore expected to be 44.7 mSv. With some residual radioactivity in the injection syringe and considering radioactive decay till time of injection, we will aim to be below 44 mSv across the study.

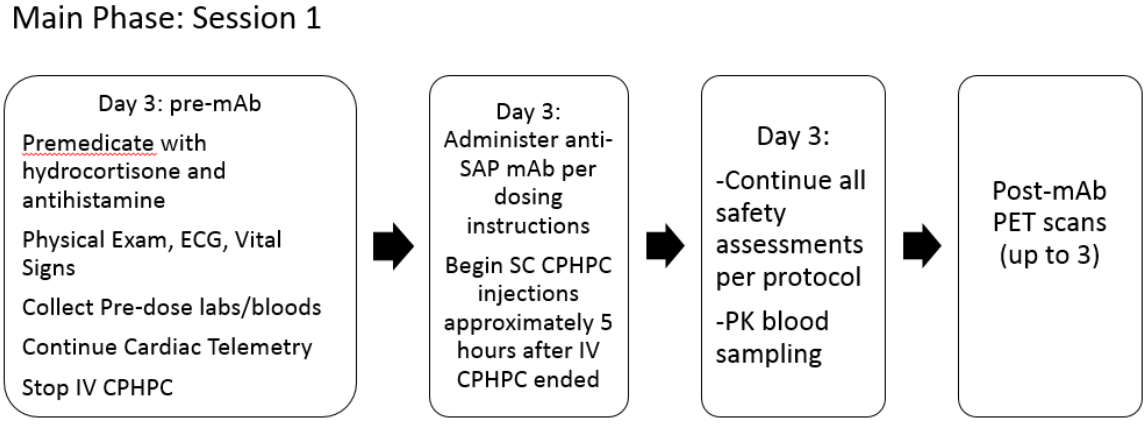
The total maximum effective dose of approximately 44 mSv in this study is equivalent to approximately 18 times the average annual exposure (2.4 mSv) from natural background radiation in Sweden (Swedish Radiation Protection Authority, SSI Report 2007-02). The additional risk of developing a fatal malignancy is 5.5% per Sv [ICRP37 2007] and hence as a result of these exposures has been estimated as approximately 1 in 400 for an adult in normal health. However, the reduced life expectancy of the ATTR-CM patient population to be studied will result in a lower risk for these individual subjects.

12.10. Appendix 10 Schedule of Activities: Flow Diagram

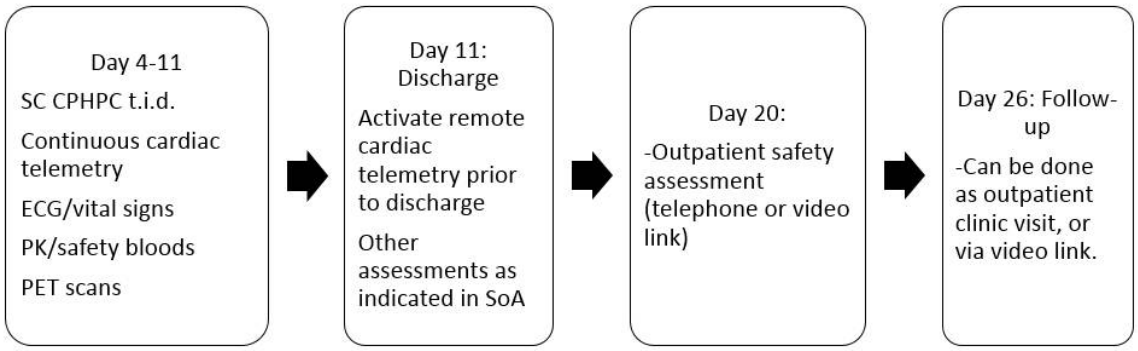
The diagrams below provide an example order of study activities for a subject who receives a TMD of >200mg. This is not a comprehensive list; refer to the SoA for additional details.







Main Phase: Session 1



Dosing Session 2 will be similar to Dosing Session 1, but will include a WAT PET scan on Day 1 or 2 (Part A only).