TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	A three-part open-label, non-randomised, dose-escalation study to investigate the safety and tolerability of GSK3039294 administered as a single dose to healthy volunteers, and as repeat dose to healthy volunteers and patients with systemic amyloidosis

Compound Number: GSK3039294

Development Phase: I

Effective Date: 30-NOV-2016

Protocol Amendment Number: 03

Author (s):

PPD

Clinical pharmacology
MPC: Metabolic Pathways & Cardiovascular
Clinical Pharmacology, Science and Study Operations
QSci: Clinical Statistics
QSci: Clinical Pharmacology Modelling and Simulation
MPC: Metabolic Pathways & Cardiovascular
QSci: Clinical Statistics

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N218204_00	**2015-AUG-06**	**Original**
2014N218204_01	**2015-OCT-07**	**Amendment No. 1**
Section 5.5 – MHRA requested edits to stopping criteria		
2014N218204_02	2016-MAR-01	Amendment No. 2
Throughout – Ethics Committee requested edits to the study design.		
2014N218204_03	2016-NOV-30	Amendment No. 3
Amended to increase cardiac monitoring in Cohort 3 and Cohort 5 with supporting text		

SPONSOR SIGNATORY

PPD

Dr Duncan Richards
VP, Medicine Development Lead

30/Nov/2016
Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): EudraCT 2015-003088-13

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201664

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

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

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

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 201664

Rationale

Objective(s)/Endpoint(s)

Part A: Single ascending dose in healthy volunteers

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

Part B: Repeat dose in healthy volunteers

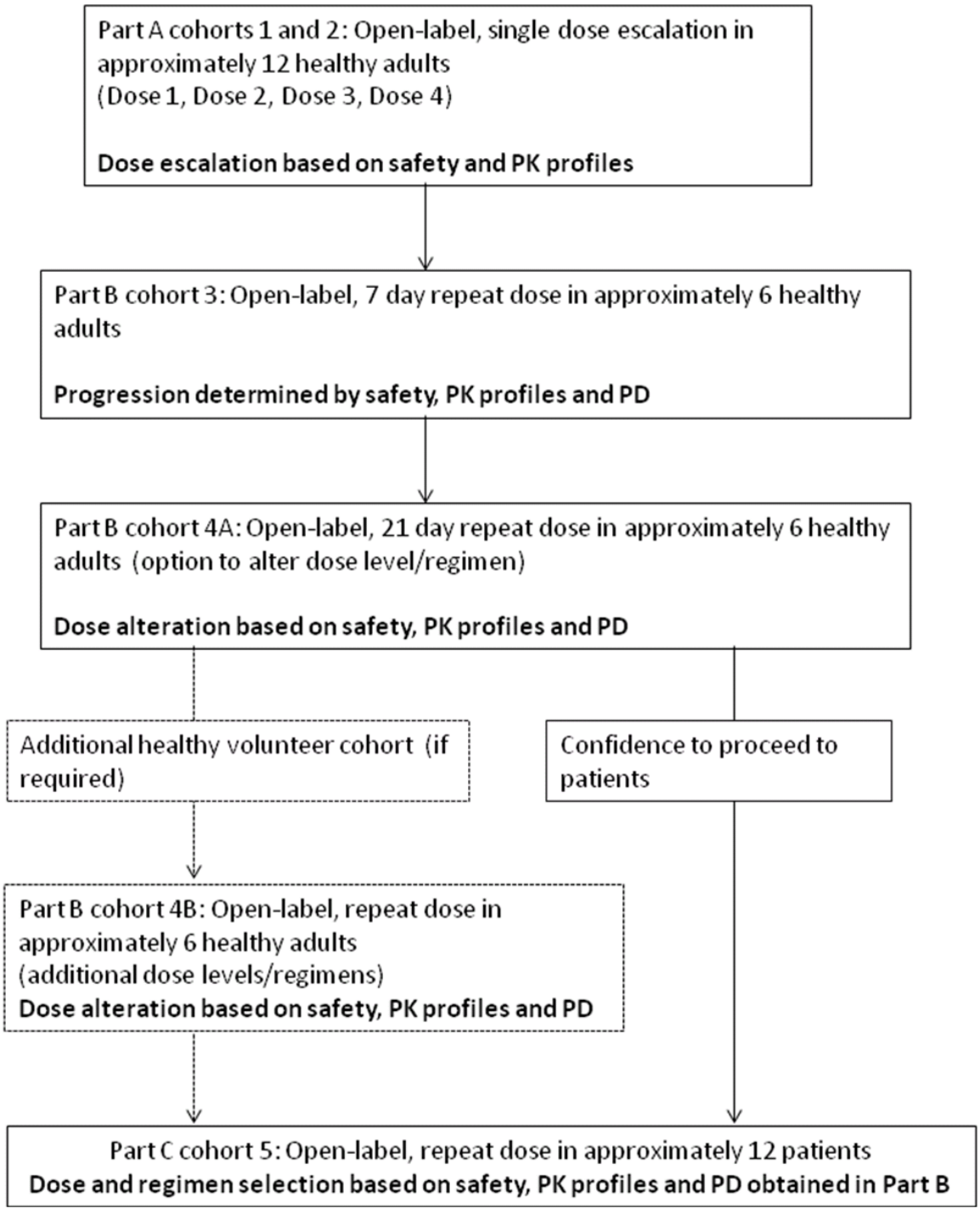
Objectives	Endpoints
Primary	
Evaluate safety and tolerability of repeat doses of GSK3039294	Adverse events, laboratory measurements, ECG, vital signs and cardiac telemetry (where applicable)
Secondary	
Evaluate pharmacokinetics of repeat doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)	PK parameters of GSK2315698 and GSK3039294
Pharmacodynamic effect of repeat doses of GSK3039294 on plasma SAP levels	Plasma SAP levels
Explore correlation of dose of GSK3039294, blood concentration of GSK2315698 and plasma SAP levels	PK parameters of GSK2315698 and GSK3039294 Plasma SAP levels
Exploratory	
Determine the effect of food on a single dose of GSK3039294	PK parameters of GSK2315698 and GSK3039294 under fasted and fed conditions.

Part C: Repeat dose in patients with systemic amyloidosis

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

Overall Design

This is a three-part, open-label, non-randomised study.



Treatment Arms and Duration

Part A: Single dose escalation in healthy volunteers

Two cohorts (cohorts 1 and 2) of subjects will be enrolled to provide data from 6 subjects per cohort and up to 4 different doses (2 dose levels per cohort) of GSK3039294 will be tested.

Subjects will be admitted to the unit on Day -1, following the dose on Day 1 subjects will remain in-house until Day 4. Wash-out will take place from Day 5 to Day 14.

Providing a review of the data from each dose (safety data: AE, vital signs, ECG and laboratory safety test and PK data up to 48 h etc) is favourable, the next dose level will be administered.

Part B: Repeat dose escalation in healthy volunteers

Cohort 3: In a group of healthy volunteers (preferably < 45 years of age) sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 7 days. The dose will be one that is expected to be well tolerated based on the single dose data and not predicted to exceed exposure limits based on single dose PK.

A sentinel subject will be dosed first with repeat GSK3039294 administration for 7 consecutive days. Subsequent subjects will only be dosed after the sentinel subject has successfully completed the full 7 days of dosing without any clinically concerning AEs being reported. If the safety data from the sentinel subject is deemed to be equivocal, a second subject can be dosed individually for 7 days at the discretion of the Investigator in consultation with the GSK study team. If the safety data from the second subject is also equivocal, at the discretion of the Investigator in consultation with the GSK study team, subsequent subjects can also be individually dosed with GSK3039294 for 7 days.

The food effect exploration in Cohort 3 will only be conducted once the Investigator in consultation with the GSK study team is satisfied with the safety profile of repeat dose GSK3039294. Following this, the food effect will be conducted on Days 4 and 5, and GSK3039294 will be administered under fasted and then under fed conditions (respectively).

Sufficient subjects will be enrolled to ensure a minimum of 6 subjects complete all study procedures, including the food effect exploration.

Providing a review of the data (safety data: AE, vital signs, ECG, telemetry, laboratory safety tests and PK) is overall acceptable, Cohort 4a will be initiated. The approving REC will be informed of the outcome of this data review.

Cohort 4a: In a group of healthy volunteers sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 21 days.

The dose level for this cohort will be determined by a review of the safety and PK data from cohort 3. The dose may be adjusted (up or down) during the 21 day dosing session based on preliminary PK collected during dosing and ongoing review of safety. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21.

The predicted maximum daily exposure will not exceed pre-clinical safety exposure limits.

Cohort 4b(*optional, only if required*): Based on data from Cohorts 3 and 4a, dose levels may be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days. The dose level and / or dosing regimen may be altered once during the 21days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.

Part C: Repeat dose escalation in patients with systemic amyloidosis

A single dose level of GSK3039294 will be tested for 21 days repeat dose, in patients with systemic amyloidosis which may include those with cardiac amyloid involvement.

Type and Number of Subjects

In **Part A**, sufficient healthy volunteers will be enrolled to ensure 6 subjects per cohort have completed the in-patient phases.

In **Part B**, sufficient healthy volunteers will be enrolled to ensure 6 subjects per cohort have completed each of the in-patient phases.

In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same cohort at the discretion of the Sponsor in consultation with the investigator. Replacement subjects do not need to have received the first dose for a given cohort to join the study in the second cohort.

In **Part C**, a minimum of 12 patients with systemic amyloidosis will be enrolled. If subjects prematurely discontinue, replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

Additional subjects/cohorts may be enrolled to allow for further evaluation of a given dose or for evaluation of additional dose levels.

Analysis

There are no formal hypotheses to be tested as part of this study.

Interim analyses

Safety, PK and PD data will be reviewed on an ongoing basis throughout the study by the study team and investigator in order to inform dosing decisions for subsequent dosing sessions, cohorts and study parts.

In addition, in all Parts of the study, individual profiles over time will also be presented graphically for selected urine and plasma laboratory parameters pertaining to the kidney. To inform dosing decisions for subsequent dosing sessions in Part A, individual values of Cmax and AUC[0-inf] will be derived by means of non-compartmental analysis. To inform dosing decisions for subsequent study parts, GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698.

Primary and secondary analyses

Safety, PK and PD data will be listed, summarised and presented graphically as appropriate. GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698.

Cohort Safety Reviews: A safety review will be performed on completion of each Cohort in Part B, as well as at completion of Cohort 5 in Part C (see Section 4.2.2. & Section 4.2.3.). Initiation of Cohort 4a will be contingent on the findings of the safety review at completion of Cohort 3 (see Section 4.2.2.)

Summary of Cardiac Arrhythmia Adverse Events in Part A of this study

A total of 4 separate arrhythmias in 3 male subjects over 45 year old were reported on 24-hour Holter after single dose administration of GSK3039294 in Part A. Three episodes of supraventricular tachycardia (SVT), all of atrial tachycardia morphology at doses of GSK3039294 at 600mg and 1200mg, and one episode of a single 5-beat accelerated idioventricular rhythm (AIVR) at 600mg GSK3039294, were reported in these 3 separate subjects. Each of the events was of short duration, completely asymptomatic, and was not associated with hemodynamic instability.

No prolongation of the QTcF interval was observed in any subject after administration of 200mg, 600mg, or 1200mg of GSK3039294 in Part A.

Both SVTs and ventricular salvos of short duration are known to occur in healthy volunteer subjects and can be considered to be within the normal (non-pathological) variation of ECG parameters. In this regard, SVTs have been reported to arise in 13.9% of healthy volunteer subjects over 45 years of age compared to an incidence of 1.1% in healthy volunteer subjects 45 years or less in FIH studies (Hingorani et al, 2016). In Part A, none of the three affected subjects had plasma levels of GSK3039294 detectable approximate to the time at which each cardiac arrhythmia occurred. Moreover, the timing

of each of the four arrhythmic events after dosing with GSK3039294 was not associated with the Tmax of CPHPC including one subject whom had no detectable plasma CPHPC present at approximately the time of the first of their two arrhythmic events.

Therefore, at this time, given that there were also no arrhythmogenic liabilities identified for GSK3039294 in preclinical toxicological studies, it is unlikely that the arrhythmias reported after dosing with GSK3039294 in Part A are attributable to its single dose administration at 600 mg or 1200mg.

2. INTRODUCTION

GSK2315698 (CPHPC), crosslinks serum amyloid P component (SAP) resulting in depletion of SAP from the plasma, but needs to be given parenterally. GSK3039294 is a pro drug of CPHPC that has been developed in order to offer the potential of an orally available alternative to parenteral CPHPC for plasma SAP depletion prior to use of anti SAP mAb in the treatment of systemic amyloidosis.

Systemic amyloidosis is a clinical disorder caused by progressive accumulation of insoluble, misfolded deposits of normally soluble precursor proteins (amyloid) in the extracellular matrix of target organs (kidney, liver, heart, spleen). Amyloid deposition is responsible for progressive and usually relentless organ dysfunction, failure and almost always death.

Although the nature of the misfolded culprit protein may vary with the type of systemic amyloidosis, (20 different proteins have been reported in the different forms of the disease), they all share a common cross-β structure, they are derived from normally soluble precursor proteins and amyloid deposits are always decorated with SAP.

SAP is a normal, non fibrillar, plasma glycoprotein circulating at 20-40 mg/L. Its circulating concentration is not affected in health and disease including amyloidosis. SAP is a normal constituent of the extracellular matrix located on the microfibrillar mantle of elastic fibers throughout the body and in the lamina rara interna of the glomerular basement membrane. However the amount of SAP in these normal tissue sites is extremely low compared to the fluid phase SAP. In systemic amyloidosis, SAP accumulates in amyloid deposits bound to fibrils and in equilibrium with fluid phase SAP pool. In patients with extensive systemic amyloidosis, as much as 20g of SAP may be bound in amyloid deposits.

CPHPC is being developed in an obligate therapeutic parternship with anti-SAP monoclonal antibodies. CPHPC or GSK3039294 would be used to acutely deplete plasma SAP to enable subsequent safe administration of an anti-SAP monoclonal antibody (mAb). Binding of the antibody to residual SAP on amyloid deposits triggers their removal [Richards, 2015].

2.1. Study Rationale

GSK3039294 has been developed in order to offer an orally available alternative to parenteral CPHPC for plasma SAP depletion prior to use of anti SAP mAb in the treatment of systemic amyloidosis.

This phase 1 study is intended to study safety, tolerability and PK profile of GSK3039294 in humans. It is expected that GSK3039294 will, after oral administration, release CPHPC in the circulation and thereby reduce plasma SAP to a level considered sufficient for safe administration of anti-SAP mAb (currently a target of below 2mg/L with IV CPHPC administration).

CPHPC PK/PD has been studied in both healthy volunteers and patients. A PK/PD model taking into account the various compartments, the equilibrium between amyloid bound SAP and plasma SAP, the affinity for CPHPC and elimination rate of the complex has been established. This model will be used in the present study for determination and comparison of the PK/PD profile of the prodrug with the profile of CPHPC [Sahota, 2015].

Past data with CPHPC have shown that the PK /PD relationship (SAP depletion) observed in healthy volunteers is predictive of that in patients with systemic amyloidosis. The Study will therefore include healthy volunteers for single and repeat ascending doses and determination of PK parameters of the GSK3039294. A group of patients with systemic amyloidosis will be included and treated with a dose predicted to be active in order to verify that transformation of GSK3039294 is similar in patients and healthy volunteers and leads to plasma SAP depletion expected with similar exposures to CPHPC.

2.2. Brief Background

CPHPC has been used in humans in order to decrease circulating SAP. In previous academic-sponsored studies patients with systemic amyloidosis, an infusion of CPHPC at doses between 0.25-6 mg/kg/day resulted into a rapid and consistent depletion of circulating SAP in all subjects. The most common daily dose for long term use was 1 mg/kg. The treatment was reported to be safe and well tolerated. Some patients with systemic amyloidosis were treated for up to 104 weeks at 1mg/kg (given in 2 daily sc administrations). Subcutaneous CPHPC administration sometimes led to minor local stinging and bruising at the injection site.

PK/PD studies with CPHPC have been conducted by GSK in both in healthy volunteers and patients with systemic amyloidosis after i.v. and s.c. administration. In all cases an iv regimen CPHPC decreased plasma SAP concentrations to 2 mg/L. In patients with systemic amyloidosis the time to nadir was longer and greatly dependent on the amyloid load and liver involvement. The time to plasma recovery was also dependent on amyloid load and took longer in patients with amyloid deposits. This indicates that most of the newly produced SAP is distributed to amyloid deposits before repleting the circulating compartment. As CPHPC is renally cleared the dose is corrected for renal function

3. OBJECTIVE(S) AND ENDPOINT(S)

Part A: Single ascending dose in healthy volunteers

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

Part B: Repeat dose in healthy volunteers

Objectives	Endpoints
Primary	
Evaluate safety and tolerability of repeat doses of GSK3039294	Adverse events, laboratory measurements, ECG, vital signs and cardiac telemetry (where applicable)
Secondary	
Evaluate pharmacokinetics of repeat doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)	PK parameters of GSK2315698 and GSK3039294
Pharmacodynamic effect of repeat doses of GSK3039294 on plasma SAP levels	Plasma SAP levels
Explore correlation of dose of GSK3039294, blood concentration of GSK2315698 and plasma SAP levels	PK parameters of GSK2315698 and GSK3039294 Plasma SAP levels
Exploratory	
Determine the effect of food on a single dose of GSK3039294	PK parameters of GSK2315698 and GSK3039294 under fasted and fed conditions.

Part C: Repeat dose in patients with systemic amyloidosis

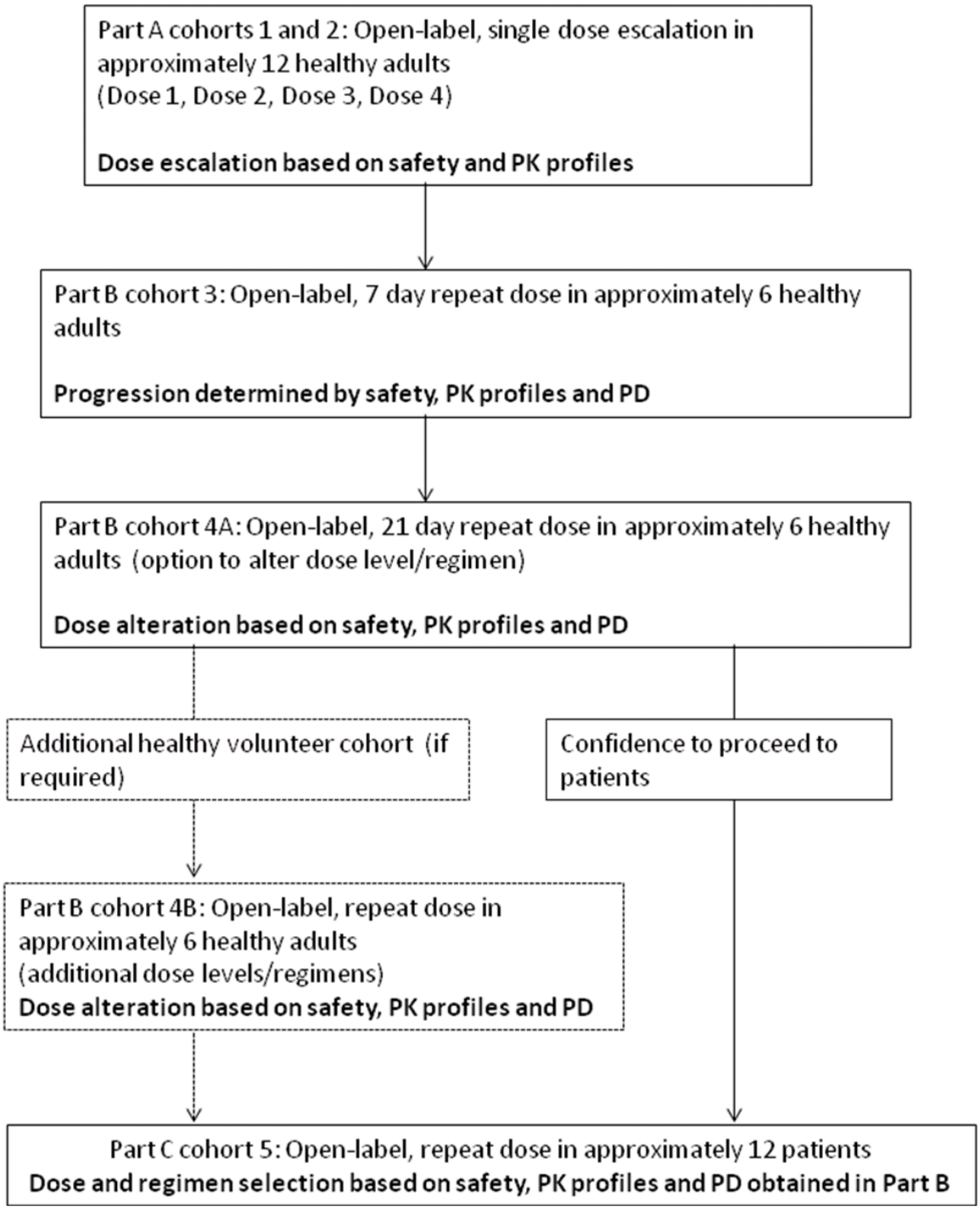
Objectives	Endpoints
Primary	
Evaluate safety and tolerability of repeat doses of GSK3039294	Adverse events, laboratory measurements, ECG, vital signs
Secondary	
Evaluate pharmacokinetics of repeat doses of GSK3039294 and its biotransformation into GSK2315698 (CPHPC)	PK parameters of GSK2315698 and GSK3039294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

4. STUDY DESIGN

4.1. Overall Design

This is a three-part, open-label, non-randomised study.

Figure 1 Study Schematic



4.2. Treatment Arms and Duration

4.2.1. Part A (single dose escalation in healthy volunteers)

Part A is a single dose, open label, dose escalation study conducted in healthy volunteers and will evaluate safety, tolerability, and PK of the compound including biotransformation of GSK3039294 into active CPHPC.

Two cohorts of subjects will be enrolled to provide data from 6 subjects per cohort and up to 4 different doses (2 dose levels per cohort) of GSK3039294 will be tested.

Doses will be administered to Cohorts using a sentinel dosing approach as described below. Subjects will be admitted to the unit on Day -1, following the dose on Day 1 subjects will remain in-house until Day 4. Wash-out will take place from Day 5 to Day 14.

Providing a review of the data from each dose (safety data: AE, vital signs, ECG and laboratory safety test and PK data up to 48 h etc) is favourable, the next dose level will be administered. Cohort 1 will be used for 2 dosing periods (Doses 1 and 2), Cohort 2 will also be used for 2 dosing periods (Doses 3 and 4). A review of the data will always be conducted prior to the administration of the next dose level.

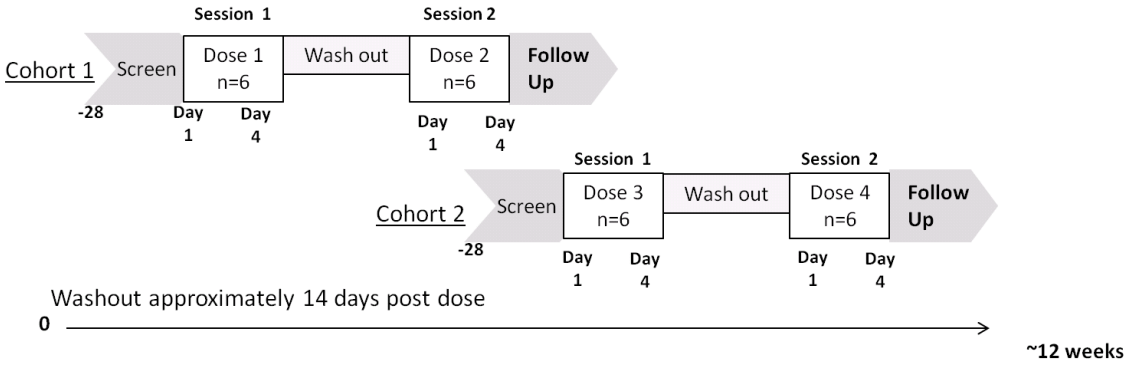
The planned doses for Dose levels 2, 3 and 4 may be modified based on emerging safety, tolerability and PK data. The number of dosing periods may be reduced or extended depending on emerging data. Replacement subjects in either Cohort do not need to have received the first dose prior to receiving the second dose.

Sentinel dosing: For all dose levels the subsequent subject will be dosed approximately 24 hrs after the preceding subject if there are no safety or tolerability concerns. The remaining subjects receiving the same dose within the cohort will receive the dose approximately 24hrs after the subsequent subject at intervals no less than 1hr apart.

Table 1 Cohorts 1 and 2 Study Duration

Screening	All screening assessments to be completed within 28 days prior to the first dose.
Treatment Period	For Cohorts 1 and 2, each subject may take part in two dosing periods. During each study period subjects will be in-house from the day prior to dosing until the Day 4 after dosing when they will be discharged after post dose assessments have been completed. Subjects will return to the unit as out-patients for any post-dose assessments.
Washout Period	From Day 5 to Day 14.
Follow-up	At least 7 days and no greater than 14 days after study drug administration. If warranted, additional follow-up visits may be scheduled.
Total Duration	Each cohort is approximately 8 weeks

Figure 2 Study Design for Healthy Volunteer Subjects Single Dose (Cohorts 1 and 2)



All data obtained from this study will be included in the existing PK model established from completed studies with CPHPC [Sahota, 2015] and will inform the dose selection for the next cohort/dosing session.

At the end of this single dose part, all PK data will be analysed (see Section 9.3.2) and reviewed together with all available safety data.

The study drug will be further evaluated in Parts B and C, unless following Part A it is determined that:

- If the safety profile is acceptable however the calculated bioavailability would mean that even following dosing of GSK3039294 at a maximum dose (which does not exceed pre-clinical safety exposure limits), insufficient CPHPC would be generated to be an effective depleter of plasma SAP.

- If the safety profile restricts the maximum well tolerated dose level to one that does not generate sufficient CPHPC to be an effective depleter of plasma SAP.

In this situation the study may be terminated.

4.2.2. Part B (repeat dose escalation in healthy volunteers)

Part B is repeat dose, open label, dose escalation conducted in healthy volunteer subjects and will evaluate the safety, tolerability, PK, pharmacodynamics of repeat dosing (7 day in Cohort 3, 21 day in Cohort 4) of GSK3039294. In addition to PK, plasma SAP levels will be measured at time points as in the Time and Events table (Section 7.1.1) to determine the ability of GSK3039294 to decrease plasma SAP levels to aid prediction of the optimal clinical dose.

4.2.2.1. Sentinel Dosing in Part B

In each individual study cohort in Part B, a sentinel subject will complete all dosing days up to and including Day 7. If there are no clinically concerning safety or tolerability issues observed, the rest of the subjects within the cohort can be dosed.

If the safety data from the sentinel subject is deemed to be equivocal, a second (and subsequent) subjects will complete all dosing days individually, up to and including Day 7, at the discretion of the Investigator in consultation with the GSK study team.

4.2.2.2. 7 Day Repeat Dosing (Cohort 3)

In a group of healthy volunteers, sufficient subjects will be enrolled to ensure a minimum of 6 subjects complete all study procedures (including evaluation of food-effect) associated with 7 days repeat dosing administration.The dose will be one that is expected to be well tolerated based on the single dose data and predicted to not exceed exposure limits based on single dose PK.

A food effect exploration will be conducted at Days 4 and 5 of this cohort once the investigator is satisfied with the safety data from the sentinel subject(s). To evaluate a potential food effect, GSK3039294 will be administered under fasted and then under fed conditions (please see SRM for details of meals), and PK samples will be taken to investigate the food effect on the PK.

Cardiac Safety Review of Cohort 3

Given that all cardiac arrhythmic events after single dose administration of GSK3039294 in Part A (where there were detectable levels of plasma CPHPC) were relatively acute and observed between approximately 4 to 7 hours after tmax of CPHPC and when no GSK3039294 was detectable, and given steady state is expected to be reached after approximately 5 days of repeat dosing, 7 day continuous cardiac telemetry in Cohort 3 is deemed to be of sufficient duration to detect any potential cardiac arrhythmias associated with repeat dosing of GSK3039294.

On completion, in addition to full safety review, a cardiac safety review will be performed where individual subject telemetry data will be reviewed in relation to the PK data of GSK3039294 and CPHPC.

4.2.2.3. 21 Day Repeat Dosing (Cohort 4a)

In a group of healthy volunteers sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 21 days.

The dose level and / or dosing regimen may be adjusted (up or down) once during the 21 days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21. The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.

Initiation of Cohort 4a: Cohort 4a will only be initiated if the conclusion of the safety review from Cohort 3 demonstrates an acceptable safety profile associated with the repeat administration of GSK3039294 for 7 days.

Individual subjects in Cohort 4a can be withdrawn from the study at the discretion of the Investigator in consultation with the GSK study team if individual subject safety review at Day 7 demonstrates any AEs which are deemed to be equivocal or clinically concerning. Affected subject(s) should be followed-up, at the discretion of the Investigator, as per local practice.

Data from cohorts 3 and 4a are expected to provide a good evaluation of the safety, tolerability and repeat-dose PK. The data will be evaluated using the PK/PD model to identify an optimal clinical dose (see Section 9.3.2.1). However, if it is determined that further investigation of dose levels are required before progressing to Part C (e.g. if the observations in cohort 4a are different from those which the PK /PD modelling predicted), then recruitment into Cohort 4b may be initiated.

4.2.2.4. 21 Day Repeat Dosing (Cohort 4b – optional, only if required)

In a group of healthy volunteers, sufficient subjects will be enrolled to ensure a minimum of 6 completers, the study drug will be administered repeatedly for a total of 21 days.

Based on data from Cohorts 3 and 4a, dose levels will be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days. The dose level and / or dosing regimen may be adjusted (up or down) once during the 21 days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21. The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.

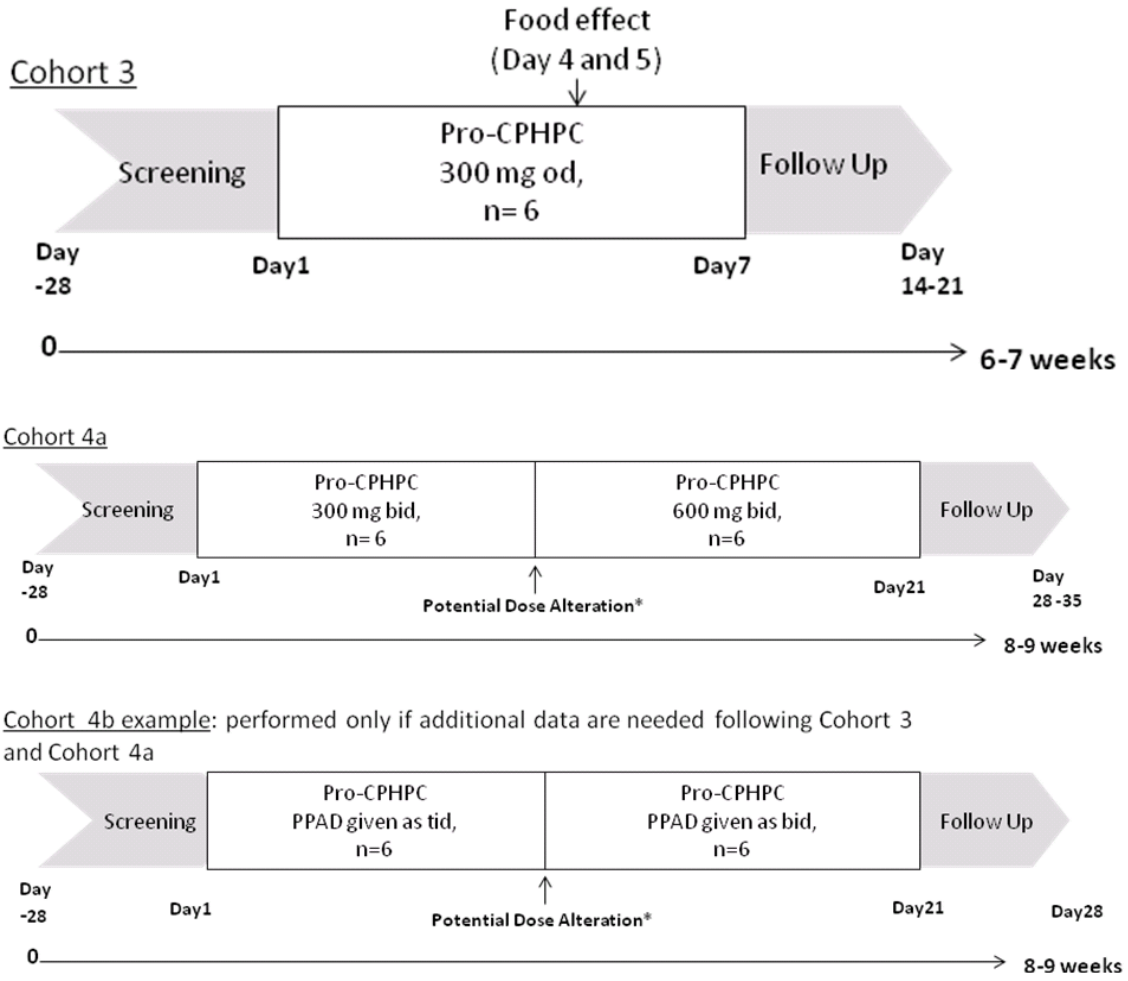
Table 2 Cohort 3

Screening	All screening assessments (including a 48hr Holter recording) to be completed within 28 days prior to the first dose
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -2 (where baseline cardiac telemetry will be performed for 24 hours immediately prior to the first dose of GSK3039294) until Day 8 when they will be discharged.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 7 weeks

Table 3 Cohort 4a (and 4b if required) Study Duration

Screening	All screening assessments to be completed within 28 days prior to the first dose
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until Day 7 when they will be discharged. Subjects will self-administer their assigned dose when not in the clinical unit. Subjects will return as outpatients on Day 21, and again for a follow-up appointment. Subjects may return to the clinic after Day 7 for an adjustment to their dose should a review of interim PK data require this. If a dose adjustment is made, subjects will be in-patient until they have received the new dose for 7 days, when they will be discharged.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 8-9 weeks

Figure 3 Study Design for Healthy Volunteer Subjects Repeat Dose (Cohorts 3, 4a and 4b – doses shown are for example only)



*In Cohort 4b multiple dose levels and different regimens may be investigated based on data from Cohort 4a. *Day of Potential Dose Alteration (no later than D16) not specified as this will be performed following review of safety and PK data from previous dose.*

4.2.3. Part C (repeat dose escalation in patients with systemic amyloidosis)

In Part C a single dose level of GSK3039294 will be tested for 21 days repeat dose, in patients with systemic amyloidosis, which may include those patients with known cardiac amyloid involvement. This will confirm the ability of GSK3039294 (given at the predicted optimal clinical dose determined from Part B) to decrease plasma SAP, and assess the ability of GSK3039294 to maintain this level over 21 days in patients with systemic amyloidosis.

Safety and tolerability will also be evaluated

Initiation of Cohort 5: Cohort 5 will only be initiated if the conclusion of the safety review from Cohort 4 demonstrates an acceptable safety profile associated with the repeat administration of GSK3039294 for 21 days.

4.2.3.1. Sentinel Dosing in Part C

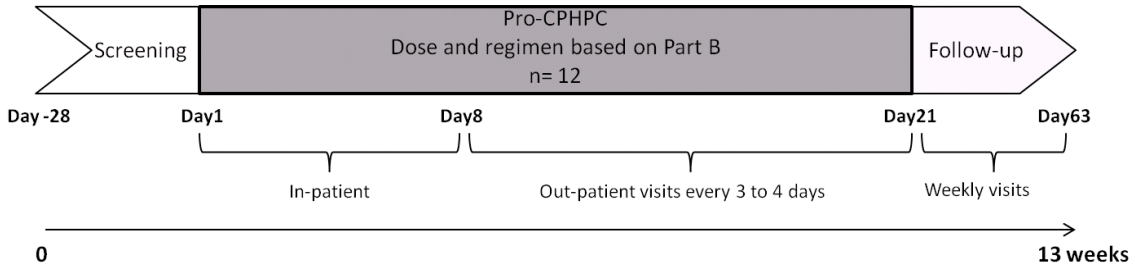
Renal Amyloidosis Sentinel Subject: A sentinel systemic amyloidosis patient (n=1) with known renal involvement and an estimated GFR ≥ 60 ml / min, *but with no known cardiac involvement*, will be dosed repeatedly with GSK3039294 for the full 21-day period before dosing any other patients begin. Following this, dosing of other patients with renal involvement (with an eGFR > 50 mL / min) but with no cardiac involvement can be initiated, provided no concerning safety signals are detected in this sentinel patient.

Cardiac Amyloidosis Sentinel Subject: Once the sentinel renal patient has successfully completed dosing, a sentinel cardiac amyloidosis patient (n=1) with eGFR≥ 60 mL / min & LV Ejection Fraction (EF) ≥ 50% will be dosed repeatedly with GSK3039294 for the full 21-day period. Following this, dosing of any other patients with cardiac involvement (NYHA ≤2) can be initiated provided no concerning safety signals are detected in the sentinel cardiac patient.

Table 4 Cohort 5 Study Duration

Screening	All screening assessments to be completed within 28 days prior to the first dose including out-patient cardiac monitoring for 7 continuous days (with external portable monitoring device) only in those patients with known cardiac amyloid involvement
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until Day 8 when they will be discharged after assessments have been completed. In-patient cardiac telemetry will be performed from at least Day -1 until Day 8 only in those patients with known cardiac amyloid involvement. Subjects will return to the unit as out-patients for regular assessments whilst continuing dosing to Day 21.
Safety Follow-up	Subjects will attend 7-14 days post last dose for a safety follow-up
PD Follow-up	Weekly PD assessments will be made up to 42 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 13 weeks

Figure 4 Illustrative Schematic of Proposed Study Design for Patient Subjects Repeat Dose (Cohort 5)



4.3. Type and Number of Subjects

In **Part A**, sufficient healthy volunteers will be enrolled to ensure 6 subjects per cohort have completed the in-patient phases.

In **Part B**, sufficient healthy volunteers will be enrolled to ensure a minimum of 6 subjects per cohort have completed the in-patient phases with all study procedures.

Subjects who participate in Part A will be eligible to participate in Part B at the discretion of the Investigator.

In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same cohort at the discretion of the Sponsor in consultation with the investigator. Replacement subjects do not need to have received the first dose for a given cohort to join the study in the second cohort.

In **Part C**, a minimum of 12 patients with systemic amyloidosis (which may include those with known cardiac amyloid involvement) will be enrolled. If subjects prematurely discontinue, replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

Additional subjects/cohorts may be enrolled to allow for further evaluation of a given dose or for evaluation of additional dose levels.

4.4. Design Justification

CPHPC has had a good safety and tolerability profile in clinical studies to date. GSK3039294 is expected to release CPHPC in the circulation. The measures of this are pharmacokinetic and pharmacodynamic (SAP depletion) and therefore no control group is included. Subjects treated with placebo are also not included because an assessment of the precision of causality that feasible numbers of subjects would give is poor (see Section 9.2).

Previous data shows that the PK/PD of CPHPC in healthy volunteers is predictive of that in the target patient population, hence the inclusion of this group in the study.

Once an effective and well-tolerated regimen has been established in healthy volunteers, this will be tested in patients with systemic amyloidosis to confirm that the PK PD of the pro drug.

Part A will allow assessment of safety, tolerability and PK including biotransformation of GSK3039294 into active CPHPC of single doses of GSK3039294. If the absorption of GSK3039294 and subsequent biotransformation of GSK3039294 to CPHPC is sufficient then repeat dosing will be investigated in Part B.

Part A washout period: In Part A of the study, subjects will receive 2 dose levels of GSK3039294, and the washout between doses will be appoximately 14 days. This washout period will allow a thorough investigation of safety, tolerability and PK, 5 days is considered sufficient to eliminate any systemic exposure carryover between dosing periods.

Part B will allow assessment of safety, tolerability and PK including biotransformation of GSK3039294 into active CPHPC of repeat doses of GSK3039294 and PD (depletion of plasma SAP). PK and PD data will be compared within a subject following repeat dosing and dose escalation and regimen adjustments. If the exposure to CPHPC and the resulting depletion of SAP is sufficient the repeat dosing of patients with systemic amyloidosis will be investigated in Part C.

The duration of 7 days for Cohort 3 Part B was selected as steady state is predicted to be achieved in this time. The duration of 21 days for Cohorts 4a and 4b in Part B was selected to reflect the likely duration of treatment needed for clinical use with the anti SAP monoclonal antibody.

Part C will confirm the ability of GSK3039294 (given at the predicted pharmacological dose determined from Part B) to decrease plasma SAP to a level suitable for mAb administration in subsequent studies and its ability to maintain this level over 21 days in patients with systemic amyloidosis. Also, safety and tolerability of the optimal clinical dose of GSK3039294 will be evaluated in systemic amyloidosis patients which may include those with known cardiac amyloid involvement.

The duration of 21 days for Part C was selected to reflect the likely duration of treatment needed for clinical use with the anti SAP monoclonal antibody.

Pharmacogenetics: Although human esterases can exhibit a high level of redundancy for specific substrates, there are particular prodrugs, such as oseltamivir which have been found to be preferentially metabolized by a specific esterase (i.e. carboxyesterase (CES)-1). Therefore, in all three parts of the study, blood samples will be collected from healthy volunteers and patients, and stored for retrospective SNP (single nucleotide polymorphism) array analysis in the event of unexpected PK profile patterns for GSK2315698 (CPHPC) and / or plasma SAP being observed. This might be indicative of either slower or accelerated pro-drug CPHPC activation which might be explained by the presence of a germline SNP affecting a specific esterase-encoding gene(s) (see Section 7.6 & Appendix 3).

Companion Diagnostic Assay Development: Blood taken for PD analysis in Part B of this study will also be used in the development and validation of a companion diagnostic assay to measure SAP levels.

4.5. Dose Justification

This study is planned to test single doses of GSK3039294 and repeat doses up to the maximum tolerated dose or the maximum allowable dose based on pre-clinical findings. The intention is to target the PK exposure of CPHPC seen in previous clinical studies producing the SAP depletion required for future studies with anti-SAP mAb.

Part A

The starting dose in Part A is planned to be 200mg of GSK3039294. This dose is selected using the PK/PD model that was developed for CPHPC (active molecule) [Sahota, 2015], adjusted for the oral absorption of GSK3039294 and the conversion of GSK3039294 to CPHPC. PK in pre-clinical species (rat and dog) show a very fast and complete conversion of GSK3039294 into CPHPC. Several marketed pro-drugs (viread, cerebyx, spectracef, hepsera) have either a fast and complete conversion into the active compound, or a tmax of the active compound that is within a few hours consistent with fast conversion.

Assuming fast and complete oral absorption of GSK3039294 and fast and complete conversion of GSK3039294 into CPHPC, then both processes are described by a single first-order process (Ka) and high bioavailability (F). For the purposes of dose estimation Ka and F have been assumed to be high: 1.3/hr and 100%, as this will result in the highest exposures to CPHPC possible. Distribution and elimination of CPHPC is expected to be the same, regardless of IV administration of CPHPC or oral administration of the pro-drug (GSK3039294). Therefore, distribution and elimination parameters, as well as between subject variability, were set to the estimates from the analysis of CPHPC itself.

The NOAEL for GSK3039294 in preclinical species is set to 1000 mg/kg/day, which is associated with CPHPC exposure of AUC[0-24] of 250 μg.hr/mL and Cmax of 22.1 μg/mL. In the rat cardiovascular changes were observed at concentrations of about 6 μg/mL. These changes were not observed in studies with dogs, and are considered species specific, however, to confirm there are no cardiovascular changes in clinic, the SD dose escalation in Part A will start at a dose that is predicted to result in CPHPC concentrations that are lower than 6 μg/mL.

Using the PK/PD model the concentration-time profiles of CPHPC after a single dose of GSK3039294 were simulated, and Cmax and AUC[0-inf] were derived. For a dose of 200 mg, this resulted in a predicted AUC[0-inf] of 14.5 μg.hr/mL (95% CI of 9.5-22.4 μg.hr/mL) and a predicted Cmax of 3.4 μg/mL (95% CI of 2.1-5.0 μg.hr/mL).

The next doses in Part A will be determined based on the data of the preceding dosing sessions. All available PK data will be analysed (see Section 9.3.2.1), and the next dose will be such that the median Cmax will be about 6 μg/mL, and the predicted 95% CI will not exceed preclinical Cmax and AUC limits.

The highest dose in Part A will not exceed pre-clinical safety exposure limits of AUC[0-24] of 250 μg.hr/mL and Cmax of 22.1μg/mL.

Part B

The dose level for Cohort 3 in Part B will be determined based on the PK data obtained in Part A, by analysing all available PK data from Part A and subsequently predicting concentration-time profiles at steady state after repeat dosing. Table 5 shows examples of dose levels and frequencies with predicted AUC[0-24] and Cmax at steady state, using the PK/PD model that was developed for CPHPC (active molecule) [Sahota, 2015], adjusted for oral absorption and conversion of GSK3039294 into CPHPC. The PK data from Part A will be used to obtain estimates for Ka and F.

Table 5 Example Doses And Predicted Exposures For Part B

Dose	Ka	F	AUC[0-24h] (µg.hr/mL) *)	Cmax (µg/mL) *)
Cohort 3				
300mg OD	1.3	1	23.4 (15.3-35.9)	5.20 (3.32-7.84)
300mg OD	1.3	0.5	11.4 (7.36-18.1)	2.61 (1.72-3.86)
300mg OD	0.6	1	22.8 (14.7-36.2)	3.83 (2.73-5.42)
Cohort 4a (first part)				
300mg BID	1.3	1	45.7 (29.4-72.5)	5.49 (3.75-8.05)
300mg BID	1.3	0.5	22.8 (14.7-36.2)	2.74 (1.87-4.02)
300mg BID	0.6	1	45.7 (29.4-72.5)	4.09 (2.94-5.76)
Cohort 4a (last part)				
600mg BID	1.3	1	91.3 (58.9-145)	11.0 (7.50-16.1)
600mg BID	1.3	0.5	45.7 (29.4-72.5)	5.49 (3.75-8.05)
600mg BID	0.6	1	91.3 (58.9-145)	8.19 (5.88-11.5)

*) Predicted AUC[0-24] and Cmax at steady state; presented are mean and 95%CI

The dose levels for subsequent cohorts in Part B will be determined based on the PK data from Part A (single dose), and cohort 3 in Part B (multiple dose). All available PK data will be analysed (see Section 9.3.2.1). The dose levels and dosing frequencies will be chosen such that the predicted 95% CI of Cmax and AUC at steady state will not exceed preclinical Cmax and AUC limits (22.1 µg/mL and 250 µg.hr/mL, respectively).

Part C

GSK3039294 will be administered at the predicted optimal clinical dose for 21 days. This dose will be determined using the PK/PD model that was developed for CPHPC (active molecule) [Sahota, 2015]. Using all available PK and plasma SAP (PD) data from Parts A and B, the model will be adjusted for the oral absorption of GSK3039294 and the conversion of GSK3039294 to CPHPC. Plasma concentration-time profiles of CPHPC as well as the plasma SAP time course after repeat dosing with GSK3039294 will be predicted in order to determine the optimal clinical dose and dose frequency. The dose level and frequency will be chosen such that the predicted 95% CI of Cmax and AUC at steady state will not exceed preclinical Cmax and AUC limits (22.1 µg/mL and 250 µg.hr/mL, respectively). See Section 9.3.2.1 for further details of the analysis.

4.6. Benefit:Risk Assessment

GSK3039294 is an oral prodrug of CPHPC (GSK2315698). CPHPC has been associated with a good safety profile in clinical studies to date (see Investigator's Brochure)

There is no clinical benefit to either healthy volunteer subjects or systemic amyloidosis patients in achieving plasma SAP depletion during any Part of the study.

A NOAEL of 1000 mg/kg/day has been identified in Wistar rats based upon adverse findings as regards urine biochemistry in the absence of any identified pathological changes within the kidney using light microscopy techniques. Close monitoring of plasma and urine biochemical parameters, including renal function and proteinuria surveillance, will be performed in all Parts of the study including in systemic amyloidosis patients in Part C (see Section 7.1 & Section 7.5).

The release of CPHPC from GSK3039294 will be accompanied by the release of 2 molecules of formaldehyde. Formaldehyde is generated by endogenous human basal metabolism is substantial amounts, (approximately 50g per day). For a dose of 1.2 g per day (a dose not likely to be exceeded in this study), the total amount of formaldehyde generated would be around 120mg. In addition, a number of prodrug compounds such as Viread, Cerebyx, Spectracef and Hepsera releasing up to 120mg/day of formaldehyde have been described in the literature and there have been no specific human toxicology findings [Dhareshwar, 2008] associated with this upper level of formaldehyde release from their metabolism Exogenous production of formaldehyde from either food stuffs or licensed prodrugs is not known, to date, to cause detectable organ or physiological dysfunction in humans.

Summaries of findings from non-clinical studies conducted with GSK3039294 can be found in the Investigator's Brochure. Summaries of findings from both clinical and non-clinical studies conducted with GSK2315698 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK3039294, GSK2315698]		
Generation of formaldehyde upon transformation of GSK3039294 (prodrug) into active (GSK2315698).	Refer to Section 4.5	Maximum dose is likely to be below 1.2g, which releases similar amounts of formaldehyde as existing prodrugs releasing formaldehyde.
GSK2315698 - Epistaxis	Small volume nose bleeds have been noted in a few patients which have been self-limited and not associated with any evidence of thrombocytopenia or coagulopathy. The relationship to GSK2315698 is unclear but subjects are closely monitored for bleeding.	Observe for incidence / severity Monitoring of haemoglobin & platelets
Potential food effect on PK of GSK3039294 (and subsequent GSK2315698)	Based on the physical-chemical properties of GSK3039294 it is not expected that the PK will be affected by food. However, as it is not feasible to give bid or tid dosing under fasted conditions, administration of GSK3039294 in Weeks 2 and 3 of Part B and in Part C will be without restrictions with respect to meal times.	A potential effect of food will be explored in this study (Cohort 3 of Part B). If the food effect exploration shows an effect of food on the PK of GSK3039294 (and subsequently GSK2315698), a formal food effect study will be considered.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Preclinical finding of potential nephrotoxicity of GSK3039294	Following 4 weeks oral dosing in rats, minor changes in urine composition comprising of low pH in males given ≥300 mg/kg/day (mean pH was 5.8 and 6.4 at 1000 mg/kg/day or control respectively) and females given 1000 mg/kg/day (mean pH was 5.6 and 5.9 at 1000 mg/kg/day or control respectively), an increase in total protein excretion in both sexes given 1000 mg/kg/day (up to 1.48X control) and increased specific gravity, creatinine and glucose output for males given 1000 mg/kg/day (1.02X, 1.14X and 1.22X control, respectively). These changes were considered not biochemically concerning, and were not associated with any renal pathological findings on H&E staining of rat kidney paraffin sections. Additionally, no change in any urinalysis parameters was observed in the dog 28 day toxicity study with GSK3039294 at doses ≤1000 mg/kg/day. Overall, in the absence of any renal pathological changes under light microscopy, the significance of these rat renal biochemical changes is unclear.	Precautions as listed in Section 7.4 to detect signals of potential nephrotoxicity from GSK3039294 in humans at the earliest time point possible during both single and repeat dose administration in both healthy volunteer subjects and systemic amyloidosis patients.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Preclinical finding of haematologic effects associated with GSK2315698	In toxicology studies using IV GSK2315698, minor reductions in red cell parameters were observed in female dogs given 200 mg/kg/day for 4 weeks. A 34% increase in platelet count was seen in rats receiving 400 mg/kg/day for 8 days. Some trends (haemoglobin increased; white cells and platelets decreased) within the reference range were observed in a single dose study in healthy volunteers (CPH113776). The clinical significance of these observations is not clear and similar changes were not observed in the patient study (CPH114527). Therefore, at this time, it is felt to be very unlikely that GSK2315698 (CPHPC) has any haematological toxicity properties in human subjects.	Haematological parameters will be monitored in the clinic. Dosing not to exceed the existing NOAEL.
Preclinical finding of testicular changes associated with GSK2315698	In one study in male rats (but not in another similar study), testicular changes (seminiferous tubular degeneration/atrophy, reduced spermatozoa, shedding of spermatogenic cells) were observed at the highest dose tested (400 mg/kg/day for 28 days). No testicular changes were observed in a rat 26 week study (terminated at week	The highest dose of GSK3039294 will not yield exposures of GSK2315698 exceeding a predicted mean AUC0-24 of 145 ug*h/mL and Cmax of 6.05 ug/mL based on the NOAEL in the rat 28 day IV repeat dose studies, and therefore the potential risk to humans during the proposed short term dosing is considered very low

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	21) at GSK2315698 doses ≤ 1000 mg/kg/day. No testicular changes were observed in rat 28 day study with GSK3039294 at doses ≤ 1000 mg/kg/day. In the dog no testicular changes have been observed with GSK2315698 or GSK3039294 at doses of ≤ 200 mg/kg/day and ≤ 1000 mg/kg/day, respectively.	
Preclinical finding of cardiovascular changes associated with GSK2315698.	Preclinical finding in preliminary cardiovascular screen (rat only) of blood pressure, pulse pressure, heart rate increase and QA interval reduction associated with GSK2315698 (See IB for further information). No arrhythmogenic safety signals were detected	Cardiovascular parameters, including blood pressure and heart rate, will be closely monitored in the clinical study.
Cardiac arrhythmias identified on 24-hour Holter after single dose administration of GSK3039294 in Part A of this study.	Four (4) asymptomatic, hemodynamically stable arrhythmias in 3 healthy volunteer subjects were seen on 24-hour Holter monitoring after single dose administration of GSK3039294 in Part A. 3 / 4 events were atrial tachycardias, and 1 / 4 event was a single 3.4 second episode of a AIVR (5 beats). All SVT (atrial) events were less	Supraventricular or ventricular arrhythmia exclusion criterion. Continuous telemetry at in-patient dosing. Sentinal subject (systemic amyloidosis patient with known cardiac amyloid) in Part C for cardiac evaluation and monitoring prior to further recruitment.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	than < 11 seconds in duration. One healthy volunteer subject had two separate arrhythmic events which consisted of a single episode of atrial tachycardia 10 minutes after administration of GSK3039294 - when neither prodrug or CPHPC were detectable - followed by a single 5-beat episode of AIVR approximately 12 hours later.	Subjects will be withdrawn from the study if the Investigator deems any cardiac AE to be clinically concerning, and / or triggers the measurement of plasma hs-cTn to exclude the possibility of arrhythmia-associated myocardial ischemia / injury (see **Section 5.4.4. & Section 7.3.7.**).

4.6.2. Benefit Assessment

No medical benefit can be expected by participating in this study.

4.6.3. Overall Benefit:Risk Conclusion

GSK3039294 is an oral prodrug of CPHPC, as such it is expected to release CPHPC after oral administration. Previous clinical experience with CPHPC shows it has a good safety and tolerability profile therefore we do not anticipate safety issues linked to the release of the active moiety.

At this time, although the cardiac arrhythmias reported in Part A are unlikely to be attributable to single dose administration of GSK3039294 at either 600mg or 1200mg, as a precaution, and to further assess and confirm this conclusion, the cardiac safety monitoring of healthy volunteer subjects during repeat dose administration of GSK3039294 for 7 consecutive days in Cohort 3 Part B has been enhanced (see **Section 7.3.7.**), and also in systemic amyloidosis patients in Cohort 5 Part C who are known to have cardiac amyloid involvement (see **Section 7.3.8.**).

Biotransformation from prodrug into active will release 2 molecules of formaldehyde. There is precedent of licensed prodrugs releasing formaldehyde with no associated toxicity on a background that formaldehyde is physiologically metabolised very rapidly within the systemic circulation (EFSA Journal, 2014; 12(2):3550).

Preclinical signs of potential nephrotoxicity were observed at very high doses which are unlikely to be reached in the clinic, however monitoring of renal function will be performed in the study in order to detect any potential changes.

There will be no medical benefit to healthy volunteers or patients with systemic amyloidosis being treated with GSK3039294 alone. The design of the study, schedule of assessments, and oversight mean that any risks to participants are minimised including those which might potentially affect the kidney and heart, and therefore the clinical study is justified.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB for GSK3039294.

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

5.1. Inclusion Criteria

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

All Subjects

[1] AGE
1. 18 to 70 years of age inclusive at the time of signing the informed consent.

[2] RELEVANT HABITS
1. Non-smokers and Smokers. Smokers (<5 /day) are permitted but must be willing to abstain for the duration of residential study sessions and / or dosing period (whichever is longer).

[3] WEIGHT
1. Body weight > 50kg and body mass index (BMI) ≥ 18 kg/m2 (inclusive) and excluding the effects of peripheral oedema.

[4] SEX
1. Male or female 2. Female subjects are eligible to participate if they are of non-childbearing potential defined as premenopausal females with a documented tubal ligation or hysterectomy or bilateral oophorectomy; or postmenopausal defined as 12 month of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MIU/ml and estradiol < 40 pg/ml (147 pmol/l) is confirmatory 3. Male subjects with female partners of child bearing potential must comply with one of the following contraception requirements from the time of first dose of study medication until completion of the follow-up visit a. Vasectomy with documentation of azoospermia. b. Male condom plus partner use of one of the contraceptive options below: • Contraceptive subdermal implant that meets the effectiveness criteria of a <1% rate of failure per year, as stated in the product label • Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a] • Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a] • Contraceptive vaginal ring [Hatcher, 2007a] • Percutaneous contraceptive patches [Hatcher, 2007a] • Occlusive cap (female diaphragm or cervical/vault cap) with a vaginal

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

[5] INFORMED CONSENT
1. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol

Additional Inclusion Criteria – Healthy Volunteers

[1] TYPE OF SUBJECT
1. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. 2. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor if required agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 3. AST, ALT, Alkaline phosphatase and bilirubin ≤1.5 ULN (isolated bilirubin >1.5 ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

Additional Inclusion Criteria – Patients

[1] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
1. Subject medically diagnosed with systemic amyloidosis 2. SAP scan identifying amyloid at any anatomical site, including subset of patients with large amyloid load in the liver 3. Up to and including NYHA class 2 4. For AL amyloidosis patients, ≥ 6 months post-chemotherapy with either a free light chain (FLC) complete response (CR) or a very good partial response (VGPR) 5. eGFR > 50mL/min 6. Alanine amino transferase (ALT) ≤ 3x upper limit of normal (ULN) and bilirubin ≤ 1.5x ULN (isolated bilirubin > 1.5 xULN is acceptable if bilirubin was fractionated and direct bilirubin <35%), irrespective of alkaline phosphatase

(ALP) level

7. Subject is ambulant and capable of attending the clinical unit

Further Inclusion Criteria for Patients with known cardiac amyloid involvement

8. *eGFR ≥ 60 mL / min*
9. *Echocardiogram – LV ejection fraction ≥ 50% within 3 months of screening.*

5.2. Exclusion Criteria

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

All Subjects

[1] CONCOMITANT MEDICATIONS
1. Use of prohibited medication (Section 6.11.2)

[2] RELEVANT HABITS
1. History of regular alcohol consumption within 6 months of the study defined as: • For UK sites – healthy volunteers: an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

[3] CONTRAINDICATIONS
1. History of sensitivity to any of the study medications, or metabolite thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation

[4] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. **Cohort 3 (Part B) subjects only:** Cardiac arrhythmia detected on the 48hr screening Holter, with the exception of physiological bradycardia, first-degree heart block, supraventricular premature complexes and / or premature ventricular complexes (PVCs) less than a single 5-beat AIVR 2. **Cohort 3 (Part B) subjects only:** High sensitivity Cardiac Troponin level at screening > ULN for the specified assay 3. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.

4. A positive pre-study drug/alcohol screen (unless a positive test is due to prescribed medications)
5. A positive test for HIV antibody
6. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 84 days
7. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). Prior to Part A for subjects participating in Parts A and B
8. Exposure to more than four new chemical entities within 12 months prior to the first dosing day
9. Lactating females
10. Poor or unsuitable venous access

Additional Exclusion Criteria – Healthy Volunteer

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 2. QTcF > 450 msec from a mean of triplicate readings triplicate readings taken 5 minutes apart

Additional Exclusion Criteria – Patients

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Non-amyloid heart diseases (e.g. epicardial coronary artery heart disease, or non-amyloid valvular heart disease) 2. Subject with mean QTcF of >480ms from a mean of triplicate readings 3. **Cardiac Amyloidosis Patients ONLY** – Within 3 months of Screening, *Or* at Screening**: a).** Sustained (≥ 10 beats) / symptomatic monomorphic ventricular tachycardia (VT), or rapid polymorphic VT; **b).** Complete heart block; **c).** Brady arrhythmias deemed clinically concerning in this patient population by the Investigator in consultation with the Medical Monitor 4. Plasma albumin < 30g/litre

5. A syncopal episode, within 4 weeks of screening
6. Average SBP ≤ 100mmHg at Screening from triplicate readings in Part C systemic amyloidosis patients with known cardiac amyloid involvement *Or*, Average SBP ≤ 90mmHg at Screening from triplicate readings in systemic amyloidosis patients *without* known cardiac amyloid involvement
7. Implantable cardiac defibrillator (ICD)
8. Insertion of permanent pacemaker in last 2 months
9. Decompensated or uncontrolled heart failure in last 2 months
10. Anaemia Hb < 9g/dL
11. Uncontrolled hypertension in a known hypertensive patient, or fulfilling diagnostic criteria of essential hypertension at screening
12. Presence of any co-morbid condition (e.g. severe or unstable coronary artery disease; moderate to severe chronic obstructive pulmonary disease) which in the opinion of the investigator would increase the potential risk to the subject
13. Non-amyloidosis causes of chronic liver disease (with the exception of Gilbert's syndrome or clinically asymptomatic gallstones)
14. Diabetes Mellitus
15. Glycosuria at Screening
16. Urine pH < 6.0 at screening
17. Hypoalbuminaemia (< 30nmol/L)
18. Hypophosphatemia (less than 0.8mmol/L)
19. Prothombin time >1.5xULN
20. Malabsorption syndrome of any aetiology

[2] CONCOMITANT MEDICATIONS
1. Compassionate use of CPHPC or participation in a separate clinical trial involving CPHPC within 3 months of screening 2. Currently taking any of the following esterase-cleaved prodrug medications: cerebyx, aquavan, spectracef, hepsera, viread 3. Anticoagulation therapy within 4 weeks of Screening 4. Currently receiving or have received within 12 weeks of screening immunosuppressive anti-cytokine monoclonal antibodies (e.g. anti-TNF or anti-IL-1), disease modifying drugs (e.g. methotrexate, gold or cyclophosphamide), or high-dose infusional steroids (e.g. methylprednisolone), with the exception of low-dose maintenance oral corticosteroids (e.g. ≤ 30 mg prednisolone per day)

5.3. Screening/Baseline/Run-in Failures

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

5.4. Withdrawal/Stopping Criteria

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

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

Non-compliance to the study regimen or withdrawal of consent (no reason has to be given by the individual subject) will lead to the removal from the study. An individual subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at her own request, or at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. The entire study will be terminated if the sponsor (GSK) stops the study at any stage.

Individual subjects may be withdrawn at the investigator's discretion at any time during the study, provided there is a valid and confirmable clinical reason. The presence of severe AEs predefined as stopping criteria below in Section 5.5, or SAE as defined in Appendix 3, will lead to the withdrawal of an individual subject. Withdrawn subjects will be replaced by new subjects as per the guidance in Section 6.4

5.4.1. Cardiovascular Safety Stopping Criteria

1. New onset or worsening symptoms of cardiac ischemia which is reasonably attributable to GSK3039294

2. Development of decompensated or uncontrolled cardiac failure which is reasonably attributable to GSK303294.

3. Systolic blood pressure > 170 mmHg as an average of triplicate readings taken at rest over 15 minutes on three consecutive days at any time after administration and is reasonably attributable to GSK3039294.

4. **Healthy Volunteers & Amyloidosis Patients without bundle branch block:** QTcF > 500 msec, (or a change from baseline of QTcF > 60 msec on a 12-lead

ECG in healthy volunteers) which is reasonably attributable to GSK3039294 on an average from triplicate readings (see Section 5.4.3).

5. **Systemic Amyloidosis patients with bundle branch block** - if baseline QTcF < 450 msec: QTcF > 500 msec on a 12-lead ECG at any time after administration of GSK3039294; If baseline QTcF 450-480 msec: QTcF > 530 msec at any time after drug administration and is reasonably attributable to GSK3039294, as an average of triplicate readings (see Section 5.4.3).

6. Any cardiovascular SAE as predefined in Appendix 4 after drug administration and is reasonably attributable to GSK3039294

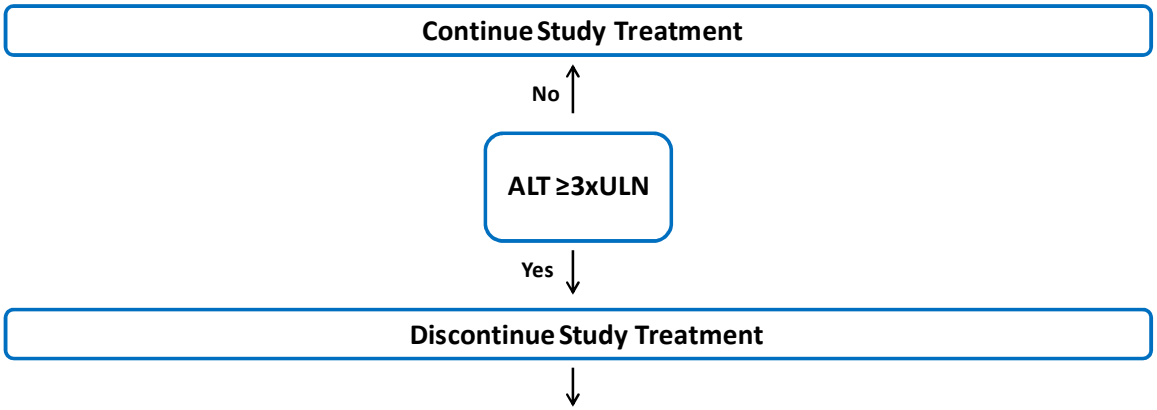
Please also see Section 5.4.4. Cardiac Arrhythmia stopping criteria

5.4.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a healthy volunteer subject in Part A or B, or a systemic amyloidosis patient without liver involvement /no biochemical liver dysfunction in Part C** with baseline liver chemistry within the normal reference range for ALT if they are reasonably attrituble to GSK3039294 and provided the following liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

In Part C, systemic amyloidosis patients will be required to return for follow-up liver chemistry assessments within 1 week of the changes from the baseline liver chemistry at Day -1 (see Table 6) being reported. Individual systemic amyloidosis patients will be withdrawn from the study if the following liver chemistry changes are reported from baseline at Day -1 (see Table 6).

Table 6 Change from baseline in liver chemistry for repeat or withdrawal

Baseline Liver Chemistry	Repeat assessment within 1 week	Withdrawal
x1 ULN < ALT ≤ x3 ULN Bilirubin ≤ x1ULN	ALT > x4 ULN Bilirubin > x 1.5 ULN	ALT > x6 ULN Bilirubin > x 1.5 ULN
x1 ULN < ALT ≤ x3 ULN Bilirubin ≤ x1.5 ULN	ALT > x4 ULN Bilirubin > x 2 ULN	ALT > x6 ULN Bilirubin > x 2 ULN

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2 (Section 12.2)

5.4.2.1. Study Treatment Restart or Rechallenge

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

5.4.3. QTc Stopping Criteria

Healthy Volunteers & Amyloidosis Patients:

A healthy volunteer or patient that meets either bulleted criterion below will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline in healthy volunteer subjects: QTcF >60 msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF with Bundle Branch Block
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

5.4.4. Cardiac Arrhythmia Stopping Criteria

All cardiac arrhythmias in individual subjects will be reviewed by the Investigator in consultation with the Medical Monitor at the earliest possible opportunity after the event, and will also be reviewed by a cardiologist where it is deemed appropriate to do so by the Investigator in consultation with the Medical Monitor on a case-by-case basis.

A clinically concerning cardiac arrhythmia in this study is any type of arrhythmia or divergent QRS complex morphology that is deemed by the Investigator to be reasonably attributable to GSK3039294 - rather than within normal variation for each type of affected subject receiving repeat dose GSK3039294; i.e. healthy volunteer subjects in Part B, or systemic amyloidosis patients with known cardiac involvement Part C.

Furthermore, a clinically concerning arrhythmia is an adverse event which is deemed by the Investigator in consultation with the Medical Monitor to be of sufficient temporal duration and / or character to potentially affect subject safety.

Detection of the following during baseline assessment or following administration of GSK3039294 will lead to withdrawal:

a). Sustained (≥ 10 beats) / symptomatic monomorphic ventricular tachycardia (VT), or rapid polymorphic VT; **b).** Complete heart block; **c).** Brady arrhythmias deemed

clinically concerning by the Investigator in consultation with the Medical Monitor (i.e. *except* physiological bradycardia or first degree heart block).

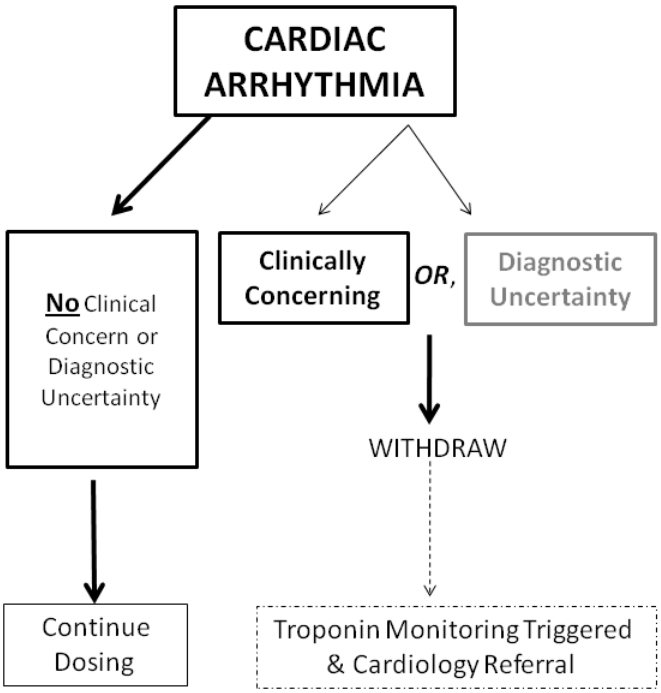
Additional cardiac arrhythmic events could include, but are not restricted, to:

- A sustained arrhythmia (i.e. ≥30 seconds) *except* physiological bradycardia.
- A non-sustained wide-complex tachyarrhythmia ≥ 100 / minute that is:
    - accompanied by symptoms or other new ECG changes (e.g. new ST depression)
    - repetitive (e.g. repeated short salvos)
    - Greater than 10 seconds in duration

Subjects who either have a clinically concerning arrhythmic event during the study, or where there is electrophysiological diagnostic uncertainty on cardiac telemetry / ECG, must be withdrawn from the study, and should have an immediate cardiac troponin level evaluated using a high-sensitivity point-of-care assay as outlined in **Section 7.3.7** & Figure 5, below.

Affected subjects should be referred to the local cardiology service and the Medical Monitor should be informed as soon as possible.

Figure 5 Algorithm for Management of Subjects having received one or more doses of GSK3039294 in Parts B & C based on Arrhythmia Characterization



In Part C, the patient's amyloidosis physician should be informed as soon as possible after any type of cardiac adverse event, by the Medical Monitor, irrespective of the patient's cardiac amyloid status at Screening.

5.4.5. Renal Stopping Criteria

The presence of any of the following which are reasonably attributable to GSK3039294 will be nominally categorised as a severe adverse event and will constitute individual stopping criteria for subjects:

Healthy volunteers (Part A or Part B):

- Spot Urine Protein Creatinine (UPC) ratio > 0.5

Healthy volunteers (Part A or Part B) & Patients (Part C):

- Increase in serum creatinine (ΔsCr) of 0.3 g/dL from baseline (or an increase of 50% at any time if the baseline is > 0.6 g/dL)

- Detectable glycosuria in the presence of concomitant normoglycaemia

- Hypophosphataemia (less than 0.8mmol/L)
- Metabolic acidosis

All abnormal results should be confirmed within 24 hours before individual subject stopping criteria are implemented.

5.4.6. Stopping Criteria Based On Disease Progression in Systemic Amyloidosis Patients in Part C

In Part C, individual systemic amyloidosis patients can be withdrawn at any time during the study where the investigator has a reasonable level of clinical suspicion that the patient's underlying systemic amyloidosis is worsening (including worsening cardiac dysfunction in those patients known to have cardiac amyloid involvement). In this setting, the investigator in consultation with the Medical Monitor must refer the patient to their primary hospital physician for further consultation and appropriate diagnostic tests

5.5. Stopping Criteria for the Entire Healthy Volunteer or Patient Study Groups

- If an SAE occurs that the investigator believes is reasonably attributable to IMP, in any subject at any one dose level of GSK3039294, continuation of the study will be temporarily halted and no further subjects will be dosed until a full safety review of the data has taken place.
- If the same severe adverse event is observed in two subjects across all study parts, and is reasonably attributable, in the opinion of the investigator, to GSK3039294, the study will be temporarily halted and no further subjects will be dosed until a full safety review of the study has taken place.
- If the study is temporarily halted, relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the applicable regulatory authority will take place prior to any resumption of dosing
- Every effort will be made to take a blood sample for pharmacokinetic analysis from each affected individual at the time of any of the adverse events described above

5.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the final follow-up visit.

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

	Study Treatment
Product name:	GSK3039294 Capsules
Dosage form:	Capsules
Unit dose strength(s)/Dosage level(s):	20 to 200mg
Route of Administration	Oral
Dosing instructions:	Swallow with water as directed in the SRM
Physical description:	White, opaque capsule
Method for individualising dosage:	A single capsule or multiple capsules to be taken depending on the dosage required

6.2. Treatment Assignment

This is an open-label, non-randomised study with no active or placebo control.

GSK3039294 doses will be administered sequentially, as detailed in Section 4.1, and will be based on the review of safety, PK and PD data from previous cohorts, dosing sessions and study parts.

6.3. Planned Dose Adjustments

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose will not exceed pre-clinical exposure limits (Cmax of 22.1 μg/mL and AUC[0-24] of 250 μg.hr/mL).

The decision to proceed to the next dose level of GSK3039294, will be made by the GSK Study Team and the investigator based on safety, tolerability and preliminary pharmacokinetic and/or pharmacodynamic data (Parts B and C) obtained in at least 6 subjects at the prior dose level (see Section 10.7.1). The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic and/or

pharmacodynamic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

6.4. Blinding

This will be an open-label, non-randomised, dose-escalation study with no active or placebo control.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of GSK3039294 will be detailed in a Study Specific Technical Agreement/Memo (TTS) or Pharmacy Manual which will be accompanied by a Quality Agreement.

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

6.7. Compliance with Study Treatment Administration

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

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each subject's hands and mouth to ensure that the study treatment was ingested.

When subjects self-administer study treatment(s) at home, compliance with GSK3039294 will be assessed through a dosing record, querying with the subject during the site visits and documented in the source documents and CRF. A record of the number of GSK3039294 capsules dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK3039294 greater than the agreed dose for a particular cohort, dosing session or study part will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK3039294 or GSK2315698 (CPHPC) can no longer be detected systemically (at least 4 days for GSK2315698 (CPHPC))
3. Obtain a plasma sample for pharmacokinetic (PK) analysis as soon as possible, but at least within 7 days from the date of the last dose of study treatment 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.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the regimens investigated are not designed as study treatments but to investigate PK/PD kinetics of various regimens of GSK3039294 dosing.

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.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Meals and Dietary Restrictions

- In Part A, and during Cohort 3 of Part B on all dosing days, subjects will be required to fast from midnight until 3 hours after administration of study treatment (with the exception of Day 5 of Cohort 3 in which subjects will be fed). At other times, snacks and meals will be provided by the clinical unit. Water will be allowed as desired except for one hour before and after drug administration.

- An investigation into a possible food effect will be conducted on Days 4 and 5 of Cohort 3 of Part B in this study (This will only be triggered by the Investigator in consultation with the Medical Monitor as per Section 4.2.2). On Day 4 subjects will be fasted until following the collection of the 4hr post-dose PK sample, on Day 5 subjects will be fed prior to PK samples being taken. This investigation will inform possible further meal restrictions in the study (rest of Part B and Part C).
- There are no meal restrictions for Cohorts 4a and 4b of Part B and all of Part C, unless the food effect exploration indicates significant effects on PK.

6.10.2. Caffeine and Alcohol, and Tobacco

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for at least 24 hours (48 hours for Cohort 3) prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.
- **Healthy Subjects:** During each treatment period, subjects will abstain from alcohol for 24 hours (48 hours for Cohort 3) prior to the start of dosing until collection of the final PK sample for each in-house session. Subjects will also abstain from alcohol for 24 hours prior to screening and follow-up. At all other times during the study, male subjects should have no more than 2 drinks per day and female subjects should have no more than 1 drink per day (1 drink is equivalent to 12 g of alcohol: 360 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled spirits).

- **Patients with raised LFT's at baseline:** No alcohol is to be consumed from D-1 until follow-up assessments are completed

- During each resident dosing session, subjects will abstain from smoking for 12 hours prior to administration and until discharge from the clinical unit.

6.10.3. Activity

Subjects must abstain from strenuous exercise for at least 48 hrs before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g. watch television, read).

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses of ≤ 2 grams/day is permitted for use any time during the study. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor.

For patients only

Subjects' usual medication can be continued during this study with the exception of those listed in Section 6.11.2

6.11.2. Prohibited Medications and Non-Drug Therapies

All Subjects:

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 14 days prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

Patients:

The following medications are not permitted in the study. If use is medically required then the subject will be withdrawn:

- Immunosuppressive anti-cytokine monoclonal antibodies (e.g. anti-TNF or anti-IL-1), disease modifying drugs (e.g. cyclophosphamide, methotrexate or gold), or high-dose infusional steroids (e.g. methylprednisolone).
- Use of anti-coagulant drugs
- Use of Domperidone as an antiemetic

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments are recommended to occur in the following order:
  1. 12-lead ECG
  2. Vital signs
  3. Blood draws.

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Tables

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

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

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

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

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

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

7.1.3. Part B – Cohort 4, 21 day repeat dose healthy volunteer subjects

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

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

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																					Follow-up (7-14 days following last dose)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Study Treatment			**Cohort 4a:** Dose and dosing frequency may be altered once during treatment period ←----------→ **Cohort 4b:** dosing regimen will be determined based on information from Cohort 4a																						D21 a.m. dosing only
Blood Sampling (PK)			For sampling time points, see Section 7.4.1																					X	For 1st dose and escalation See Section 7.4.1
Blood Sampling (PD)			For sampling time points, see Section 7.5																					X	
Discharge from Clinical Unit									X																Following completion of all assessments
PGx Sample			X																						Pre-dose if possible. Informed consent for optional genetics research must be obtained before collecting a sample
AE/SAE review		←----------→																						X	
Concomitant medication review	X	←----------→																						X	

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

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

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

Procedure	Dose Days								Notes
	-1	1	2	3	4	5	6	7	
Discharge from Clinical Unit								X	Following completion of all assessments
AE/SAE review	←----------							----------→	
Concomitant medication review	←----------							----------→	

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

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																	Safety Follow-up (7-14 days after last dose)	PD Follow-up (weekly up to D63)
		-1	1	2	3	4	5	6	7	8	9-11	12	13+14	15	16+17	18	19+20	21		
Outpatient Visit	X											X		X		X		X	X	
Admission to Clinical Unit		X																		
Inpatient Stay at Clinical Unit			←----------																	
Informed consent	X																			
Inclusion and exclusion criteria	X	X																		
Demography	X																			
Full physical exam incl height and weight	X																			
Medical history (includes substance usage)[1]	X																			
Past and current medical conditions	X																			
FSH and oestradiol (women)	X											X		X		X		X	X	

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																Safety Follow-up (7-14 days after last dose)	PD Follow-up (weekly up to D63)
		-1	1	2	3	4	5	6	7	8	9-11	12	13+14	15	16+17	18	19+20	21	
Clinical Safety Laboratory Assessments[2] *(HIV, Hep B and Hep C Screen at screening only*[3]*)* – except Core Urine Monitoring Asssessments	X	X		X			X			X		X		X		X		X	X	X
Clinical Chemistry Only			X		X				X											
High-sensitivity cardiac Troponin[3]	X		X																	
Core Urine Monitoring Asssessments (except Spot UPC ratio)[4]	X		X		X		X		X	X		X		X		X		X	X	X
Urine Sample (for storage)		X																		
Urine Drug/Alcohol Breath Test	X	X										X		X		X		X	X	
Echocardiogram[5]	X																			
12-lead ECG and vital signs	X	X	X	X			X			X		X		X		X		X	X	
Lead II monitoring[6]	X[8]	←----------																		
Home Dosing Record											X	X	X	X	X	X	X	X		
Study Treatment			←----------																	
Blood Sampling (PK)			For sampling time points, see Section 7.4.1																	
Blood Sampling (PD)			For sampling time points, see Section 7.5																X	X
Brief Physical		X																	X	
Discharge from Clinical Unit										X										

Procedure	Screening (within 28 days of Day 1)	Treatment Period (Days)																Safety Follow-up (7-14 days after last dose)	PD Follow-up (weekly up to D63)
		-1	1	2	3	4	5	6	7	8	9-11	12	13+14	15	16+17	18	19+20	21	
PGx Sample [7]			X																
AE/SAE review		←----------																→	X	X
Concomitant medication review	X	←----------																→	X	

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

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

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

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

Procedures conducted as part of the subject's routine clinical management e.g. blood count and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3. Safety

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

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 4 and Section 12.4

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

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4 .
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the

event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4

7.3.1.2. Method of Detecting AEs and SAEs

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

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

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4 .

7.3.1.4. Regulatory Reporting Requirements for SAEs

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

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

7.3.2. Pregnancy

- Details of all pregnancies in female partners of male subjects will be collected after the start of dosing and until follow-up.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

7.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the 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 lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.3.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse.
- Triplicate readings of blood pressure and pulse rate will be taken and averaged at all times.

7.3.5. Cardiac Monitoring – Electrocardiogram (ECG), Telemetry & Non-Implantable Devices for Remote Monitoring

- 12-lead ECGs will be measured in semi-supine position after 5 minutes rest (triplicate readings will be taken and averaged at all times) will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.3 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

7.3.5.1. Cardiac Safety Monitoring in Cohort 3 (Part B) at Screening & Baseline

This will consist of a 48 hour Holter at Screening and continuous telemetry for 24 hours immediately preceding the first dose of GSK303294 at baseline.

- **In-Patient Dosing with GSK3039294**: Continuous telemetry during repeat 7 day dosing of healthy volunteer subjects in Cohort 3 will be performed for up to approximately 24 hours after Day 7 to detect any cardiac arrhythmias potentially attributable to repeat dosing with GSK3039294 for 7 days in Cohort 3.

7.3.5.2. Cardiac Safety Monitoring in Cohort 5 (Part C) patients with known cardiac amyloid involvement

- **Screening:** 7-day out-patient cardiac monitoring using an appropriate non-implantable recording device which is acceptable to the patient – this will evaluate the arrhythmic background of eligible cardiac amyloidosis patients such that false positive attribution of arrhythmias to GSK3039294 during repeat dosing will be minimized.

- **Baseline:** 24 hour in-patient telemetry immediately before the first dose of GSK3039294.

- **In-patient dosing with GSK3039294:** Continuous telemetry will be performed for up to 24 hours after Day 7 administration of GSK3039294 to detect any arrhythmias in patients with known cardiac amyloidosis potentially attributable to repeat dosing with GSK3039294 including worsening of known patient-specific arrhythmias from Screening and / or Baseline assessments.

- **Optional cardiac monitoring after completion of in-patient dosing:** At Investigator discretion, on a case by case basis determined by in-patient cardiac telemetry / ECG findings, and in consultation with the Medical Monitor, cardiac monitoring can be extended either as an in-patient or as an out-patient (using a portable non-implantable device of Investigator choosing) in patients with known cardiac amyloidosis.

Cardiac monitoring should continue in cardiac amyloidosis patients based on emerging safety data until it is deemed to be clinically appropriate for monitoring to stop after consultation with the Medical Monitor.

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 7, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 7.

Table 7 Protocol Required Clinical Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
	Prothrombin Time		Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Phosphate	Bicarbonate		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein in healthy subjects is abnormal)			
Core Urine Monitoring Asssessments	• Spot UPC ratio • Glycosuria using dipstix • Urine pH using a pH meter			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)			

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 6 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

7.3.7. High Sensitivity Cardiac Troponin-T (hs-cTnT) Monitoring after a Cardiac Arrhythmia in Part B, or Part C

Baseline hs-cTnT: In Part B and Part C, all subjects will have hs-cTn level for purposes of screening as well as to provide baseline with which to compare, in the event that a subject develops a clinically concerning cardiac arrhythmic event after dosing with GSK3039294.

Subjects should be advised by the local study site to abstain from strenuous exercise (e.g. running or gym work) ≤ 24 hours before a baseline hs-cTn level is taken.

Monitoring of hs-cTnT after an Arrhythmia Event: A blood samples for hs-cTnT will be taken immediately at the time of onset of a cardiac arrhythmia which is deemed by the Investigator to be of clinical concern (see Section 5.4.4), *or* where there is electrophysiological diagnostic uncertainty.

High-sensitivity 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 if this is deemed clinically necessary by the Investigator.

Additional investigations, including but not restricted to serial ECGs and evaluation of cardiac function using echocardiogram and / or cardiac magnetic resonance (CMR) imaging, can be performed at the discretion of the Investigator in consultation with the Medical Monitor and a cardiologist.

7.3.8. Renal Safety Monitoring

All urine studies will be performed in the early morning prior to eating in healthy volunteers (with the expection of the Part B, Day 4 which will be fasting) and patients.

For all Parts of the study, a urine sample will be taken and stored from individual subjects at baseline for each dose level in Part A, at the beginning of week 1 for repeat dosing in Parts B & C, and at the beginning of week 2 in Part B only (see T&E Table).

Core renal parameters will assessed frequently as shown in the T&E Tables.

Table 8 Monitoring of Renal Functions

Subject Group	Core Renal Parameters	Assessments
Healthy Volunteers	Detection of Protinuria	Spot UPC ratio
Healthy Volunteers & Patients	Assessments of Renal Function	Changes in Serum Creatinine
Healthy Volunteers & Patients	Assessment of Tubule Function	-Glycosuria using dipstix -Urine pH using a pH meter

Subject Group	Core Renal Parameters	Assessments
		-Plasma phosphate levels
Healthy Volunteers & Patients	Assessment of Metabolic Acidosis (if required)	Whenever urine pH is confirmed to be < 6.0 on an average of three readings over 10 minutes from the same urine sample additional assesments e.g. a venous bicarbonate analysis will be initially performed. If this is deemed to be low, an arterial blood gas (ABG) must then be performed to investigate development of metabolic acidosis.

7.3.8.1. Guidance on the Clinical Approach for Suspected Renal Injury

If Renal Injury is Suspected (any subject), additional urine samples will be taken on a prospective basis if biochemical signatures of renal injury are detected at any time during the study. Urine samples will be analysed for biomarkers of renal injury (e.g. KIM-1 and NGAL), as well as for the presence of small molecular proteins (e.g. cystatin C & α1-microglobulin). The Investigator should liaise with a local nephrologist as regards any additional investigations which may be necessary to confirm either that renal injury has occurred or its nature.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of GSK3039294 (pro-drug), and GSK2315698 (CPHPC) will be collected at the time points indicated. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Part A (Single dose to Healthy Volunteers):

Pre-dose, and 0.25; 0.5; 0.75; 1; 1.5; 2; 3; 4; 5; 6; 8; 10; 12; 16; 24 and 48 hrs post-dose.

Part B – Cohort 3 (7 day repeat dose to Healthy Volunteers):

Study Day	PK sampling timepoint(s)
1	Pre-dose, and 0.5, 1, 2, 3, 4, 6 hrs post-dose
2&3	Pre-dose
4*	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
Follow-up (7 – 14 days post-dose)	Single sample

*Day 4 PK samples will not be collected for sentinel subjects

Part B – Cohort 4a/b (21 day repeat dose to Healthy Volunteers):

Study Day	PK sampling timepoint(s)
1	Pre-dose, and 2hr post-dose (1st dose of the day only)
2-4	Pre-dose (before 1st dose of the day only)
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose (1st dose of the day only)
21	Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before next dose administration
Follow-up (7 – 14 days post-dose)	Single sample

If a dose adjustment is required within the 21 day repeat dose period, PK samples will also taken at timepoints indicated below. **Note:** The 'Dose Day' relates to the first day of the adjusted dose, and not the study day.

Dose Day	PK sampling timepoint(s)
-1	Pre-dose
1	Pre-dose, and 2hr post-dose (1st dose of the day only)
2-4	Pre-dose (before 1st dose of the day only)
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose (1st dose of the day only)
Study Day	
21	Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before next dose administration
Follow-up (7 – 14 days post-dose)	Single sample

Part C (Repeat dose to patients):

Study Day	PK sampling timepoint(s)
1	Pre-dose, and 0.25; 0.5; 0.75; 1; 1.5; 2; 3; 4; 5; 6; 8; 10 and 12 hrs post-dose (note: 12hr post-dose sample to be taken before next dose administration)
2-7	Pre-dose (before 1st dose of the day only)
8-20	Pre-dose (before 1st dose of the day only) on days that a visit is planned
21	Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before next dose administration)
During Follow-up	1 sample/wk (for first 2 weeks only)

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

7.4.2. Urine Collection

Urine samples for exploratory analysis of GSK3039294, GSK2315698 and possible metabolites will be collected. Details of PK urine sample collection, processing, storage and shipping procedures are provided in the SRM.

7.4.3. Sample Analysis

Pharmacokinetic sample analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the Study Reference Manual (SRM). Concentrations of GSK3039294 and GSK2315698 will be determined in blood and plasma samples, respectively, using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once blood / plasma has been analyzed for GSK3039294 and GSK2315698 any remaining blood and plasma extracts may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK, GlaxoSmithKline protocol. The urine samples will be analysed for compound-related material and the results will be reported under a separate DMPK protocol.

7.5. Biomarker(s)/Pharmacodynamic Markers

Blood samples for pharmacodynamic (PD) analysis will be collected at the time points indicated . The actual date and time of each blood sample collection will be recorded. The timing of PD samples may be altered and/or PD samples may be obtained at additional time points to ensure thorough PD monitoring.

Sampling times for SAP samples are given in Table 9 and Table 10 The timing of SAP samples may be altered and/or SAP samples may be obtained at additional time points to ensure thorough SAP monitoring. At each time point samples will be taken from all subjects, however, samples will be analysed on a needs basis.

Blood samples taken in Part B for PD analysis will also be used for the development and validation of a companion diagnostic assay for the analysis of SAP. Blood for this will be taken as an aliquot and stored from the sample that is already being taken for PD analysis.

Table 9 Part B (repeat dose to Healthy Volunteers)

Cohort 3 (7 day repeat dose to Healthy Volunteers):

Study Day	**PD sampling timepoint(s)**
1	Pre-dose, and 2hr post-dose
2 and 4	Pre-dose
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
7	Pre-dose (before 1st dose of the day only)
Follow-up (7 – 14 days post-dose)	Single sample

Cohort 4a/b (21 day repeat dose to Healthy Volunteers):

Study Day	**PD sampling timepoint(s)**
1	Pre-dose, and 2hr post-dose (1st dose only)
2 and 4	Pre-dose (before 1st dose of the day only)
5	Pre-dose, and 2hr post-dose (1st dose of the day only)
Follow-up (7 – 14 days post-dose)	Single sample

If a dose adjustment is required within the 21 day repeat dose period (Cohort 4a/4b), PD samples will also taken at timepoints indicated below. **Note:** The 'Dose Day' relates to the first day of the adjusted dose, and not the study day.

Dose Day	**PD sampling timepoint(s)**
-1	Pre-dose
1	Pre-dose, and 2hr post-dose (1st dose only)
2-4	Pre-dose (before 1st dose of the day only)
5	Pre-dose, and 2hr post-dose (1st dose of the day only)
Study Day	
Follow-up (7 – 14 days post-dose)	Single sample

Table 10 Part C (Repeat dose to Patients)

Study Day	**PD sampling timepoint(s)**
1	Pre-dose, and; 2; 4; 6; and 12 hrs post-dose (note: 12hr post-dose sample to be taken before next dose administration)
2-7	Pre-dose (before 1st dose of the day only)
8-20	Pre-dose (before 1st dose of the day only) on days that a visit is planned
21	Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before

Study Day	PD sampling timepoint(s)
	next dose administration)
Safety Follow-up	Single sample
PD Follow-up	1 sample/wk up to 6 weeks

7.6. Genetics

In the event of an unexpected PK profile (i.e. increased or decreased metabolism of GSK3039294) being observed in an individual subject during any Part of the study, germline SNP analysis for recognised esterase-encoded genes which have been previously implicated in the dysfunctional metabolism of other esterase-cleaved prodrugs (e.g. CES-1 in oseltamivir), or genome-wide locus agnostic analysis, will be initiated from the stored blood samples of the affected individual subject(s). In addition, the stored blood samples of the remaining unaffected subjects within that particular part of the study will also undergo SNP analysis. This will facilitate comparative SNP data analysis of the affected subject(s) versus the rest of the study population.

Information regarding genetic research will be included in Appendix 3.

8. DATA MANAGEMENT

- For this study, the data collection tool will be PIMS, a validated computer software program. In all cases, subject initials will be collected in source documentation at the site but will not be transmitted to GSK sponsor team.
- Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK. Subject initials will not be transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

No formal hypotheses will be tested in this study.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size for this study is based primarily on feasibility. An assessment of the planned sample size has been based on the level of precision the study would provide

around the estimated true rate of a given safety event and around the estimated SAP depletion levels for a given dose.

9.2.1.1. Safety

Table 11 presents the 95% credible interval for the true event rate of a specific AE, assuming various observed AE rates and a sample size of 6 and 12. Here the credible interval specifies with a fixed probability of 95%, a range of values for the true AE rate after updating some prior position on the true AE rate with the AE data observed during the study. In general, a larger sample size will yield a narrower 95% credible interval.

For example, if we observe one specific adverse event in a single cohort/dosing session with n=6, ie an observed AE rate of 17%, then there is a 95% probability that the true AE rate lies between 4 and 58%. This implies that a true AE rate of greater than 58% could occur, though with a 2.5% probability.

Similarly, if we observe one specific adverse event in a single cohort/dosing session with n=12, ie an observed AE rate of 8%, then there is a 95% probability that the true AE rate lies between 2 and 36%. This implies that a true AE rate of greater than 36% could occur, though with a 2.5% probability.

Table 11 95% credible intervals for observed adverse event rate

Number of subjects per cohort/dose (n)	Observed number subjects with adverse event	Observed adverse event rate	95% credible interval for adverse event rate, given observed data[1]
6	0	0.00	(0.00, 0.41)
6	1	0.17	(0.04, 0.58)
6	2	0.33	(0.10, 0.71)
12	0	0.00	(0.00, 0.25)
12	1	0.08	(0.02, 0.36)
12	2	0.17	(0.05, 0.45)

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

9.2.1.2. Pharmacodynamics (Plasma SAP)

The standard deviation of log-transformed post-dose plasma SAP depletion levels, based on completed CPHPC studies to date, is assumed to be approximately 0.3 in healthy volunteers and between 0.7 and 0.9 in systemic amyloidosis patients.

With an assumed standard deviation of 0.9 for log-transformed post-dose plasma SAP depletion levels, and 6 subjects, the upper limit of the 95% confidence interval (CI) around the observed geometric mean post-dose plasma SAP level will be 2.57 times the observed geometric mean. Hence, if we observe a geometric mean post-dose plasma SAP level of 2mg/L, then the upper limit of the 95% CI around this observed geometric mean

will be approximately 5.1mg/L. Similarly, if we observe a geometric mean post-dose plasma SAP level of 0.5mg/L, then the upper limit of the 95% CI around this observed geometric mean will be approximately 1.3mg/L.

A small gain in precision is achieved with more than 6 subjects (see Section 9.2.2, Sample Size Sensitivity).

9.2.2. Sample Size Sensitivity

An assessment of sample size sensitivity has been based on the level of precision the study would provide around the estimated true rate of a given safety event and around the estimated SAP depletion levels for a given dose.

9.2.2.1. Safety

Table 12 presents the 95% credible interval for the true event rate of a given AE, assuming various observed AE rates and selected sample sizes between 5 and 20.

Sample sizes of less than 6 per cohort/dosing session were not planned since this would mean, irrespective of the number of events for a given AE in a single cohort/dosing session (i.e. an observed AE rate of ≥0%) that the upper limit of the 95% credible interval for the true AE rate would range as high as approximately 50% or more.

Sample sizes greater than 12 per cohort/dosing session were not planned since in order to provide significant gains in terms of safety information, the sample size would need to be increased beyond feasibility. For example, with a sample size of 20, if we observe one given adverse event (ie an observed AE rate of 5%) then a 95% credible interval about the true AE rate would still have an upper limit as high as 24%.

Table 12 95% credible intervals for observed adverse event rate

N	Observed number subjects with adverse event	Observed adverse event rate	95% credible interval for adverse event rate, given observed data[1]
5	0	0.00	(0.00, 0.46)
5	1	0.20	(0.04, 0.64)
6	0	0.00	(0.00, 0.41)
6	1	0.17	(0.04, 0.58)
8	0	0.00	(0.00, 0.34)
8	1	0.13	(0.03, 0.48)
10	0	0.00	(0.00, 0.28)
10	1	0.10	(0.02, 0.41)

N	Observed number subjects with adverse event	Observed adverse event rate	95% credible interval for adverse event rate, given observed data[1]
12	0	0.00	(0.00, 0.25)
12	1	0.08	(0.02, 0.36)
14	0	0.00	(0.00, 0.22)
14	1	0.07	(0.02, 0.32)
16	0	0.00	(0.00, 0.20)
16	1	0.06	(0.01, 0.29)
18	0	0.00	(0.00, 0.18)
18	1	0.06	(0.01, 0.26)
20	0	0.00	(0.00, 0.16)
20	1	0.05	(0.01, 0.24)

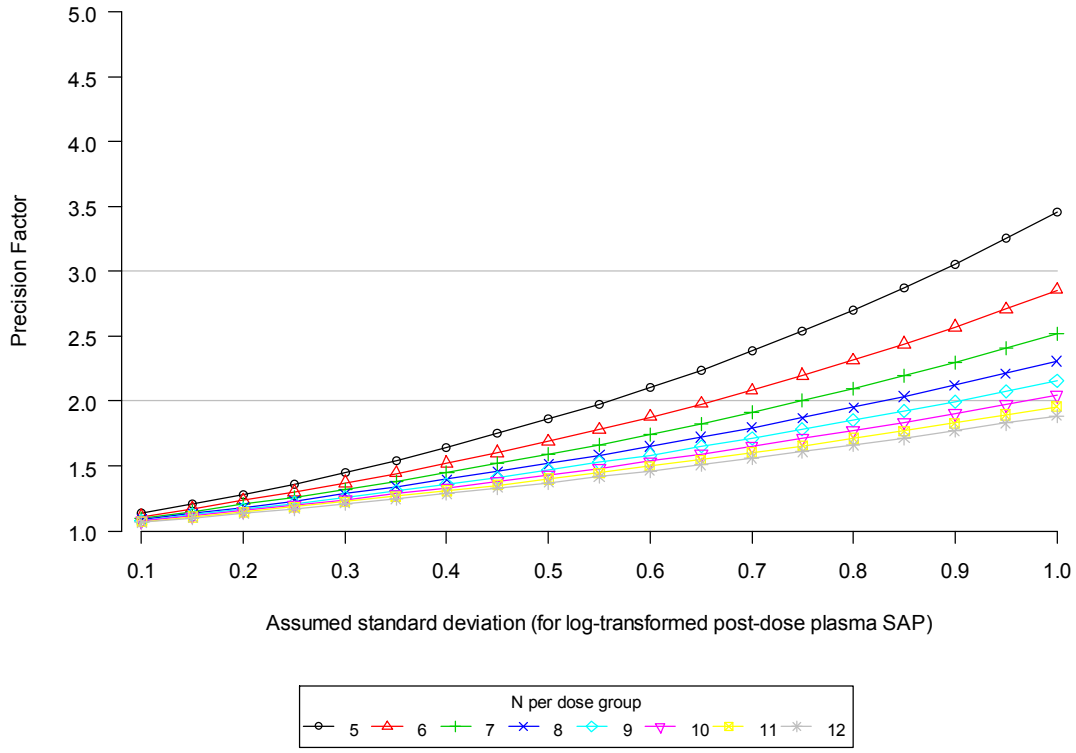
(1) derived within a Bayesian framework with a non-informative conjugate prior distribution Beta(1,1)

9.2.2.2. Pharmacodynamics (Plasma SAP)

Figure 5 shows how the precision around the observed geometric mean post-dose plasma SAP levels improves with decreasing standard deviation and increasing sample size (i.e. the factor by which the upper 95% CI is above the observed geometric mean decreases with decreasing standard deviation and increasing sample size).

Given an expected post-dose depletion level for plasma SAP to less than 2mg/L, no significant improvement in precision would be achieved with greater than 6 subjects. Similarly, precision levels across the explored range of standard deviations would not differ significantly.

Figure 6 Impact of standard deviation and sample size on precision



Upper limit of 95% CI = (estimated post-dose plasma SAP) x (precision factor)
Lower limit of 95% CI = (estimated post-dose plasma SAP) / (precision factor)

9.2.3. Sample Size Re-estimation or Adjustment

Additional subjects/cohorts may be enrolled to allow for further evaluation of a given dose or for evaluation of additional dose levels.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Safety Population:

This population is defined as all subjects who received at least one dose of study medication. This will be the primary population for assessing safety.

PK Population:

This population is defined as all subjects administered at least one dose of study medication and who have at least one PK sample taken and analysed. This will be the primary population for assessing PK. Subjects will be classified by the actual dose received.

PD Population:

This population is defined as all subjects who received at least one dose of study medication and who also have a baseline measurement and at least one post-treatment PD measure. This will be the primary population for assessing PD. Subjects will be classified by the actual dose received.

PK/PD Population:

This population is defined as all subjects included in both the PK and PD populations. This will be the primary population for PK/PD modelling. Subjects will be classified by the actual dose received.

9.3.2. Interim Analysis

Data will be reviewed on an ongoing basis throughout the study by the study team and investigator in order to inform dosing decisions for subsequent dosing sessions, cohorts and study parts. Dose escalation meetings will be held prior to increasing the dose. Key data to inform dosing decisions will include but not be limited to: safety (AEs, clinical laboratory data, vital signs and ECGs), PK (concentrations of GSK2315698, and if possible, GSK3039294 and the intermediate molecule GSK3037412), and plasma SAP levels (Parts B & C only).

In addition to the ongoing review of data throughout the study, at the end of Part B, individual profiles over time will be presented graphically for selected urine and plasma laboratory parameters pertaining to the kidney. Individual profiles will be presented for both single and repeat-dose healthy volunteer data to further inform the evaluation of renal safety and the decision to progress to repeat dosing in systemic amyloidosis patients in Part C.

9.3.2.1. Pharmacokinetics and pharmacodynamics

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

To inform dosing decisions for subsequent study parts, GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698 [Sahota, 2015]. Based on pre-clinical data it is expected that the conversion of GSK3039294 to GSK2315698 is very fast. Therefore, it can be assumed that this conversion will occur mainly during the absorption phase, and that the

distribution and elimination of GSK2315968 are not altered. Therefore, all distribution and elimination parameters (PK/PD) will be fixed to the reported parameter estimates, and only bioavailability (F) and absorption related parameters (e.g. Ka) will be estimated. Nominal time points will be used for this interim analysis. This updated model will be used to simulate concentration-time data and plasma SAP levels using different dose levels and dosing regimens, which will be used to inform dosing decisions for subsequent dosing sessions, cohorts and study parts.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Safety data will be listed and presented in tabular and/or graphical format, as appropriate, and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.2. Secondary Analyses

9.4.2.1. Pharmacokinetics, pharmacodynamics and PK/PD model

Concentration data of GSK2315698 and GSK3039294 will be listed and presented in tabular and graphical format, as appropriate, and summarised descriptively. Further details will be described in the RAP.

Individual plasma SAP profiles over time will be listed and presented graphically. Plasma SAP levels will be log-transformed, or other transformation as appropriate, and summarised over time by cohort/dose, together with corresponding 95% confidence intervals. Further details will be described in the RAP.

GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698 [Sahota, 2015]. Based on pre-clinical data it is expected that the conversion of GSK3039294 to GSK2315698 is very fast. Therefore, it can be assumed that this conversion will occur mainly during the absorption phase, and that the distribution and elimination of GSK2315698 are not altered. GSK3039294 and the intermediate molecule GSK3037412 do not affect plasma SAP levels, and therefore it can be assumed that the PK/PD relationship between GSK2315698 and SAP is not changed. Therefore, all distribution and elimination parameters and all PD parameters will be fixed to the reported parameter estimates, and only bioavailability (F) and absorption related parameters (e.g. Ka) will be estimated. If needed, the PK/PD model may be updated in a data driven fashion. Actual time points will be used for this final analysis. Further details will be described in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the PIMS record will serve as the source document.

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

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

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

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

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

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

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

10.7.1. Dose Escalation Committee

The decision to proceed to the next dose level of GSK3039294 in Parts A and B, or to proceed to the next study part will be made by a Dose Escalation Committee (DEC) consisting of the Principal Investigator, Medical Monitor, GSK Study Team Leader, GSK Pharmacokineticist and GSK Statistician (or appropriate designee's)**.**

For Part A, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK3039294 at the prior dose level(s). The review data set will at a minimum consist of all available PK data, adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings.

The decision and selection of dose to proceed to Part B as well as any dose escalation decisions, will be made by the DEC based on all available PK data. the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings.

The decision and selection of dose to proceed to Part C, will be made by the DEC based at a minimum on available PK data the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available PD data from the dose levels investigated in Part A, and available PK the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available PD data from the dose levels investigated in Part B.

For further details related to the planned PK and PK/PD analyses to support the dose escalations, see Section 9.3.2.1. A maximum Cmax of 22.1 μg/mL and AUC[0-24] of 250 μg.hr/mL will not be exceeded in any cohort or study part.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

µg	Micrograms
AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area Under the Curve
BID	Twice Dialy
BMI	Body Mass Index
CI	Confidence Interval
Cmax	Concentration (maximal)
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DEC	Dose Escalation Committee
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Echocardiogram
EDTA	Ethylenediaminetetraacetic acid
F	Bioavailability
FDA	Food and Drug Administration
FLC	Free Light Chain
FSH	Follicle-Stimulating Hormone
g	Grams
GFR	Glomerular filtration rate
GI	GastroIntestinal
GSK	GlaxoSmithKline
h(r)	Hour
i.v.	Intravenous
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	Kilograms
L	Litres
mAb	Monoclonal Antibody
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
msec	Millisecond
NYHA	New York Heart Association
OD	Once Dialy

PD	Pharmacodynamic
pg	Picograms
PIMS	Phase 1 Monitoring System
PK	Pharmacokinetic
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Serum Amyloid P component
SNP	Single Nucleotide Polymorphism
SRM	Study Referene Manual
ULN	Upper Limit of Normal
UPC	Urine Protein Creatinine

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: 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 (in alignment with the FDA premarketing clinical liver safety guidance).

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

12.2.1. Healthy Volunteers:

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 following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• 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 event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, 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</td><td colspan="2">• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 48 hours of last dose[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 report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
within baseline • A specialist or hepatology consultation is recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • 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 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; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

12.2.2. Patients

Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	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

Required Actions and Follow up Assessments following Liver Stopping Event	
Actions	**Follow Up Assessments**
• **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 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. Permanently discontinue study treatment and may 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, 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>**	• Viral hepatitis serology[3] • Blood sample for pharmacokinetic (PK) analysis, obtained within 48 hours of last dose[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 report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<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).

Liver Chemistry Stopping Criteria – Liver Stopping Event	
• 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	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **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 (excludingstudies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

12.3. Appendix 3 - Genetic Investigation of Individuals

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to any treatment regimens under investigation in this study

Genetic data may be generated while the study is underway or following completion of the study. Single Nucleotide Polymorphism (SNP) analysis for recognised esterase-encoded genes which have been previously implicated in the dysfunctional metabolism of other esterase-cleaved prodrugs (e.g. CES-1 in oseltamivir), or genome-wide locus agnostic analysis, may be performed to investigate (for example) an unexpected PK or plasma SAP profile, and / or clinically concerning AEs being observed in an individual subject. Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

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

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies.

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

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

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

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

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

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

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

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

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

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

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

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

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or 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 disability/incapacity

NOTE:

- 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 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 reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.4.3. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs,

symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.4. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

information, amending the SAE data collection tool accordingly.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

12.4.5. Reporting of SAEs to GSK

SAE reporting to GSK via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail
- Initial notification via the 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 receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Protocol Amendment Changes

AMENDMENT 1

Where the Amendment Applies

Section 5.5 and Appendix 1.

Summary of Amendment Changes with Rationale

Changes requested by MHRA – Clarification of the stopping criteria. Addition of 'FLC' and definition to the Abbreviations table.

List of Specific Changes

Section 12.1 Appendix 1 – Abbreviations and Trademarks

REVISED TEXT

Addition of "FLC – Free Light Chain"

Section 5.5 – Stopping Criteria for the Entire Healthy Volunteer or Patient Study Groups

PREVIOUS TEXT

- If a suspected unexpected serious adverse reaction (SUSAR) is observed, as deemed by the investigator, in any subject at any one dose level of GSK3039294, continuation of the study will be temporarily halted and no further subjects will be dosed until a full safety review of the data has taken place.
- If the same severe adverse event is observed in two subjects across all study parts, and is reasonably attributable, in the opinion of the investigator, to GSK3039294, the study will be temporarily halted and no further subjects will be dosed until a full safety review of the study has taken place.
- If the study is temporarily halted, relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the applicable regulatory authority will take place as appropriate prior to any resumption of dosing
- Every effort will be made to take a blood sample for pharmacokinetic analysis from each affected individual at the time of any of the adverse events described above

REVISED TEXT

- ~~If a suspected unexpected serious adverse reaction (SUSAR) is observed, as deemed by the investigator~~, **If an SAE occurs that the investigator believes is reasonably attributable to IMP,** in any subject at any one dose level of GSK3039294, continuation of the study will be temporarily halted and no further subjects will be dosed until a full safety review of the data has taken place.

- If the same severe adverse event is observed in two subjects across all study parts, and is reasonably attributable, in the opinion of the investigator, to GSK3039294, the study will be temporarily halted and no further subjects will be dosed until a full safety review of the study has taken place.
- If the study is temporarily halted, relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the applicable regulatory authority will take place ~~as appropriate~~ prior to any resumption of dosing
- Every effort will be made to take a blood sample for pharmacokinetic analysis from each affected individual at the time of any of the adverse events described above

AMENDMENT 2

Where the Amendment Applies

Throughout the protocol.

Summary of Amendment Changes with Rationale

Changes requested by REC – Alteration of Part B of this study include a 7 days repeat dose and perform PK and safety review prior to starting 21 day repeat dose in healthy subjects.

List of Specific Changes

Protocol Synopsis – Treatment Arms and Duration

PREVIOUS TEXT

Two cohorts of subjects will be enrolled to provide data from 6 subjects per cohort and up to 4 different doses (2 dose levels per cohort) of GSK3039294 will be tested.

Subjects will be admitted to the unit on Day -1, following the dose on Day 1 subjects will remain in-house until Day 4. Wash-out will take place from Day 5 to Day 14.

Providing a review of the data from Dose 1 (safety data: AE, vital signs, ECG and laboratory safety test and PK data up to 48 h etc) is favourable, the next dose level will be administered.

Part B: Repeat dose escalation in healthy volunteers

A food effect exploration will be conducted at Days 4 and 5 of this repeat dose study cohort. On these days GSK3039294 will be administered under fasted and then under fed conditions

In a group of sufficient healthy volunteers to ensure 6 completers, the compound will be administered repeatedly for a total of 21 days.

the dose will be escalated every week throughout the study duration. Subjects will first receive a low dose given once daily. After 7 days, if well tolerated, the total daily dose will be increased and GSK3039294 will be given e.g. as bid dosing for 7 days. At the end of this 7 day period and if previous dosing was well tolerated, the dose will be increased to a maximum daily dose that will not exceed pre-clinical safety exposure limits.

Cohort 3b(*optional, only if required*): Based on data from, dose levels may be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days.

REVISED TEXT

Two cohorts **(cohorts 1 and 2)** of subjects will be enrolled to provide data from 6 subjects per cohort and up to 4 different doses (2 dose levels per cohort) of GSK3039294 will be tested.

Subjects will be admitted to the unit on Day -1, following the dose on Day 1 subjects will remain in-house until Day 4. Wash-out will take place from Day 5 to Day 14.

Providing a review of the data from **each dose** ~~Dose 1~~ (safety data: AE, vital signs, ECG and laboratory safety test and PK data up to 48 h etc) is favourable, the next dose level will be administered.

Part B: Repeat dose escalation in healthy volunteers

Cohort 3: In a group of healthy volunteers sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 7 days. The dose will be one that is expected to be well tolerated based on the single dose data and not predicted to exceed exposure limits based on single dose PK. Providing a review of the data (safety data: AE, vital signs, ECG, laboratory safety tests and PK) is favourable, Cohort 4 will be initiated.

A food effect exploration will be conducted at Days 4 and 5 of this ~~repeat dose study~~ cohort. On these days GSK3039294 will be administered under fasted and then under fed conditions

Cohort 4a: In a group of ~~sufficient~~ healthy volunteers **sufficient subjects will be enrolled** to ensure 6 completers, the ~~compound~~ **study drug** will be administered repeatedly for a total of 21 days.

The dose level for this cohort will be determined by a review of the safety and PK data from cohort 3. The dose may be adjusted (up or down) during the 21 dosing session based on preliminary PK collected during dosing and ongoing review of safety. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21.

~~the dose will be escalated every week throughout the study duration. Subjects will first receive a low dose given once daily. After 7 days, if well tolerated, the total daily dose will be increased and GSK3039294 will be given e.g. as bid dosing for 7 days. At the end of this 7 day period and if previous dosing was well tolerated, the dose will be increased to a~~ **The predicted** maximum daily **exposure** ~~dose that~~ will not exceed pre-clinical safety exposure limits.

Cohort 4b(*optional, only if required*): Based on data from **Cohorts 3 and 4a**, dose levels may be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days. ~~and more than one~~ **The dose level and / or dosing regimen may be altered once during the 21days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.**

Protocol Synopsis – Type and Number of Subjects

PREVIOUS TEXT

In **Part A**, sufficient healthy volunteers will be enrolled to ensure a total of 6 subjects per cohort have completed the in-patient phases.

In **Part B**, sufficient healthy volunteers will be enrolled to ensure a total of 6 subjects per cohort have completed the in-patient phases.

In **Part C**, 12 patients with systemic amyloidosis will be enrolled.

REVISED TEXT

In **Part A**, sufficient healthy volunteers will be enrolled to ensure ~~a total of~~ 6 subjects per cohort have completed the in-patient phases.

In **Part B**, sufficient healthy volunteers will be enrolled to ensure ~~a total of~~ 6 subjects per cohort have completed **each of** the in-patient phases.

In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same cohort at the discretion of the

Sponsor in consultation with the investigator. Replacement subjects do not need to have received the first dose for a given cohort to join the study in the second cohort.

In **Part C**, 12 patients with systemic amyloidosis will be enrolled. **If subjects prematurely discontinue, replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.**

Additional subjects/cohorts may be enrolled to allow for further evaluation of a given dose or for evaluation of additional dose levels.

Section 4.2.1 – Part A (single dose escalation in healthy volunteers)

PREVIOUS TEXT

Doses will be administered to Cohorts using a sentinel dosing approach. Subjects will be admitted to the unit on Day -1, following the dose on Day 1 subjects will remain in-house until Day 4. Wash-out will take place from Day 5 to Day 14.

Providing a review of the data from Dose 1 (safety data: AE, vital signs, ECG and laboratory safety test and PK data up to 48 h etc) is favourable, Dose level 2 will be administered. Cohort 1 will be used for 2 dosing periods (Doses 1 and 2), Cohort 2 will also be used for 2 dosing periods (Doses 3 and 4). A review of the data will always be conducted prior to the administration of the next dose level.

The planned doses for Dose levels 2, 3 and 4 may be modified based on emerging safety, tolerability and PK data. The number of dosing periods may be reduced or extended depending on emerging data. Replacement subjects in either Cohort do not need to have received the first dose prior to receiving the second dose.

Sentinel dosing: For all dose levels and if necessary (based on evaluation of the gathered safety data) for next dose levels, only 2 subjects will be dosed on Day 1, separated by at least 1 hour. If there are no safety or tolerability concerns, the rest of the cohort will be dosed the next day at appropriate intervals.

REVISED TEXT

Doses will be administered to Cohorts using a sentinel dosing approach **as described below.** Subjects will be admitted to the unit on Day -1, following the dose on Day 1 subjects will remain in-house until Day 4. Wash-out will take place from Day 5 to Day 14.

Providing a review of the data from **each dose** ~~Dose 1~~ (safety data: AE, vital signs, ECG and laboratory safety test and PK data up to 48 h etc) is favourable, **the next dose level** ~~Dose level 2~~ will be administered. Cohort 1 will be used for 2 dosing periods (Doses 1

and 2), Cohort 2 will also be used for 2 dosing periods (Doses 3 and 4). A review of the data will always be conducted prior to the administration of the next dose level.

The planned doses for Dose levels 2, 3 and 4 may be modified based on emerging safety, tolerability and PK data. The number of dosing periods may be reduced or extended depending on emerging data. Replacement subjects in either Cohort do not need to have received the first dose prior to receiving the second dose.

Sentinel dosing: For all dose levels **the subsequent subject will be dosed approximately 24 hrs after the preceding subject if there are no safety or tolerability concerns. The remaining subjects receiving the same dose within the cohort will receive the dose approximately 24hrs after the subsequent subject at intervals no less than 1hr apart**. ~~and if necessary (based on evaluation of the gathered safety data) for next dose levels, only 2 subjects will be dosed on Day 1, separated by at least 1 hour. If there are no safety or tolerability concerns, the rest of the cohort will be dosed the next day at appropriate intervals.~~

Table 1 – Cohorts 1 and 2 Study Duration

PREVIOUS TEXT

Washout Period	Up to 14 days

REVISED TEXT

Washout Period	**From Day 5 to Day 14**. ~~Up to 14 days~~

Section 4.2.1 – Part A (single dose escalation in healthy volunteers)

PREVIOUS TEXT

At the end of this single dose part, all PK data will be analysed (see Section 9.3.2) with all available safety data.

REVISED TEXT

At the end of this single dose part, all PK data will be analysed (see Section 9.3.2) **and reviewed together** with all available safety data.

Section 4.2.2 – Part B (repeat dose escalation in healthy volunteers)

PREVIOUS TEXT

A food effect exploration will be conducted at Days 4 and 5 of this repeat dose study. On these days GSK3039294 will be administered under fasted and then under fed conditions (please see SRM for details of meals), and PK samples will be taken to investigate the food effect on the PK.

Cohort 3a: In a group of sufficient healthy volunteers to ensure 6 completers, the compound will be administered repeatedly for a total of 21 days.

The dose will be escalated every week throughout the study duration. Subjects will first receive a low dose given once daily. After 7 days, if well tolerated, the total daily dose will be increased and GSK3039294 will be given e.g. as bid dosing for 7 days. At the end of this 7 day period and if previous dosing was well tolerated, the dose will be increased to a maximum daily dose that will not exceed pre-clinical safety exposure limits.

Data from Cohort 3a is expected to provide a good evaluation of the safety, tolerability and repeat-dose PK. The data will be evaluated using the PK/PD model to identify an optimal clinical dose (see Section 9.3.2.1). However, if it is determined that further investigation of dose levels are required before progressing to Part C (e.g. if the observations in Cohort 3a are different from those which the PK /PD modelling predicted), then recruitment into Cohort 3b may be initiated.

Cohort 3b (*optional, only if required*): Based on data from Cohorts 2 and 3a, dose levels will be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days.

Table 3 Cohort 3a (and 3b if required) Study Duration

Screening	All screening assessments to be completed within 28 days prior to the first dose
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until Day 5 when they will be discharged. Additional in-patient stays will be from Day 7 to 11, and Day 14 to 18. Subjects will self-administer their assigned dose when not in the clinical unit. Subjects will return as outpatients on Day 21, and again for a follow-up appointment.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 8-9 weeks

In Cohort 4b multiple dose levels and different regimens may be investigated based on data from Cohort 4a.

REVISED TEXT

Cohort 3: In a group of healthy volunteers sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 7 days. The dose will be one that is expected to be well tolerated based on the single dose data and predicted to not exceed exposure limits based on single dose PK. Providing a review of the data (safety data: AE, vital signs, ECG, laboratory safety tests and PK) is favourable, Cohort 4 will be initiated.

Sentinel dosing: The subsequent subjects will be dosed after the first subject has completed all dosing days if there are no safety or tolerability concerns.

A food effect exploration will be conducted at Days 4 and 5 of this ~~repeat dose study~~ **cohort**. On these days GSK3039294 will be administered under fasted and then under fed conditions (please see SRM for details of meals), and PK samples will be taken to investigate the food effect on the PK.

Cohort 4a: In a group of ~~sufficient~~ healthy volunteers **sufficient subjects will be enrolled** to ensure 6 completers, the ~~compound~~ **study drug** will be administered repeatedly for a total of 21 days.

The dose level for this cohort will be determined by a review of the safety and PK data from cohort 3. The dose may be adjusted (up or down) during the 21 day dosing session based on preliminary PK collected during dosing and ongoing review of safety. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21.

~~the dose will be escalated every week throughout the study duration. Subjects will first receive a low dose given once daily. After 7 days, if well tolerated, the total daily dose will be increased and GSK3039294 will be given e.g. as bid dosing for 7 days. At the end of this 7 day period and if previous dosing was well tolerated, the dose will be increased to a~~ **The predicted** maximum daily **exposure** ~~dose that~~ will not exceed pre-clinical safety exposure limits.

Data from **cohorts 3 and 4a** ~~3a~~ **are** ~~is~~ expected to provide a good evaluation of the safety, tolerability and repeat-dose PK. The data will be evaluated using the PK/PD model to identify an optimal clinical dose (see Section 9.3.2.1). However, if it is determined that further investigation of dose levels are required before progressing to Part C (e.g. if the observations in **cohort 4a** ~~3a~~ are different from those which the PK /PD modelling predicted), then recruitment into **Cohort 4b**~~3b~~ may be initiated.

Cohort 4b (*optional, only if required*): Based on data from **Cohorts 3 and 4a**, dose levels will be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days. ~~and more than one~~ **The dose level and / or dosing regimen may be altered once during the 21 days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.**

Table 2 Cohort 3

Screening	**All screening assessments to be completed within 28 days prior to the first dose**
Treatment Period	**Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until Day 8 when they will be discharged.**
Follow-up	**At least 7 days and no greater than 21 days after last study drug administration** **Additional follow-up visits may be scheduled, if warranted**
Total Duration	**Approximately 7 weeks**

Table 3 Cohort 4a (and 4b if required) Study Duration

Screening	All screening assessments to be completed within 28 days prior to the first dose
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until ~~Day 5~~ **Day 7** when they will be discharged. ~~Additional in-patient stays will be from Day 7 to 11, and Day 14 to 18.~~ Subjects will self-administer their assigned dose when not in the clinical unit. Subjects will return as outpatients on Day 21, and again for a follow-up appointment. **Subjects may return to the clinic after Day 7 for an adjustment to their dose should a review of interim PK data require this. If a dose adjustment is made, subjects will be in-patient until they have received the new dose for 7 days, when they will be discharged.**
Follow-up	At least 7 days and no greater than 14 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 8-9 weeks

In Cohort 4b multiple dose levels and different regimens may be investigated based on data from Cohort 4a. ****Day of Potential Dose Alteration not specified as this will be performed following review of safety and PK data from previous dose.***

Section 4.3 – Type and Number of Subjects

PREVIOUS TEXT

In **Part A**, sufficient healthy volunteers will be enrolled to ensure a total of 6 subjects per cohort have completed the in-patient phases.

In **Part B**, sufficient healthy volunteers will be enrolled to ensure a total of 6 subjects per cohort have completed the in-patient phases

In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same treatment at the discretion of the Sponsor in consultation with the investigator.

REVISED TEXT

In **Part A**, sufficient healthy volunteers will be enrolled to ensure ~~a total of~~ 6 subjects per cohort have completed the in-patient phases.

In **Part B**, sufficient healthy volunteers will be enrolled to ensure ~~a total of~~ 6 subjects per cohort have completed the in-patient phases

~~In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same treatment at the discretion of the Sponsor in consultation with the investigator.~~

In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same cohort at the discretion of the Sponsor in consultation with the investigator. Replacement subjects do not need to have received the first dose for a given cohort to join the study in the second cohort.

Section 4.4 – Design Justification

PREVIOUS TEXT

The maximum duration of 21 days for Part B was selected to reflect the likely duration of treatment needed for clinical use with the anti SAP monoclonal antibody. The duration of 7 days treatment before dose escalation was chosen as, based on the half life of CPHPC of approximately 18 hrs, steady state PK will be achieved by 4 days.

REVISED TEXT

The duration of 7 days for Cohort 3 Part B was selected as steady state is predicted to be achieved in this time. The ~~maximum~~ duration of 21 days for **Cohorts 4a and 4b in** Part B was selected to reflect the likely duration of treatment needed for clinical use with the anti SAP monoclonal antibody. ~~The duration of 7 days treatment before dose escalation was chosen as, based on the half life of CPHPC of approximately 18 hrs, steady state PK will be achieved by 4 days.~~

Section 4.5 – Dose Justification

PREVIOUS TEXT

Part B

The dose level in Part B will be determined based on the PK data obtained in Part A, by analysing all available PK data from Part A and subsequently predicting concentration-time profiles at steady state after repeat dosing (see Section 9.3.2.1). The dose levels and dosing frequencies will be chosen such that the predicted 95% CI of Cmax and AUC at steady state will not exceed preclinical Cmax and AUC limits (22.1 μg/mL and 250 μg.hr/mL, respectively).

REVISED TEXT

Part B

The dose level **for Cohort 3** in Part B will be determined based on the PK data obtained in Part A, by analysing all available PK data from Part A and subsequently predicting concentration-time profiles at steady state after repeat dosing. **Table 3 shows examples of dose levels and frequencies with predicted AUC[0-24] and Cmax at steady state, using the PK/PD model that was developed for CPHPC (active molecule) [Sahota, 2015], adjusted for oral absorption and conversion of GSK3039294 into CPHPC. The PK data from Part A will be used to obtain estimates for Ka and F.**

Table 5 Example Doses And Predicted Exposures For Part B

Dose	Ka	F	AUC[0-24h] (μg.hr/mL) *)	Cmax (μg/mL) *)
Cohort 3				
300mg OD	1.3	1	23.4 (15.3-35.9)	5.20 (3.32-7.84)
300mg OD	1.3	0.5	11.4 (7.36-18.1)	2.61 (1.72-3.86)
300mg OD	0.6	1	22.8 (14.7-36.2)	3.83 (2.73-5.42)
Cohort 4a (first part)				

Dose	**Ka**	**F**	**AUC[0-24h] (µg.hr/mL) *)**	**Cmax (µg/mL) *)**
300mg BID	**1.3**	**1**	**45.7 (29.4-72.5)**	**5.49 (3.75-8.05)**
300mg BID	**1.3**	**0.5**	**22.8 (14.7-36.2)**	**2.74 (1.87-4.02)**
300mg BID	**0.6**	**1**	**45.7 (29.4-72.5)**	**4.09 (2.94-5.76)**
Cohort 4a (last part)				
600mg BID	**1.3**	**1**	**91.3 (58.9-145)**	**11.0 (7.50-16.1)**
600mg BID	**1.3**	**0.5**	**45.7 (29.4-72.5)**	**5.49 (3.75-8.05)**
600mg BID	**0.6**	**1**	**91.3 (58.9-145)**	**8.19 (5.88-11.5)**

***) Predicted AUC[0-24] and Cmax at steady state; presented are mean and 95%CI**

The dose levels for subsequent cohorts in Part B will be determined based on the PK data from Part A (single dose), and cohort 3 in Part B (multiple dose). All available PK data will be analysed (see Section 9.3.2.1). The dose levels and dosing frequencies will be chosen such that the predicted 95% CI of Cmax and AUC at steady state will not exceed preclinical Cmax and AUC limits (22.1 µg/mL and 250 µg.hr/mL, respectively).

Section 4.6.1 – Risk Assessment

PREVIOUS TEXT

A potential effect of food will be explored in this study (Week 1 of Part B).

REVISED TEXT

A potential effect of food will be explored in this study (~~Week 1~~ **Cohort 3** of Part B).

Section 5.1 – Inclusion Criteria, All Subjects, 3 Weight

PREVIOUS TEXT

Body weight > 50kg and body mass index (BMI) within the range 18.5-32 kg/m2 (inclusive) and excluding the effects of peripheral oedema.

REVISED TEXT

Body weight > 50kg and body mass index (BMI) ~~within the range~~ **≥** 18~~.5-32~~ kg/m2 (inclusive) and excluding the effects of peripheral oedema.

Section 5.1 – Additional Inclusion Criteria – Patients

PREVIOUS TEXT

SAP scan identifying amyloid at any anatomical site, including subset of patients with moderate-large amyloid load in the liver

Up to and including NYHA class 2 with a stable clinical cardiac status 12 weeks prior to screening

For AL amyloidosis patients, ≥12 months post-chemotherapy with a stable FLC ratio in the preceding 4 months

REVISED TEXT

SAP scan identifying amyloid at any anatomical site, including subset of patients with ~~moderate-~~large amyloid load in the liver

Up to and including NYHA class 2 ~~with a stable clinical cardiac status 12 weeks prior to screening~~

For AL amyloidosis patients, ≥~~12~~ **6** months post-chemotherapy with a stable FLC ratio ~~in the preceding 4 months~~

Section 5.2. – Exclusion Criteria – All Subjects

PREVIOUS TEXT

A positive pre-study drug/alcohol screen

REVISED TEXT

A positive pre-study drug/alcohol screen **(unless a positive test is due to prescribed medications)**

Section 5.2. – Additional Exclusion Criteria – Patients

PREVIOUS TEXT

First degree heart block deemed to require pacing; Second degree AV block Mobitz Type II; Trifasicular block; Ventricular tachyarrthymias – with the exception of

bundle branch block, atrial fibrillation & first degree heart block not requiring pacing, or second degree AV block Mobitz Type I

24 hour proteinuria ≥5g

A syncopal episode, of any causation, within 4 weeks of screening

Average SBP ≤ 90 mmHg at Screening from triplicate readings

Implantable cardiac defibrillator (ICD)

Evidence of severe cardiac dysfunction within 12 months of screening, as diagnosed by a cardiologist, using Echocardiography or cardiac MRI i.e. markedly impaired ejection fraction (EF < 50% for cardiac amyloidosis patients), or cardiac imaging parameters of severe diastolic dysfunction (grade 3 or 4)

REVISED TEXT

~~First degree heart block deemed to require pacing; Second degree AV block Mobitz Type II; Trifasicular block; Ventricular tachyarrthymias – with the exception of bundle branch block, atrial fibrillation & first degree heart block not requiring pacing, or second degree AV block Mobitz Type I~~

~~24 hour proteinuria ≥5g~~ **Plasma albumin < 30g/litre**

A syncopal episode~~, of any causation,~~ within 4 weeks of screening

Average SBP ≤ 90 mmHg at Screening from triplicate readings

Implantable cardiac defibrillator (ICD)

Insertion of permanent pacemaker in last 2 months

~~Evidence of severe cardiac dysfunction within 12 months of screening, as diagnosed by a cardiologist, using Echocardiography or cardiac MRI i.e. markedly impaired ejection fraction (EF < 50% for cardiac amyloidosis patients), or cardiac imaging parameters of severe diastolic dysfunction (grade 3 or 4)~~ **Decompensated or uncontrolled heart failure in last 2 months**

Section 5.4.1 – Cardiovascular Safety Stopping Criteria

PREVIOUS TEXT

Chest pain at rest or exertion at any time after drug administration and is reasonably attributable to GSK3039294, with proven or suspected changes of cardiac ischaemia on a 12-lead ECG.

Development of pulmonary oedema or uncontrolled congestive cardiac failure which is reasonably attributable to GSK303294.

Systolic blood pressure > 170 mmHg as an average of triplicate readings taken at rest over 15 minutes on three consecutive days at any time after drug administration and is reasonably attributable to GSK3039294.

Healthy Volunteers & Amyloidosis Patients without bundle branch block: QTcF > 500 msec, (or a change from baseline of QTcF > 60 msec on a 12-lead ECG in healthy volunteers) at any time after drug administration and is reasonably attributable to GSK3039294 on an average from triplicate readings (see Section 5.4.3).

Systemic Amyloidosis patients with bundle branch block - if baseline QTcF < 450 msec: QTcF > 500 msec on a 12-lead ECG at any time after administration of GSK3039294; If baseline QTcF 450-480 msec: QTcF > 530 msec at any time after drug administration and is reasonably attributable to GSK3039294, as an average of triplicate readings (see Section 5.4.3).

Arrhythmias which have developed from a baseline of sinus rhythm: Development of Atrial fibrillation, any type of tachy-arrhythmia (e.g. pulsed ventricular tachycardia or SVT), or any type of heart block (with the exception of transient first degree heart block in healthy volunteers), confirmed on a 12-lead ECG at any time after drug administration and is reasonably attributable to GSK3039294.

In systemic amyloidosis patients only: Development of sinus bradycardia ≤ 40 beats per minute (from a non-bradycardic baseline) lasting ≥ 10 minutes at any time after drug administration and is reasonably attributable to GSK3039294, or progression of first degree heart block (or second degree AV block Mobitz Type I) to any type of heart block requiring pacing.

REVISED TEXT

~~Chest pain at rest or exertion at any time after drug administration and is reasonably attributable to~~ **New onset or worsening symptoms of cardiac ischemia which is reasonably attributable to** GSK3039294~~, with proven or suspected changes of cardiac ischaemia on a 12-lead ECG.~~

Development of ~~pulmonary oedema or~~ **decompensated or** uncontrolled ~~congestive~~ cardiac failure which is reasonably attributable to GSK303294.

Systolic blood pressure > 170 mmHg as an average of triplicate readings taken at rest over 15 minutes on three consecutive days at any time after ~~drug~~ administration and is reasonably attributable to GSK3039294.

Healthy Volunteers & Amyloidosis Patients without bundle branch block: QTcF > 500 msec, (or a change from baseline of QTcF > 60 msec on a 12-lead ECG in healthy volunteers) ~~at any time after drug administration and is~~ **which is** reasonably

attributable to GSK3039294 on an average from triplicate readings (see Section 5.4.3).

Systemic Amyloidosis patients with bundle branch block - if baseline QTcF < 450 msec: QTcF > 500 msec on a 12-lead ECG at any time after administration of GSK3039294; If baseline QTcF 450-480 msec: QTcF > 530 msec at any time after drug administration and is reasonably attributable to GSK3039294, as an average of triplicate readings (see Section 5.4.3).

~~Arrhythmias~~ **Development of a new arrhythmia** ~~which have developed~~ from a baseline of sinus rhythm~~: Development of Atrial fibrillation, any type of tachy-arrhythmia (e.g. pulsed ventricular tachycardia or SVT), or any type of heart block (~~with the exception of transient first degree heart block ~~in healthy volunteers), confirmed on a 12-lead ECG at any time after drug administration~~ and **which** is reasonably attributable to GSK3039294.

~~In systemic amyloidosis patients only: Development of sinus bradycardia ≤ 40 beats per minute (from a non-bradycardic baseline) lasting ≥ 10 minutes at any time after drug administration and is reasonably attributable to GSK3039294, or progression of first degree heart block (or second degree AV block Mobitz Type I) to any type of heart block requiring pacing.~~

Section 6.10.1 – Meals and Dietary Restrictions

PREVIOUS TEXT

- In Part A, and during Week 1 of Part B, on all dosing days, subjects will be required to fast from midnight until 3 hours after administration of study treatment (with the exception of Day 5 of Part B in which subjects will be fed). At other times, snacks and meals will be provided by the clinical unit. Water will be allowed as desired except for one hour before and after drug administration.

- An investigation into a possible food effect will be conducted on Days 4 and 5 of Part B in this study. On Day 4 subjects will be fasted until following the collection of the 4hr post-dose PK sample, on Day 5 subjects will be fed prior to PK samples being taken. This investigation will inform possible further meal restrictions in the study (rest of Part B and Part C).
- There are no meal restrictions for Weeks 2 and 3 of Part B and all of Part C, unless the food effect exploration indicates significant effects on PK.

REVISED TEXT

- In Part A, and during **Cohort 3 of Part B** ~~Week 1 of Part B,~~ on all dosing days, subjects will be required to fast from midnight until 3 hours after administration of study treatment (with the exception of Day 5 of **Cohort 3** ~~Part B~~ in which subjects will be fed). At other times, snacks and meals will be provided by the clinical unit.

Water will be allowed as desired except for one hour before and after drug administration.

- An investigation into a possible food effect will be conducted on Days 4 and 5 of **Cohort 3 of** Part B in this study. On Day 4 subjects will be fasted until following the collection of the 4hr post-dose PK sample, on Day 5 subjects will be fed prior to PK samples being taken. This investigation will inform possible further meal restrictions in the study (rest of Part B and Part C).
- There are no meal restrictions for **Cohorts 4a and 4b** ~~Weeks 2 and 3~~ of Part B and all of Part C, unless the food effect exploration indicates significant effects on PK.

Section 7.1 – Time and Events Tables

Multiple Changes throughout, addition of table for 7 day repeat dose, and addition of table for optional dose alteration in 21 day repeat dose (healthy subjects).

Section 7.3.4 – Vital Signs

PREVIOUS TEXT

Triplicate readings of blood pressure and pulse rate will be taken and averaged at screening and at pre-first dose for each dose level, single readings will be collected at all other times.

REVISED TEXT

Triplicate readings of blood pressure and pulse rate will be taken and averaged at ~~screening and at pre-first dose for each dose level, single readings will be collected at~~ all ~~other~~ times.

Section 7.3.5 – Electrocardiogram (ECG)

PREVIOUS TEXT

12-lead ECGs (triplicate readings at screening and at pre-first dose for each dose level, single readings will be collected at all other times)

REVISED TEXT

12-lead ECGs **will be measured in semi-supine position after 5 minutes rest** (triplicate readings ~~at screening and at pre-first dose for each dose level, single readings will be collected at~~ **will be taken and averaged at** all ~~other~~ times)

Section 7.4.1 – Blood Sample Collection

PREVIOUS TEXT

Part A (Single dose to Healthy Volunteers):

Pre-dose, and 0.25; 0.5; 0.75; 1; 1.5; 2; 3; 4; 5; 6; 8; 10; 12; 16; 24 and 48 hrs post-dose.

REVISED TEXT

Part A (Single dose to Healthy Volunteers):

Pre-dose, and 0.25; 0.5; 0.75; 1; 1.5; 2; 3; 4; 5; 6; 8; 10; 12; 16; 24 and 48 hrs post-dose.

Part B – Cohort 3 (7 day repeat dose to Healthy Volunteers):

Study Day	PK sampling timepoint(s)
1	Pre-dose, and 2hr post-dose
2&3	Pre-dose
4	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
Follow-up (7 – 14 days post-dose)	Single sample

Part B – Cohort 4a/b (21 day repeat dose to Healthy Volunteers):

Study Day	PK sampling timepoint(s)
1	Pre-dose, and 2hr post-dose (1st dose of the day only)
2-4	Pre-dose (before 1st dose of the day only)
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose (1st dose of the day only)
21	Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before next dose administration
Follow-up (7 – 14 days post-dose)	Single sample

If a dose adjustment is required within the 21 day repeat dose period, PK samples will also taken at timepoints indicated below. Note: The 'Dose Day' relates to the first day of the adjusted dose, and not the study day.

Dose Day	PK sampling timepoint(s)
-1	Pre-dose
1	Pre-dose, and 2hr post-dose (1st dose of the day only)
2-4	Pre-dose (before 1st dose of the day only)

5	**Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose (1st dose of the day only)**
Study Day	
21	**Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before next dose administration**
Follow-up (7 – 14 days post-dose)	**Single sample**

Section 7.5 – Biomarker(s)/Pharmacodynamic Marker

Study Day	PD sampling timepoint(s)
1	Pre-dose, and; 2; 4; 6; and 12 hrs post-dose (note: 12hr post-dose sample to be taken before next dose administration)
2-7	Pre-dose (before 1st dose of the day only)
8-20	Pre-dose (before 1st dose of the day only) on days that a visit is planned
21	Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before next dose administration)
During Follow-up	1 sample/wk up to 6 weeks

REVISED TEXT

Cohort 3 (7 day repeat dose to Healthy Volunteers):

Study Day	**PD sampling timepoint(s)**
1	**Pre-dose, and 2hr post-dose**
2 and 4	**Pre-dose**
5	**Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose**
7	**Pre-dose (before 1st dose of the day only)**
Follow-up (7 – 14 days post-dose)	**Single sample**

Cohort 4a/b (21 day repeat dose to Healthy Volunteers):

Study Day	**PD sampling timepoint(s)**
1	**Pre-dose, and 2hr post-dose (1st dose only)**
2 and 4	**Pre-dose (before 1st dose of the day only)**
5	**Pre-dose, and 2hr post-dose (1st dose of the day only)**
Follow-up (7 – 14 days post-dose)	**Single sample**

If a dose adjustment is required within the 21 day repeat dose period (Cohort 4a/4b), PD samples will also taken at timepoints indicated below. Note: The 'Dose Day' relates to the first day of the adjusted dose, and not the study day.

Dose Day	PD sampling timepoint(s)
-1	Pre-dose
1	Pre-dose, and 2hr post-dose (1st dose only)
2-4	Pre-dose (before 1st dose of the day only)
5	Pre-dose, and 2hr post-dose (1st dose of the day only)
Study Day	
Follow-up (7 – 14 days post-dose)	Single sample

Study Day	PD sampling timepoint(s)
1	Pre-dose, and; 2; 4; 6; and 12 hrs post-dose (note: 12hr post-dose sample to be taken before next dose administration)
2-7	Pre-dose (before 1st dose of the day only)
8-20	Pre-dose (before 1st dose of the day only) on days that a visit is planned
21	Pre-dose, and 0.5; 1; 2; 3; 4; 6; 8 and 12 hrs post-dose (1st dose; note: 12hr post dose sample to be taken before next dose administration)
Safety Follow-up	**Single sample**
PD ~~During~~ Follow-up	1 sample/wk up to 6 weeks

Section 8 – Data Management

PREVIOUS TEXT

For this study, the data collection tool will be PIMS, a validated computer software program. In all cases, subject initials will be collected in source documentation at the site but will not be transmitted to GSK sponsor team

REVISED TEXT

For this study, the data collection tool will be PIMS, a validated computer software program. In all cases, subject ~~initials~~ **numbers** will be collected in source documentation at the site but will not be transmitted to GSK sponsor team

Section 10.7.1 – Dose Escalation Committee

PREVIOUS TEXT

For Part A, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK3039294 at the prior dose level(s). The review data set will at minimum consist of all available PK data, the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available pharmacodynamic (PD) data.

The decision and selection of dose to proceed to Part B will be made by the DEC based on all available PK data. the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available pharmacodynamic (PD) data from the dose levels investigated in Part A

The decision and selection of dose to proceed to Part C, will be made by the DEC basedon available PK data the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available PD data from the dose levels investigated in Part A, and available PK the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available PD data from the dose levels investigated in Part B.

REVISED TEXT

For Part A, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK3039294 at the prior dose level(s). The review data set will at **a** minimum consist of all available PK data, ~~the listings of any~~ adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings~~, together with any available pharmacodynamic (PD) data~~.

The decision and selection of dose to proceed to Part B **as well as any dose escalation decisions,** will be made by the DEC based on all available PK data. the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings~~, together with any available pharmacodynamic (PD) data from the dose levels investigated in Part A~~

The decision and selection of dose to proceed to Part C, will be made by the DEC based **at a minimum** on available PK data the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available PD data from the dose levels investigated in Part A, and available PK the listings of any adverse events, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and laboratory findings, together with any available PD data from the dose levels investigated in Part B.

AMENDMENT 2

Where the Amendment Applies

Throughout the protocol.

Summary of Amendment Changes with Rationale

Changes made are to reflect an increase in cardiac monitoring in Cohort 3 (Healthy subjects in Part B) and Cohort 5 (patients in Part C), in order obtain further safety data in these groups.

List of Specific Changes

Protocol Synopsis: Objectives and Endpoints (Parts B and C)

PREVIOUS TEXT

Adverse events, laboratory measurements, ECG, vital signs

REVISED TEXT

Adverse events, laboratory measurements, ECG, vital signs **and cardiac telemetry (where applicable)**

Protocol Synopsis: Treatment Arms and Duration

PREVIOUS TEXT

Part B: Repeat dose escalation in healthy volunteers

Cohort 3: In a group of healthy volunteers sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 7 days. The dose will be one that is expected to be well tolerated based on the single dose data and not predicted to exceed exposure limits based on single dose PK. Providing a review of the data (safety data: AE, vital signs, ECG, laboratory safety tests and PK) is favourable, Cohort 4 will be initiated.

A food effect exploration will be conducted at Days 4 and 5 of this cohort. On these days GSK3039294 will be administered under fasted and then under fed conditions

REVISED TEXT

Part B: Repeat dose escalation in healthy volunteers

Cohort 3: In a group of healthy volunteers **(preferably < 45 years of age)** sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 7 days. The dose will be one that is expected to be well tolerated based on the single dose data and not predicted to exceed exposure limits based on single dose PK. ~~Providing a review of the data (safety data: AE, vital signs, ECG, laboratory safety tests and PK) is favourable, Cohort 4 will be initiated.~~

~~A food effect exploration will be conducted at Days 4 and 5 of this cohort. On these days GSK3039294 will be administered under fasted and then under fed conditions~~

A sentinel subject will be dosed first with repeat GSK3039294 administration for 7 consecutive days. Subsequent subjects will only be dosed after the sentinel subject has successfully completed the full 7 days of dosing without any clinically concerning AEs being reported. If the safety data from the sentinel subject is deemed to be equivocal, a second subject can be dosed individually for 7 days at the discretion of the Investigator in consultation with the GSK study team. If the safety data from the second subject is also equivocal, at the discretion of the Investigator in consultation with the GSK study team, subsequent subjects can also be individually dosed with GSK3039294 for 7 days.

The food effect exploration in Cohort 3 will only be conducted once the Investigator in consultation with the GSK study team is satisfied with the safety profile of repeat dose GSK3039294. Following this, the food effect will be conducted on Days 4 and 5, and GSK3039294 will be administered under fasted and then under fed conditions (respectively).

Sufficient subjects will be enrolled to ensure a minimum of 6 subjects complete all study procedures, including the food effect exploration.

Providing a review of the data (safety data: AE, vital signs, ECG, telemetry, laboratory safety tests and PK) is overall acceptable, Cohort 4a will be initiated. The approving REC will be informed of the outcome of this data review.

Protocol Synopsis: Treatment Arms and Duration

PREVIOUS TEXT

Part C: Repeat dose escalation in patients with systemic amyloidosis

A single dose level of GSK3039294 will be tested for 21 days repeat dose, in patients with systemic amyloidosis.

REVISED TEXT

Part C: Repeat dose escalation in patients with systemic amyloidosis

A single dose level of GSK3039294 will be tested for 21 days repeat dose, in patients with systemic amyloidosis **which may include those with cardiac amyloid involvement.**

Protocol Synopsis: Type and Number of Subjects

PREVIOUS TEXT

In **Part C**, 12 patients with systemic amyloidosis will be enrolled. If subjects prematurely discontinue, replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

REVISED TEXT

In **Part C**, **a minimum of** 12 patients with systemic amyloidosis will be enrolled. If subjects prematurely discontinue, replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

Protocol Synopsis: Analysis

PREVIOUS TEXT

Interim analyses

Safety, PK and PD data will be reviewed on an ongoing basis throughout the study by the study team and investigator in order to inform dosing decisions for subsequent dosing sessions, cohorts and study parts.

At the end of Part B, individual profiles over time will also be presented graphically for selected urine and plasma laboratory parameters pertaining to the kidney. To inform dosing decisions for subsequent dosing sessions in Part A, individual values of Cmax and AUC[0-inf] will be derived by means of non-compartmental analysis. To inform dosing decisions for subsequent study parts, GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698.

Primary and secondary analyses

Safety, PK and PD data will be listed, summarised and presented graphically as appropriate. GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698.

REVISED TEXT

Interim analyses

Safety, PK and PD data will be reviewed on an ongoing basis throughout the study by the study team and investigator in order to inform dosing decisions for subsequent dosing sessions, cohorts and study parts.

In addition, in all Parts of the study, individual profiles over time will also be presented graphically for selected urine and plasma laboratory parameters pertaining to the kidney. To inform dosing decisions for subsequent dosing sessions in Part A, individual values of Cmax and AUC[0-inf] will be derived by means of non-compartmental analysis. To inform dosing decisions for subsequent study parts, GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698.

Primary and secondary analyses

Safety, PK and PD data will be listed, summarised and presented graphically as appropriate. GSK2315698 concentration data and plasma SAP levels will be analysed using the PK/PD model that was developed for GSK2315698.

Cohort Safety Reviews: A safety review will be performed on completion of each Cohort in Part B, as well as at completion of Cohort 5 in Part C (see Section 4.2.2. & Section 4.2.3.). Initiation of Cohort 4a will be contingent on the findings of the safety review at completion of Cohort 3 (see Section 4.2.2.)

Summary of Cardiac Arrhythmia Adverse Events in Part A of this study

A total of 4 separate arrhythmias in 3 male subjects over 45 year old were reported on 24-hour Holter after single dose administration of GSK3039294 in Part A. Three episodes of supraventricular tachycardia (SVT), all of atrial tachycardia morphology at doses of GSK3039294 at 600mg and 1200mg, and one episode of a single 5-beat accelerated idioventricular rhythm (AIVR) at 600mg GSK3039294, were reported in these 3 separate subjects. Each of the events was of short duration, completely asymptomatic, and was not associated with hemodynamic instability.

No prolongation of the QTcF interval was observed in any subject after administration of 200mg, 600mg, or 1200mg of GSK3039294 in Part A.

Both SVTs and ventricular salvos of short duration are known to occur in healthy volunteer subjects and can be considered to be within the normal (non-pathological) variation of ECG parameters. In this regard, SVTs have been reported to arise in 13.9% of healthy volunteer subjects over 45 years of age compared to an incidence of 1.1% in healthy volunteer subjects 45 years or less in FIH studies (Hingorani et al, 2016). In Part A, none of the three affected subjects had plasma levels of GSK3039294 detectable approximate to the time at which each cardiac arrhythmia occurred. Moreover, the timing of each of the four arrhythmic events after dosing with GSK3039294 was not associated with the Tmax of CPHPC including one subject whom had no detectable plasma CPHPC present at approximately the time of the first of their two arrhythmic events.

Therefore, at this time, given that there were also no arrhythmogenic liabilities identified for GSK3039294 in preclinical toxicological studies, it is unlikely that the arrhythmias reported after dosing with GSK3039294 in Part A are attributable to its single dose administration at 600 mg or 1200mg.

Section 3. Objectives and Endpoints (Parts B and C)

PREVIOUS TEXT

Adverse events, laboratory measurements, ECG, vital signs

REVISED TEXT

Adverse events, laboratory measurements, ECG, vital signs **and cardiac telemetry (where applicable)**

Section 4.2.2. Part B (repeat dose escalation in healthy volunteers

PREVIOUS TEXT

Part B is repeat dose, open label, dose escalation conducted in healthy volunteer subjects and will evaluate the safety, tolerability, PK, pharmacodynamics of repeat dosing of GSK3039294. In addition to PK, plasma SAP levels will be measured at time points as in the Time and Events table (Section 7.1.1) to determine the ability of GSK3039294 to decrease plasma SAP levels to aid prediction of the optimal clinical dose.

In a group of healthy volunteers sufficient subjects will be enrolled to ensure a minimum of 6 subjects complete all study procedures (including the food-effect part) completers, the study drug will be administered repeatedly for a total of 7 days.–The dose will be one that is expected to be well tolerated based on the single dose data and predicted to not exceed exposure limits based on single dose PK. Providing a review of the data (safety

data: AE, vital signs, ECG, laboratory safety tests and PK) is favourable, Cohort 4 will be initiated.

Sentinel dosing: The subsequent subjects will be dosed after the first subject has completed all dosing days if there are no safety or tolerability concerns.

A food effect exploration will be conducted at Days 4 and 5 of this cohort. On these days GSK3039294 will be administered under fasted and then under fed conditions (please see SRM for details of meals), and PK samples will be taken to investigate the food effect on the PK.

In a group of healthy volunteers sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 21 days.

The dose level for this cohort will be determined by a review of the safety and PK data from cohort 3. The dose may be adjusted (up or down) during the 21 day dosing session based on preliminary PK collected during dosing and ongoing review of safety. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21.

The predicted maximum daily exposure dose that will not exceed pre-clinical safety exposure limits.

Data from cohorts 3 and 4a are expected to provide a good evaluation of the safety, tolerability and repeat-dose PK. The data will be evaluated using the PK/PD model to identify an optimal clinical dose (see Section 9.3.2.1). However, if it is determined that further investigation of dose levels are required before progressing to Part C (e.g. if the observations in cohort 4a are different from those which the PK /PD modelling predicted), then recruitment into Cohort 4b may be initiated.

Based on data from Cohorts 3 and 4a, dose levels will be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days. The dose level and / or dosing regimen may be altered once during the 21 days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.

Table 2 Cohort 3

Screening	All screening assessments to be completed within 28 days prior to the first dose
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until Day 8 when they will be discharged.
Follow-up	At least 7 days and no greater than 21 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 7 weeks

REVISED TEXT

Part B is repeat dose, open label, dose escalation conducted in healthy volunteer subjects and will evaluate the safety, tolerability, PK, pharmacodynamics of repeat dosing **(7 day in Cohort 3, 21 day in Cohort 4)** of GSK3039294. In addition to PK, plasma SAP levels will be measured at time points as in the Time and Events table (Section 7.1.1) to determine the ability of GSK3039294 to decrease plasma SAP levels to aid prediction of the optimal clinical dose.

Sentinel Dosing in Part B

In each individual study cohort in Part B, a sentinel subject will complete all dosing days up to and including Day 7. If there are no clinically concerning safety or tolerability issues observed, the rest of the subjects within the cohort can be dosed.

If the safety data from the sentinel subject is deemed to be equivocal, a second (and subsequent) subjects will complete all dosing days individually, up to and including Day 7, at the discretion of the Investigator in consultation with the GSK study team.

7 Day Repeat Dosing (Cohort 3)

In a group of healthy volunteers, sufficient subjects will be enrolled to ensure a minimum of 6 subjects complete all study procedures (including evaluation of food-effect) associated with 7 days repeat dosing administration.~~In a group of healthy volunteers sufficient subjects will be enrolled to ensure a minimum of 6 subjects complete all study procedures (including the food-effect part) completers, the study drug will be administered repeatedly for a total of 7 days.~~ The dose will be one that is expected to be well tolerated based on the single dose data and predicted to not exceed exposure limits based on single dose PK. ~~Providing a review of the data (safety data: AE, vital signs, ECG, laboratory safety tests and PK) is favourable, Cohort 4 will be initiated.~~

~~**Sentinel dosing:** The subsequent subjects will be dosed after the first subject has completed all dosing days if there are no safety or tolerability concerns.~~

A food effect exploration will be conducted at Days 4 and 5 of this cohort **once the investigator is satisfied with the safety data from the sentinel subject(s). To evaluate a potential food effect,** ~~On these days~~ GSK3039294 will be administered under fasted and then under fed conditions (please see SRM for details of meals), and PK samples will be taken to investigate the food effect on the PK.

Cardiac Safety Review of Cohort 3

Given that all cardiac arrhythmic events after single dose administration of GSK3039294 in Part A (where there were detectable levels of plasma CPHPC) were relatively acute and observed between approximately 4 to 7 hours after tmax of CPHPC and when no GSK3039294 was detectable, and given steady state is expected to be reached after approximately 5 days of repeat dosing, 7 day continuous cardiac telemetry in Cohort 3 is deemed to be of sufficient duration to detect any potential cardiac arrhythmias associated with repeat dosing of GSK3039294.

On completion, in addition to full safety review, a cardiac safety review will be performed where individual subject telemetry data will be reviewed in relation to the PK data of GSK3039294 and CPHPC.

21 Day Repeat Dosing (Cohort 4a)

In a group of healthy volunteers sufficient subjects will be enrolled to ensure 6 completers, the study drug will be administered repeatedly for a total of 21 days.

~~The dose level for this cohort will be determined by a review of the safety and PK data from cohort 3. The dose may be adjusted (up or down) during the 21 day dosing session based on preliminary PK collected during dosing and ongoing review of safety. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21.~~

~~The predicted maximum daily exposure dose that will not exceed pre-clinical safety exposure limits.~~

The dose level and / or dosing regimen may be adjusted (up or down) once during the 21 days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21. The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.

Initiation of Cohort 4a: Cohort 4a will only be initiated if the conclusion of the safety review from Cohort 3 demonstrates an acceptable safety profile associated with the repeat administration of GSK3039294 for 7 days.

Individual subjects in Cohort 4a can be withdrawn from the study at the discretion of the Investigator in consultation with the GSK study team if individual subject safety review at Day 7 demonstrates any AEs which are deemed to be equivocal or clinically concerning. Affected subject(s) should be followed-up, at the discretion of the Investigator, as per local practice.

Data from cohorts 3 and 4a are expected to provide a good evaluation of the safety, tolerability and repeat-dose PK. The data will be evaluated using the PK/PD model to identify an optimal clinical dose (see Section 9.3.2.1). However, if it is determined that further investigation of dose levels are required before progressing to Part C (e.g. if the observations in cohort 4a are different from those which the PK /PD modelling predicted), then recruitment into Cohort 4b may be initiated.

21 Day Repeat Dosing (Cohort 4b – optional, only if required)

In a group of healthy volunteers, sufficient subjects will be enrolled to ensure a minimum of 6 completers, the study drug will be administered repeatedly for a total of 21 days.

Based on data from Cohorts 3 and 4a, dose levels will be selected for further investigation in a further cohort of healthy volunteers (recruitment to ensure 6 completers). For this purpose the compound will be dosed for 21 consecutive days. The dose level and / or dosing regimen may be ~~altered~~ **adjusted (up or down)** once during the 21 days providing a review of the data from the starting dose (safety data: AE, vital signs, ECG, laboratory safety tests and PK – all obtained once steady state has been achieved) is favourable. **If the dose is to be altered, this will be done no later than Day 16 in order to achieve a new steady-state at Day 21.** The predicted maximum daily dose administered will not exceed pre-clinical safety exposure limits.

Table 2 Cohort 3

Screening	All screening assessments **(including a 48hr Holter recording)** to be completed within 28 days prior to the first dose
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from ~~Day -1~~ **Day -2 (where baseline cardiac telemetry will be performed for 24 hours immediately prior to the first dose of GSK3039294)** until Day 8 when they will be discharged.
Follow-up	At least 7 days and no greater than **14** ~~21~~ days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 7 weeks

Section 4.2.2. Figure 3 (footnote)

PREVIOUS TEXT

*In Cohort 4b multiple dose levels and different regimens may be investigated based on data from Cohort 4a. *Day of Potential Dose Alteration not specified as this will be performed following review of safety and PK data from previous dose.*

REVISED TEXT

*In Cohort 4b multiple dose levels and different regimens may be investigated based on data from Cohort 4a. *Day of Potential Dose Alteration **(no later than D16)** not specified as this will be performed following review of safety and PK data from previous dose.*

Section 4.2.3. Part C (repeat dose escalation in patients with systemic amyloidosis)

PREVIOUS TEXT

In Part C a single dose level of GSK3039294 will be tested for 21 days repeat dose, in patients with systemic amyloidosis. This will confirm the ability of GSK3039294 (given at the predicted optimal clinical dose determined from Part B) to decrease plasma SAP, and assess the ability of GSK3039294 to maintain this level over 21 days in patients with systemic amyloidosis.

Safety and tolerability will also be evaluated

Table 4 Cohort 5 Study Duration

Screening	All screening assessments to be completed within 28 days prior to the first dose
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until Day 8 when they will be discharged after assessments have been completed. Subjects will return to the unit as out-patients for regular assessments whilst continuing dosing to Day 21.
Safety Follow-up	Subjects will attend 7-14 days post last dose for a safety follow-up
PD Follow-up	Weekly PD assessments will be made up to 42 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 13 weeks

REVISED TEXT

In Part C a single dose level of GSK3039294 will be tested for 21 days repeat dose, in patients with systemic amyloidosis**, which may include those patients with known cardiac amyloid involvement**. This will confirm the ability of GSK3039294 (given at the predicted optimal clinical dose determined from Part B) to decrease plasma SAP, and assess the ability of GSK3039294 to maintain this level over 21 days in patients with systemic amyloidosis.

Safety and tolerability will also be evaluated

Initiation of Cohort 5: Cohort 5 will only be initiated if the conclusion of the safety review from Cohort 4 demonstrates an acceptable safety profile associated with the repeat administration of GSK3039294 for 21 days.

Sentinel Dosing in Part C

Renal Amyloidosis Sentinel Subject: A sentinel systemic amyloidosis patient (n=1) with known renal involvement and an estimated GFR ≥ 60 ml / min, *but with no known cardiac involvement*, will be dosed repeatedly with GSK3039294 for the full 21-day period before dosing any other patients begin. Following this, dosing of other patients with renal involvement (with an eGFR > 50 mL / min) but with no cardiac involvement can be initiated, provided no concerning safety signals are detected in this sentinel patient.

Cardiac Amyloidosis Sentinel Subject: Once the sentinel renal patient has successfully completed dosing, a sentinel cardiac amyloidosis patient (n=1) with eGFR≥ 60 mL / min & LV Ejection Fraction (EF) ≥ 50% will be dosed repeatedly with GSK3039294 for the full 21-day period. Following this, dosing of any other patients with cardiac involvement (NYHA ≤2) can be initiated provided no concerning safety signals are detected in the sentinel cardiac patient.

Table 4 Cohort 5 Study Duration

Screening	All screening assessments to be completed within 28 days prior to the first dose **including out-patient cardiac monitoring for 7 continuous days (with external portable monitoring device) only in those patients with known cardiac amyloid involvement**
Treatment Period	Each subject will take part in a single study period. Subjects will be in-patient from Day -1 until Day 8 when they will be discharged after assessments have been completed. **In-patient cardiac telemetry will be performed from at least Day -1 until Day 8 only in those patients with known cardiac amyloid involvement.** Subjects will return to the unit as out-patients for regular assessments whilst continuing dosing to Day 21.
Safety Follow-up	Subjects will attend 7-14 days post last dose for a safety follow-up
PD Follow-up	Weekly PD assessments will be made up to 42 days after last study drug administration Additional follow-up visits may be scheduled, if warranted
Total Duration	Approximately 13 weeks

Section 4.3. Type and Number of Subjects

PREVIOUS TEXT

In **Part B**, sufficient healthy volunteers will be enrolled to ensure 6 subjects per cohort have completed the in-patient phases.

Subjects who participate in Part A will be eligible to participate in Part B at the discretion of the Investigator.

In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same cohort at the discretion of the Sponsor in

consultation with the investigator. Replacement subjects do not need to have received the first dose for a given cohort to join the study in the second cohort.

In **Part C**, 12 patients with systemic amyloidosis will be enrolled. If subjects prematurely discontinue, replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

REVISED TEXT

In **Part B**, sufficient healthy volunteers will be enrolled to ensure **a minimum of** 6 subjects per cohort have completed the in-patient phases **with all study procedures.**

Subjects who participate in Part A will be eligible to participate in Part B at the discretion of the Investigator.

In Part A and B of the study, if subjects prematurely discontinue, replacement subjects may be enrolled and assigned to the same cohort at the discretion of the Sponsor in consultation with the investigator. Replacement subjects do not need to have received the first dose for a given cohort to join the study in the second cohort.

In **Part C**, **a minimum of** 12 patients with systemic amyloidosis **(which may include those with known cardiac amyloid involvement)** will be enrolled. If subjects prematurely discontinue, replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

Section 4.4. Design Justification

PREVIOUS TEXT

Part C will confirm the ability of GSK3039294 (given at the predicted pharmacological dose determined from Part B) to decrease plasma SAP to a level suitable for mAb administration in subsequent studies and its ability to maintain this level over 21 days in patients with systemic amyloidosis. Also, safety and tolerability of the optimal clinical dose of GSK3039294 will be evaluated in systemic amyloidosis patients.

REVISED TEXT

Part C will confirm the ability of GSK3039294 (given at the predicted pharmacological dose determined from Part B) to decrease plasma SAP to a level suitable for mAb administration in subsequent studies and its ability to maintain this level over 21 days in patients with systemic amyloidosis. Also, safety and tolerability of the optimal clinical dose of GSK3039294 will be evaluated in systemic amyloidosis patients **which may include those with known cardiac amyloid involvement.**

Section 4.6.1. Risk Assessment

- Inclusion of "**Monitoring of haemoglobin & platelets**" as a mitigation strategy for "GSK2315698 - Epistaxis"
- Inclusion of further information in "Summary of Data / rationale for Risk mitigation strategy" for "Preclinical finding of potential nephrotoxicity of GSK3039294"
- Inclusion of "Preclinical finding of haematologic effects associated with GSK2315698" and associated Summary of Data and Mitigation Strategy
- Inclusion of "Preclinical finding of testicular changes associated with GSK2315698" and associated Summary of Data and Mitigation Strategy
- Inclusion of "**No arrhythmogenic safety signals were detected**" and "**Cardiovascular parameters, including blood pressure and heart rate, will be closely monitored in the clinical study"** against "Summary of Data" and "Mitigation Strategy" (respectively) for "Preclinical finding of cardiovascular changes associated with GSK2315698".
- Inclusion of "Cardiac arrhythmias identified on 24-hour Holter after single dose administration of GSK3039294 in Part A of this study" and associated Summary of Data and Mitigation Strategy

Section 4.6.3. Overall Benefit:Risk Conclusion

PREVIOUS TEXT

GSK3039294 is an oral prodrug of CPHPC, as such it is expected to release CPHPC after oral administration. Previous clinical experience with CPHPC shows it has a good safety and tolerability profile therefore we do not anticipate safety issues linked to the release of the active moiety.

Biotransformation from prodrug into active will release 2 molecules of formaldehyde. There is precedent of drugs releasing formaldehyde with no associated toxicity.

Preclinical signs of potential nephrotoxicity were observed at very high doses which are unlikely to be reached in the clinic, however monitoring of renal function will be performed in the study in order to detect any potential changes.

There will be no medical benefit to healthy volunteers or patients with systemic amyloidosis being treated with GSK3039294 alone. The design of the study, schedule of assessments, and oversight mean that any risks to participants are minimised including those which might potentially affect the kidney, and therefore the clinical study is justified.

REVISED TEXT

GSK3039294 is an oral prodrug of CPHPC, as such it is expected to release CPHPC after oral administration. Previous clinical experience with CPHPC shows it has a good safety

and tolerability profile therefore we do not anticipate safety issues linked to the release of the active moiety.

At this time, although the cardiac arrhythmias reported in Part A are unlikely to be attributable to single dose administration of GSK3039294 at either 600mg or 1200mg, as a precaution, and to further assess and confirm this conclusion, the cardiac safety monitoring of healthy volunteer subjects during repeat dose administration of GSK3039294 for 7 consecutive days in Cohort 3 Part B has been enhanced (see Section 7.3.7.), and also in systemic amyloidosis patients in Cohort 5 Part C who are known to have cardiac amyloid involvement (see Section 7.3.8.).

Biotransformation from prodrug into active will release 2 molecules of formaldehyde. There is precedent of **licensed prodrugs** ~~drugs~~ releasing formaldehyde with no associated toxicity **on a background that formaldehyde is physiologically metabolised very rapidly within the systemic circulation (EFSA Journal, 2014; 12(2):3550).**

Preclinical signs of potential nephrotoxicity were observed at very high doses which are unlikely to be reached in the clinic, however monitoring of renal function will be performed in the study in order to detect any potential changes.

There will be no medical benefit to healthy volunteers or patients with systemic amyloidosis being treated with GSK3039294 alone. The design of the study, schedule of assessments, and oversight mean that any risks to participants are minimised including those which might potentially affect the kidney **and heart**, and therefore the clinical study is justified.

Section 5.1. Inclusion Criteria (Patients)

Addition of the following inclusion criteria:

- **For AL amyloidosis patients, ≥ 6 months post-chemotherapy with either a free light chain (FLC) complete response (CR) or a very good partial response (VGPR)**

Further Inclusion Criteria for Patients with known cardiac amyloid involvement

- ***eGFR ≥ 60 mL / min***
- ***Echocardiogram – LV ejection fraction ≥ 50% within 3 months of screening***

Section 5.2. Exclusion Criteria

Addition of the following exclusion criteria under "Diagnostic Assessments and Other Criteria"

- **Cohort 3 (Part B) subjects only: Cardiac arrhythmia detected on the 48hr screening Holter, with the exception of physiological bradycardia, first-**

degree heart block, supraventricular premature complexes and / or premature ventricular complexes (PVCs) less than a single 5-beat AIVR

- **Cohort 3 (Part B) subjects only: High sensitivity Cardiac Troponin level at screening > ULN for the specified assay**

Alterations to the following exclusion criteria under "Additional Exclusion Criteria - Patients"

- **Non-amyloid heart diseases (e.g. epicardial coronary artery heart disease, or non-amyloid valvular heart disease)**
- Subject with mean QTcF of >480ms from a mean of triplicate readings ~~triplicate readings~~
- **Cardiac Amyloidosis Patients ONLY – Within 3 months of Screening, *Or* at Screening: a). Sustained (≥ 10 beats) / symptomatic monomorphic ventricular tachycardia (VT), or rapid polymorphic VT; b). Complete heart block; c). Brady arrhythmias deemed clinically concerning in this patient population by the Investigator in consultation with the Medical Monitor**
- **Average SBP ≤ 100mmHg at Screening from triplicate readings in Part C systemic amyloidosis patients with known cardiac amyloid involvement *Or*, Average SBP ≤ 90mmHg at Screening from triplicate readings in systemic amyloidosis patients *without* known cardiac amyloid involvement**

Section 5.4.4. Cardiac Arrhythmia Stopping Criteria

Additional Text and Figure:

All cardiac arrhythmias in individual subjects will be reviewed by the Investigator in consultation with the Medical Monitor at the earliest possible opportunity after the event, and will also be reviewed by a cardiologist where it is deemed appropriate to do so by the Investigator in consultation with the Medical Monitor on a case-by-case basis.

A clinically concerning cardiac arrhythmia in this study is any type of arrhythmia or divergent QRS complex morphology that is deemed by the Investigator to be reasonably attributable to GSK3039294 - rather than within normal variation for each type of affected subject receiving repeat dose GSK3039294; i.e. healthy volunteer subjects in Part B, or systemic amyloidosis patients with known cardiac involvement Part C.

Furthermore, a clinically concerning arrhythmia is an adverse event which is deemed by the Investigator in consultation with the Medical Monitor to be of sufficient temporal duration and / or character to potentially affect subject safety.

Detection of the following during baseline assessment or following administration of GSK3039294 will lead to withdrawal:

a). Sustained (≥ 10 beats) / symptomatic monomorphic ventricular tachycardia (VT), or rapid polymorphic VT; b). Complete heart block; c). Brady arrhythmias deemed clinically concerning by the Investigator in consultation with the Medical Monitor (i.e. *except* physiological bradycardia or first degree heart block).

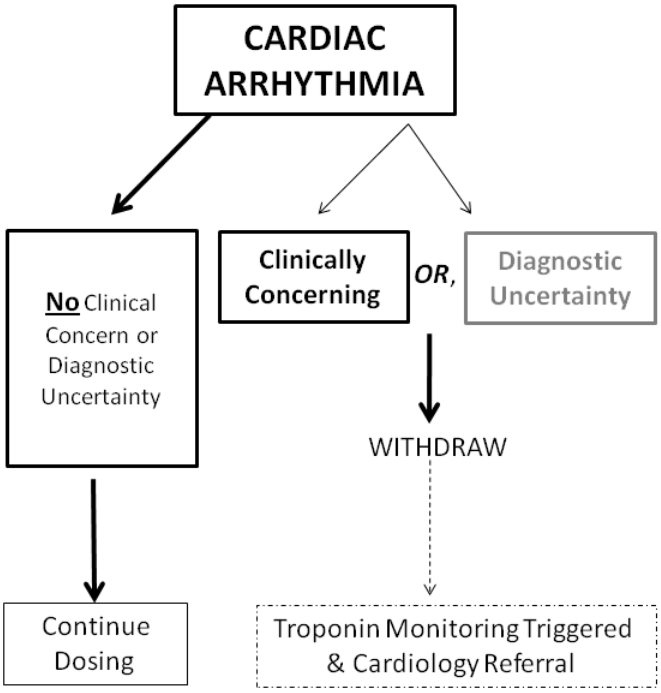
Additional cardiac arrhythmic events could include, but are not restricted, to:

- **A sustained arrhythmia (i.e. ≥30 seconds) *except* physiological bradycardia.**
- **A non-sustained wide-complex tachyarrhythmia ≥ 100 / minute that is:**
  - **accompanied by symptoms or other new ECG changes (e.g. new ST depression)**
  - **repetitive (e.g. repeated short salvos)**
  - **Greater than 10 seconds in duration**

Subjects who either have a clinically concerning arrhythmic event during the study, or where there is electrophysiological diagnostic uncertainty on cardiac telemetry / ECG, must be withdrawn from the study, and should have an immediate cardiac troponin level evaluated using a high-sensitivity point-of-care assay as outlined in Section 7.3.9 & Figure 5, below.

Affected subjects should be referred to the local cardiology service and the Medical Monitor should be informed as soon as possible.

Figure 5 Algorithm for Management of Subjects having received one or more doses of GSK3039294 in Parts B & C based on Arrhythmia Characterization



In Part C, the patient's amyloidosis physician should be informed as soon as possible after any type of cardiac adverse event, by the Medical Monitor, irrespective of the patient's cardiac amyloid status at Screening.

Section 5.4.6. Stopping Criteria Based On Disease Progression in Systemic Amyloidosis Patients in Part C

PREVIOUS TEXT

In Part C, individual patients can be withdrawn at any time during the study where the investigator has a reasonable level of clinical suspicion that the patient's underlying systemic amyloidosis is worsening. In this setting, the investigator in consultation with the Medical Monitor must refer the patient to their primary hospital physician for further consultation and appropriate diagnostic tests

REVISED TEXT

In Part C, individual **systemic amyloidosis** patients can be withdrawn at any time during the study where the investigator has a reasonable level of clinical suspicion that the patient's underlying systemic amyloidosis is worsening **(including worsening cardiac dysfunction in those patients known to have cardiac amyloid involvement).** In this

setting, the investigator in consultation with the Medical Monitor must refer the patient to their primary hospital physician for further consultation and appropriate diagnostic tests

Section 6.10.1 Meals and Dietary Restrictions

PREVIOUS TEXT

An investigation into a possible food effect will be conducted on Days 4 and 5 of Cohort 3 of Part B in this study. On Day 4 subjects will be fasted until following the collection of the 4hr post-dose PK sample, on Day 5 subjects will be fed prior to PK samples being taken. This investigation will inform possible further meal restrictions in the study (rest of Part B and Part C).

REVISED TEXT

An investigation into a possible food effect will be conducted on Days 4 and 5 of Cohort 3 of Part B in this study **(This will only be triggered by the Investigator in consultation with the Medical Monitor as per Section 4.2.2).** On Day 4 subjects will be fasted until following the collection of the 4hr post-dose PK sample, on Day 5 subjects will be fed prior to PK samples being taken. This investigation will inform possible further meal restrictions in the study (rest of Part B and Part C).

Section 6.10.2. Caffeine and Alcohol, and Tobacco

PREVIOUS TEXT

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for at least 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.
- **Healthy Subjects:** During each treatment period, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final PK sample for each in-house session. Subjects will also abstain from alcohol for 24 hours prior to screening and follow-up. At all other times during the study, male subjects should have no more than 2 drinks per day and female subjects should have no more than 1 drink per day (1 drink is equivalent to 12 g of alcohol: 360 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled spirits).

REVISED TEXT

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for at least 24 hours **(48 hours for Cohort 3)** prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.

- **Healthy Subjects:** During each treatment period, subjects will abstain from alcohol for 24 hours **(48 hours for Cohort 3)** prior to the start of dosing until collection of the final PK sample for each in-house session. Subjects will also abstain from alcohol for 24 hours prior to screening and follow-up. At all other times during the study, male subjects should have no more than 2 drinks per day and female subjects should have no more than 1 drink per day (1 drink is equivalent to 12 g of alcohol: 360 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled spirits).

Section 7.1. Time and Events Tables

Changes to assessments for Cohorts 3 and 5 and associated endnotes / footnotes

Section 7.3.5. Cardiac Monitoring – Electrocardiogram (ECG), Telemetry & Non-Implantable Devices for Remote Monitoring

PREVIOUS TEXT

- 12-lead ECGs will be measured in semi-supine position after 5 minutes rest (triplicate readings will be taken and averaged at all times) will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.3 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- Continuous ambulatory cardiac telemetry will be performed from 12hrs pre-dose to 72 hours post-dose of GSK3039294 in systemic amyloidosis patients with known cardiac involvement during Part C, and thereafter, at any time during any part of the study, at the investigator's discretion. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

REVISED TEXT

- 12-lead ECGs will be measured in semi-supine position after 5 minutes rest (triplicate readings will be taken and averaged at all times) will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.3 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- ~~Continuous ambulatory cardiac telemetry will be performed from 12hrs pre-dose to 72 hours post-dose of GSK3039294 in systemic amyloidosis patients with known cardiac involvement during Part C, and thereafter, at any time during any part of the study, at the investigator's discretion. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.~~

Cardiac Safety Monitoring in Cohort 3 (Part B) at Screening & Baseline

This will consist of a 48 hour Holter at Screening and continuous telemetry for 24 hours immediately preceding the first dose of GSK303294 at baseline.

- **In-Patient Dosing with GSK3039294: Continuous telemetry during repeat 7 day dosing of healthy volunteer subjects in Cohort 3 will be performed for up to approximately 24 hours after Day 7 to detect any cardiac arrhythmias potentially attributable to repeat dosing with GSK3039294 for 7 days in Cohort 3.**

Cardiac Safety Monitoring in Cohort 5 (Part C) patients with known cardiac amyloid involvement

- **Screening: 7-day out-patient cardiac monitoring using an appropriate non-implantable recording device which is acceptable to the patient – this will evaluate the arrhythmic background of eligible cardiac amyloidosis patients such that false positive attribution of arrhythmias to GSK3039294 during repeat dosing will be minimized.**

- **Baseline: 24 hour in-patient telemetry immediately before the first dose of GSK3039294.**

- **In-patient dosing with GSK3039294: Continuous telemetry will be performed for up to 24 hours after Day 7 administration of GSK3039294 to detect any arrhythmias in patients with known cardiac amyloidosis potentially attributable to repeat dosing with GSK3039294 including worsening of known patient-specific arrhythmias from Screening and / or Baseline assessments.**

- **Optional cardiac monitoring after completion of in-patient dosing: At Investigator discretion, on a case by case basis determined by in-patient cardiac telemetry / ECG findings, and in consultation with the Medical Monitor, cardiac monitoring can be extended either as an in-patient or as an out-patient (using a portable non-implantable device of Investigator choosing) in patients with known cardiac amyloidosis.**

Cardiac monitoring should continue in cardiac amyloidosis patients based on emerging safety data until it is deemed to be clinically appropriate for monitoring to stop after consultation with the Medical Monitor.

Section 7.3.7. High Sensitivity Cardiac Troponin-T (hs-cTnT) Monitoring after a Cardiac Arrhythmia in Part B, or Part C

Addition of Section:

Baseline hs-cTnT: In Part B and Part C, all subjects will have hs-cTn level for purposes of screening as well as to provide baseline with which to compare, in the event that a subject develops a clinically concerning cardiac arrhythmic event after dosing with GSK3039294.

***Subjects should be advised by the local study site to abstain from strenuous exercise (e.g. running or gym work) ≤ 24 hours before a baseline hs-cTn level is taken*.**

Monitoring of hs-cTnT after an Arrhythmia Event: A blood samples for hs-cTnT will be taken immediately at the time of onset of a cardiac arrhythmia which is deemed by the Investigator to be of clinical concern (see Section 5.4.4), *or* where there is electrophysiological diagnostic uncertainty.

High-sensitivity 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 if this is deemed clinically necessary by the Investigator.

Additional investigations, including but not restricted to serial ECGs and evaluation of cardiac function using echocardiogram and / or cardiac magnetic resonance (CMR) imaging, can be performed at the discretion of the Investigator in consultation with the Medical Monitor and a cardiologist.

Section 7.4.1. Blood Sample Collection

PREVIOUS TEXT

Part B – Cohort 3 (7 day repeat dose to Healthy Volunteers):

Study Day	PK sampling timepoint(s)
1	Pre-dose, and 2hr post-dose
2&3	Pre-dose
4	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
Follow-up (7 – 14 days post-dose)	Single sample

REVISED TEXT

Part B – Cohort 3 (7 day repeat dose to Healthy Volunteers):

Study Day	PK sampling timepoint(s)
1	Pre-dose, and 0.5, 1, 2, 3, 4, 6 hrs post-dose
2&3	Pre-dose
4*	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
5	Pre-dose, and 0.5; 1; 2; 3; 4; 6 hrs post-dose
Follow-up (7 – 14 days post-dose)	Single sample

***Day 4 PK samples will not be collected for sentinel subjects**

SECTION 8. DATA MANAGEMENT

PREVIOUS TEXT

- For this study, the data collection tool will be PIMS, a validated computer software program. In all cases, subject numbers will be collected in source documentation at the site but will not be transmitted to GSK sponsor team.

REVISED TEXT

- For this study, the data collection tool will be PIMS, a validated computer software program. In all cases, subject ~~numbers~~ **initials** will be collected in source documentation at the site but will not be transmitted to GSK sponsor team.

SECTION 11. REFERENCES

Addition of the following reference:

Hingorani et al., Arrhythmias Seen in Baseline 24-Hour Holter ECG Recordings in Healthy Normal Volunteers During Phase 1 Clinical Trials., The Journal of Clinical Pharmacology 2016, 56(7) 885–893