TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A 29-day, randomized, double-blinded, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of GSK1278863 in hemodialysis-dependent subjects with anemia associated with chronic kidney disease who are switched from a stable dose of an erythropoiesis-stimulating agent

Compound Number: GSK1278863

Development Phase: IIA

Effective Date: 11-MAY-2016

Protocol Amendment Number: 01

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N241222_00	2015-OCT-16	Original
2015N241222_01	2016-MAY-11	Amendment No. 1
Inclusion criterion #5 was modified to include the complete timeframe in which this criterion is applicable. Other eligibility criteria have been clarified or updated for consistency with project level requirements. Minor clarifications were made throughout the protocol, including clarifications related to hemoglobin stopping criteria, wording of the AEs of special interest, visit windows and the Time and Events Table. References to IB Supplements 1 and 2 were added, and corresponding updates to the Risk Assessment Table were made. Flexible language was added to allow for subjects to be dosed outside of the study clinic in exceptional circumstances. The definition of the PK analysis population was added.		

SPONSOR SIGNATORY

PPD

11 May 2016

Alexander R. Cobitz, M.D., Ph.D. Date

Executive Director, Clinical Development
Metabolic Pathways & Cardiovascular Unit
GlaxoSmithKline

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitors and Serious Adverse Events (SAE) Contact Information:

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Primary Medical Monitor - PPD	PPD M.D.	PPD		PPD, Inc. 3900 Paramount Parkway, Suite 353 Morrisville, NC 27560-7200
Secondary Medical Monitor - GSK	PPD M.D.			GlaxoSmithKline 1250 S. Collegeville Road, UP4400 Collegeville, PA 19426
SAE Contact Information[1]	PPD Hotline			

1 PPD Hotline for reporting of SAEs is only to be used in the event of the electronic data capture system being unavailable.

Sponsor Legal Registered Address:

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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):

IND Number: 101,291

EudraCT: 2015-004790-32

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204836:

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 204836

Rationale

In clinical studies to date, GSK1278863 has been administered as a once daily (QD) regimen. However, the preferred practice in countries that utilize a three-times weekly hemodialysis (HD) schedule is administration of anemia therapy at the time of the HD session. In order to accommodate this preference, and to provide additional flexibility for administration of GSK1278863, GSK proposes to also assess the ability of GSK1278863 to maintain hemoglobin (Hgb) levels when administered three-times weekly. This study will describe the dose-Hgb response relationship of three-times weekly dosing over a 29-day treatment period. It is anticipated that the data generated from this study will enable conversion of QD starting and maintenance dose regimens to three-times weekly doses/regimens.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• Characterize the dose-response relationship between GSK1278863 administered three-times weekly and Hgb at Day 29	• Hgb change from baseline at Day 29
Secondary	
• Characterize the pharmacodynamic (PD) effect of GSK1278863 dose regimens on EPO, vascular endothelial growth factor (VEGF), hepcidin and red blood cells	• Maximum observed change from baseline in EPO • Maximum observed % change from baseline in VEGF • Change from baseline in hepcidin at Day 29 • Change from baseline in hematocrit, red blood cell (RBC) count, reticulocyte count and reticulocyte Hgb (CHr) at Day 29
• Characterize the steady-state PK of GSK1278863 and major metabolites	• Descriptive PK summaries of GSK1278863 and major metabolites
• Assess the safety and tolerability of GSK1278863 with three-times weekly administration for 29 days	• Incidence and severity of AEs and SAEs • Reasons for discontinuation of investigational product • Discontinuation for safety-related reasons, e.g., pre-specified stopping criteria or AE • Absolute values and changes from baseline over time in laboratory parameters, ECGs and vital signs
Exploratory	
• Evaluate exposure-response relationships between GSK1278863 and PD endpoints	• Further models (as appropriate) to describe the GSK1278863 exposure (PK or dose) response relationship with PD endpoints

Overall Design

This is a randomized, double-blinded, dose-ranging, placebo-controlled, parallel group study. There is a 28-day Screening period, a 29-day Treatment period, and a Follow-up visit 14 ±3 days after completing treatment.

Treatment Arms and Duration

The total duration of subject involvement is up to 10 weeks (Screening to Follow-up) as described below:

- Screening will be for at least 28 days prior to randomization. A window of ±2 days will be allowed for visits during the Screening period.
- Subjects who meet eligibility criteria will be randomized and begin dosing on Day 1. Subjects will discontinue their current ESA therapy and will be randomized 1:1:1:1:1 to receive one of four three-times weekly doses (10 mg, 15 mg, 25 mg, 30 mg), or placebo on a dialysis day.
    - This should be timed such that randomization (Day 1) occurs on the date that would have been the next scheduled dose of ESA (or as close as practicable).
    - For subjects with a three-times weekly dialysis schedule, Day 1 must not occur on the first dialysis session of the week (e.g., if Monday-Wednesday-Friday schedule, the study visit cannot be on Monday).
    - For subjects with a four- to five-times weekly dialysis schedule, Day 1 can be on any hemodialysis session of the week.
- The Treatment period will be for a total of 29 days. A window of ±2 days is allowed for visits during the Treatment period.
    - At Day 29, all subjects will receive their last dose of study treatment and should not re-start ESA therapy until after the follow-up visit (Day 43). However, if the Investigator has a compelling clinical reason why a subject should restart ESA between Day 29 and Day 43, then ESA may be restarted prior to Day 43.
- A Follow-up visit will be scheduled to occur 14 ±3 days after completing treatment.

Type and Number of Subjects

The study will enroll subjects on HD with anemia associated with CKD switching from ESA treatment. The range of Hgb values for study eligibility is 9.0 - 11.5 g/dL and the subjects must have received the same ESA product with total weekly doses that varied by no more than 50% from 4 weeks prior to the Day -28 Screening visit through to Day 1.

Approximately 200 subjects will be screened to achieve approximately 90 randomized and 75 evaluable subjects, with approximately 15 evaluable subjects per treatment group.

Analysis

The primary objective of the study is to estimate the relationship between three-times weekly doses of GSK1278863 and Hgb response after 29 days of treatment. To achieve this, a model-based dose-response analysis is planned with the primary endpoint of change in Hgb from baseline at Day 29. It is anticipated that the data and the estimated parameters generated from this model will enable conversion of QD starting and maintenance dose regimens to three-times weekly doses/regimens.

Three-times weekly data from this study will be compared to the QD data from study PHI113633, which was a phase 2B dose-ranging study to evaluate the dose-response relationship of GSK1278863 over the first 4 weeks of treatment and evaluate the safety and efficacy of GSK1278863 over 24 weeks in hemodialysis-dependent subjects with anemia associated with CKD.

2. INTRODUCTION

2.1. Brief Background

Anemia is a common complication of chronic kidney disease (CKD). The cause of anemia in this population is multi-factorial, including relative or absolute deficiency of erythropoietin (EPO), reduced iron availability related to chronic inflammation, and gastrointestinal blood loss.

Current treatments for anemia associated with CKD include supplemental iron therapy (intravenous and/or oral), erythropoiesis-stimulating agents (ESAs) such as recombinant human (rh) EPO and blood transfusions. However, each of these treatments has significant limitations:

- **Iron**: Poor compliance is seen with oral iron therapy due to gastrointestinal intolerance while intravenous (IV) iron may have an increased risk of infection and/or iron overload as well as an increased risk for congestive heart failure [Agarwal, 2015].
- **ESAs**: In order to achieve target Hgb levels (which are lower than normal Hgb levels), treatment with ESAs markedly increases plasma EPO concentrations to supra-physiologic levels. Treatment with ESAs has been associated with increased cancer-related morbidity and mortality and increased risk of major cardiovascular events (e.g., stroke, myocardial infarction and all-cause mortality) [FDA, 2011], as well as ESA-induced hypertension.
- **Blood transfusions**: These are avoided when possible because of potential allo-immunization, which can preclude the possibility of receiving a kidney transplant as well as a risk of infection.

Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors (PHIs), such as GSK1278863, are an emerging new class of agents under investigation for the treatment of anemia associated with CKD. These molecules stimulate erythropoiesis through inhibition of HIF-prolyl hydroxylase domain enzymes (PHD1, PHD2, PHD3). This activity results in the accumulation of HIFα transcription factors which leads to increased transcription of HIF-responsive genes, stimulating components of the natural response to hypoxia. During hypoxia, the PHDs are inhibited, resulting in the accumulation of unhydroxylated HIFα subunits, which dimerize with HIFβ subunits to effect the transcription of HIF-responsive genes, including EPO and others involved in increasing oxygen availability and utilization. Other functions regulated by HIFs include iron metabolism and utilization, angiogenesis, extracellular matrix metabolism, apoptosis, energy and glucose metabolism, vascular tone, cell adhesion, and motility [Haase, 2013].

GSK1278863 may present several important advantages over other ESAs. It is an oral medication and does not require cold-chain storage as do some ESAs, thus increasing ease of use for patients. Moreover, data indicate that GSK1278863 can effectively raise hemoglobin (Hgb) concentrations with lower EPO exposures than those observed after administration of ESAs [Provenzano, 2011]. Because of the increased cardiovascular (CV) risk associated with raising Hgb concentrations through large increases in EPO exposure [Pfeffer, 2009], GSK1278863 has the potential to raise Hgb with less CV risk than other ESAs. Additional benefits include the potential to improve iron availability for erythropoiesis, the potential to successfully treat ESA-hyporesponders, and the potential to treat anemia without causing ESA-induced hypertension.

GSK1278863 is a HIF-PHI currently being investigated as a treatment for anemia associated with CKD in both dialysis (DD) and non-dialysis (ND) subjects, with adequate safety and efficacy in clinical trials having been demonstrated up to 24 weeks. Both pre-clinical and clinical data show that GSK1278863 stimulates EPO production resulting in increased erythropoiesis and elevation in Hgb concentrations. These increases in Hgb are achieved with peak EPO exposures substantially lower than those observed with ESAs. Data from completed clinical and preclinical studies are provided in the GSK1278863 Investigator Brochure (IB) and IB Supplements [GlaxoSmithKline Document Number RM2008/00267/07, GlaxoSmithKline Document Number 2015N266524_00, GlaxoSmithKline Document Number 2015N266524_01].

2.2. Study Rationale

In clinical studies to date, GSK1278863 has been administered as a once daily (QD) regimen. However, the preferred practice in countries that utilize a three-times weekly hemodialysis (HD) schedule is administration of anemia therapy at the time of the HD session. In order to accommodate this preference, and to provide additional flexibility for administration of GSK1278863, GSK proposes to also assess the ability of GSK1278863 to maintain Hgb levels when administered three-times weekly. This study will describe the dose-Hgb response relationship of three-times weekly dosing over a 29-day treatment period. It is anticipated that the data generated from this study will enable conversion of QD starting and maintenance dose regimens to three-times weekly doses/regimens.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• Characterize the dose-response relationship between GSK1278863 administered three-times weekly and Hgb at Day 29	• Hgb change from baseline at Day 29
Secondary	
• Characterize the pharmacodynamic (PD) effect of GSK1278863 dose regimens on EPO, vascular endothelial growth factor (VEGF), hepcidin and red blood cells	• Maximum observed change from baseline in EPO • Maximum observed % change from baseline in VEGF • Change from baseline in hepcidin at Day 29 • Change from baseline in hematocrit, red blood cell (RBC) count, reticulocyte count and reticulocyte Hgb (CHr) at Day 29
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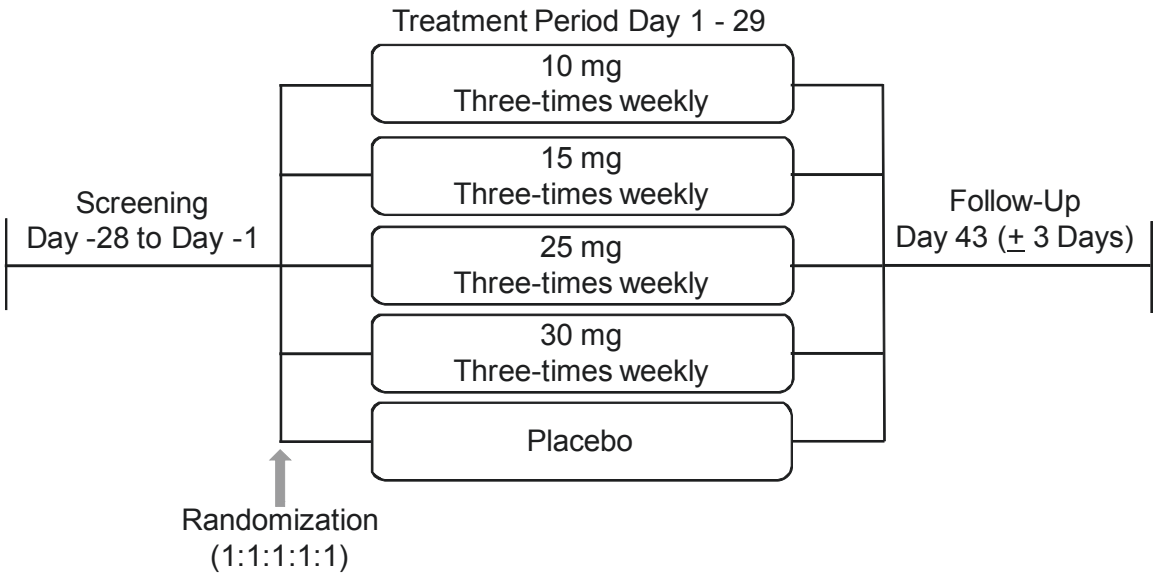
Exploratory	
• Evaluate exposure-response relationships between GSK1278863 and PD endpoints	• Further models (as appropriate) to describe the GSK1278863 exposure (PK or dose) response relationship with PD endpoints

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blinded, dose-ranging, placebo-controlled, parallel group study. There is a 28-day Screening period, a 29-day Treatment period, and a Follow-up visit 14 ± 3 days after completing treatment. The study design is outlined in Figure 1.

Figure 1 Study Design



This will be a double-blinded study. The subjects, investigator and sponsor will not be aware of the treatment received.

Subjects will be stratified by prior ESA dose based on the average weekly (for epoetins or darbepoetin) or monthly (for methoxy PEG-epoetin beta) dosing during the 12 weeks prior to randomization (Day 1) as follows:

- Low ESA dose: <100 IU/kg/week epoetin OR <0.5 µg/kg/week darbepoetin OR <0.6 µg/kg/week methoxy PEG-epoetin beta
- High ESA dose: ≥100 IU/kg/week epoetin OR ≥0.5 µg/kg/week darbepoetin OR ≥0.6 µg/kg/week methoxy PEG-epoetin beta

4.2. Treatment Arms and Duration

The total duration of subject involvement is up to 10 weeks (Screening to Follow-up) as described below:

- Screening will be for at least 28 days prior to randomization. A window of ±2 days will be allowed for visits during the Screening period.
- Subjects who meet eligibility criteria will be randomized and begin dosing on Day 1. Subjects will discontinue their current ESA therapy and will be randomized to receive one of four three-times weekly doses, or placebo on a dialysis day as listed in Table 1. Examples of switching are provided in the Study Reference Manual (SRM).
    - This should be timed such that randomization (Day 1) occurs on the date that would have been the next scheduled dose of ESA (or as close as practicable).

- For subjects with a three-times weekly dialysis schedule, Day 1 must not occur on the first dialysis session of the week (e.g., if Monday-Wednesday-Friday schedule, the study visit cannot be on Monday).

- For subjects with a four- to five-times weekly dialysis schedule, Day 1 can be on any hemodialysis session of the week.

- The Treatment period will be for a total of 29 days. A window of ±2 days is allowed for visits during the Treatment period.

  - At Day 29, all subjects will receive their last dose of study treatment and should not re-start ESA therapy until after the follow-up visit (Day 43). However, if the Investigator has a compelling clinical reason why a subject should restart ESA between Day 29 and Day 43, then ESA may be restarted prior to Day 43.

- A Follow-up visit will be scheduled to occur 14 ±3 days after completing treatment.

Subjects will be randomized 1:1:1:1:1 to one of 5 treatment arms:

Table 1 Study Treatment Arm Descriptions

Treatment Arm	Description
A	10 mg GSK1278863 three-times weekly
B	15 mg GSK1278863 three-times weekly
C	25 mg GSK1278863 three-times weekly
D	30 mg GSK1278863 three-times weekly
E	Placebo three-times weekly

Stopping algorithms are provided in Section 5.6.2 if Hgb values meet protocol pre-specified ranges.

4.3. Type and Number of Subjects

The study will enroll subjects on HD with anemia associated with CKD switching from ESA treatment. The range of Hgb values for study eligibility is 9.0 - 11.5 g/dL and the subjects must have received the same ESA product with total weekly doses that varied by no more than 50% from 4 weeks prior to the Day -28 Screening visit through to Day 1.

Approximately 200 subjects will be screened to achieve approximately 90 randomized and 75 evaluable subjects, with approximately 15 evaluable subjects per treatment group.

4.4. Design Justification

The purpose of this study is to describe the Hgb dose-response relationship for three-times weekly dosing of GSK1278863 at 29 days in order to describe the efficacy relationship between once-daily (QD) and three-times weekly administration. To date,

GSK1278863 has been administered to the HD population only by a QD dosing regimen, and this study is planned to enable three-times weekly dosing to be evaluated in future clinical studies. This is a randomized, double-blinded, dose-ranging, placebo-controlled, parallel group study with a treatment period of 29 days.

The dose-response relationship for QD dosing of GSK1278863 in the HD population has been established in a 24-week Phase 2 study. In that study, the Hgb response (change from baseline) was determined at 4 weeks over the dose range of 4 mg to 12 mg; therefore, in order to make a direct comparison between the QD and three-times weekly regimens, a 29-day treatment period will be utilized.

This study will be placebo controlled in order to establish a no-effect dose response relationship. In a previous study, for subjects on placebo, Hgb levels were observed to decline on average 0.72 g/dL (GSK study PHI113633; range: -2.3 to 0.9 g/dL) with no subjects requiring rescue medication. Therefore, there is little risk for a subject's Hgb to decline to levels requiring rescue; however, stopping criteria for Hgb are included in this protocol.

This will be a double-blind study with subjects, investigator, site and sponsor staff blinded to treatment received. Although Hgb response is an objective endpoint that is unlikely to be affected by knowledge of treatment received, as safety and tolerability will be assessed in this study, a double-blind design will decrease the likelihood of reporting bias. In addition, as some subjects will be administered placebo, the knowledge of their study treatment may influence their study completion and/or withdrawal.

4.5. Dose Justification

To date, GSK has conducted four clinical trials with GSK1278863 in the treatment of anemia associated with CKD in patients on HD. In all of these studies, GSK1278863 has been administered as a QD dose regimen. However, as clinical practice (standard of care) in the treatment of anemia in CKD patients on HD often utilizes a three-times a week regimen consistent with their hemodialysis schedule, GSK proposes to assess this regimen as part of our planned Phase 3 clinical program in hemodialysis patients.

In addition to administration on a three-times weekly dosing schedule, extended interval dosing (i.e., weekly to monthly) is also routinely used with ESAs. Evidence with epoetin alfa (Epogen), with Dosing and Administration guidance for three-times weekly dosing, has shown that increases in dosing interval (i.e., extended time between doses) can be achieved by a proportionate increase in the dose administered at each interval. As reported in a small study, epoetin alfa was administered subcutaneously at either 50 IU/kg three-times weekly, 10,000 IU/week, 20,000 IU every two weeks or 40,000 IU every 4 weeks with consistent management of Hgb levels for all 4 regimens in anemia patients with CKD not on dialysis [McGowan, 2008]. As GSK1278863 dose response with Hgb is generally linear between 4 and 24 mg QD, it is anticipated that a similar time-proportional efficacy relationship will exist for GSK1278863 and the management of Hgb levels as the dosing is extended from once every day to three-times weekly.

These data suggest that the efficacy of PHIs is most likely related to total dose or AUC, rather than Cmax or Cmin. Additionally, the time to reach the steady-state response is determined by the RBC lifespan which on average is 2-3 months. These data further support that three-times weekly administration of GSK1278863 is feasible, and that three-times weekly doses may be selected based on efficacy data collected after QD administration. The hypothesized three-times weekly dose 'equivalent' would be approximately 2.3 times that of the QD dose (e.g., 9 mg three-times weekly would be expected to result in equivalent efficacy as 4 mg QD). To match a similar Hgb response range to the once daily regimen, doses of 10, 15, 25 and 30 mg three-times weekly will be investigated for 29 days to match the 4, 6, 10 and 12 mg QD doses. Studying multiple doses allows a robust analysis of a range of three-times weekly doses to determine the 'equivalent' ratio to bridge to QD dose levels. The dose-Hgb response relationship is generally linear in the QD dose range of interest (4 to 24 mg) but it is not known if this will be maintained with the higher doses needed for three-times weekly dosing.

Based on review of available safety data received to date, no risks were identified which would preclude dosing patients with anemia associated with CKD on dialysis with GSK1278863 up to 25 mg QD as well as with an extended dosing interval of three-times weekly at doses up to 30 mg in clinical trials in which appropriate risk minimization and monitoring processes are in place.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK1278863 can be found in the GSK1278863 Investigator's Brochure (IB) and IB Supplements [GlaxoSmithKline Document Number RM2008/00267/07, GlaxoSmithKline Document Number 2015N266524_00, GlaxoSmithKline Document Number 2015N266524_01].

4.6.1. Benefit Assessment

GSK1278863 has been shown to be generally well tolerated and effective for up to 24 weeks in a recently-completed Phase 2 study (GSK study PHI113633) in the management of Hgb levels in patients with anemia associated with CKD that are hemodialysis-dependent. However, as the present study is designed to characterize the dose-response relationship between GSK1278863 and the change from baseline in Hgb, it is anticipated that some subjects will experience a decrease, and some an increase in Hgb which may fall outside of target during the 29 days of treatment. Therefore, a proportion of subjects enrolled in this study will not gain a benefit from participation in this study.

4.6.2. Risk Assessment

The potential risks of clinical significance and the mitigation strategies for this protocol taking into account the results of clinical and nonclinical studies with GSK1278863 are outlined in Section 12.3. In addition to the mitigation strategies outlined, an internal GSK Safety Review Team (SRT) will monitor accruing safety data in a blinded fashion for this trial.

4.6.3. Overall Benefit:Risk Conclusion

GSK1278863 demonstrates a positive benefit vs. risk based on the evidence as follows. In clinical trials up to 24 weeks in duration, GSK1278863 treats Hgb to target range, and there were no adverse events that had been identified as related to treatment with GSK1278863.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (See Section 12.3 Appendix 3). Given these precautions, as well as the potential benefit that GSK1278863 holds for the treatment of anemia in CKD patients compared to the current standard, the overall benefit risk balance is considered to be positive.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

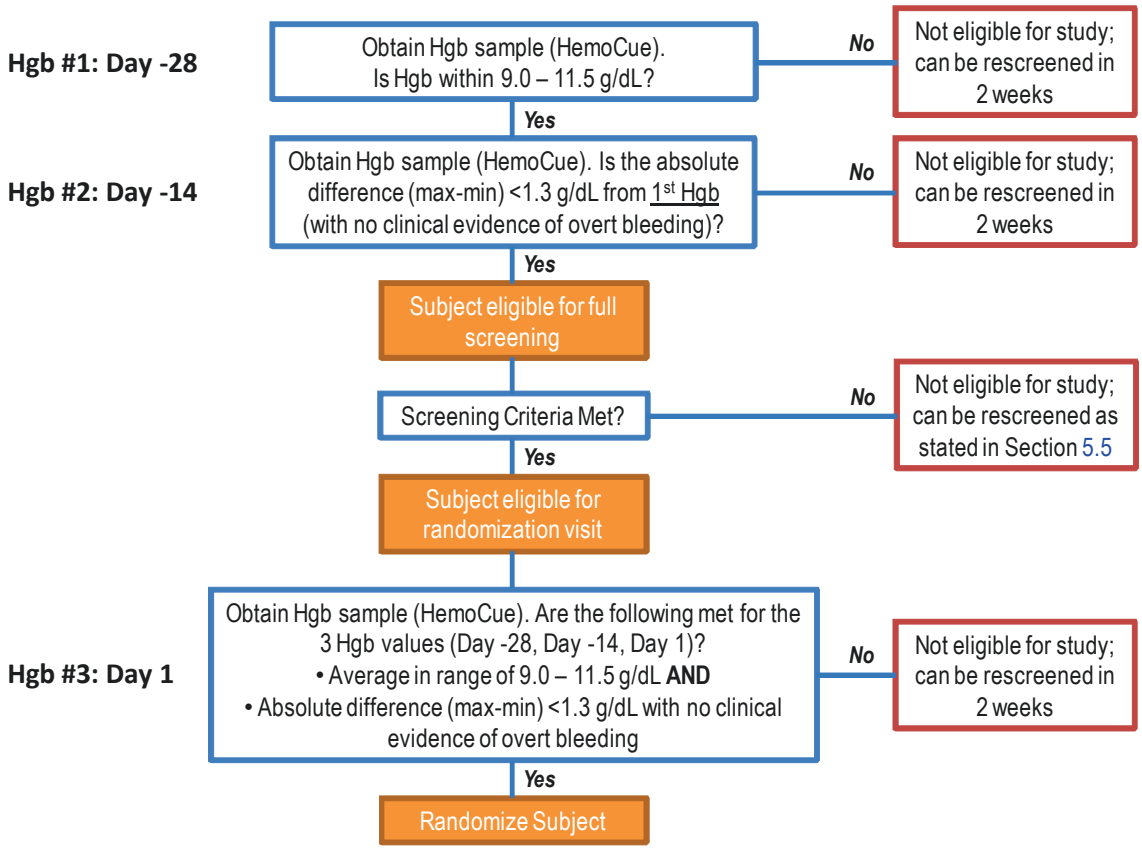
Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator's Brochure and IB Supplements [GlaxoSmithKline Document Number RM2008/00267/07, GlaxoSmithKline Document Number 2015N266524_00, GlaxoSmithKline Document Number 2015N266524_01].

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

5.1. Hemoglobin Stability Criteria

Entry into the study requires a stable Hgb between **9.0 - 11.5 g/dL**. This is confirmed from an average of **three** Hgb values obtained via a validated point-of-care device to measure Hgb (HemoCue) on site during the screening period at Day -28, Day -14 and Day 1 (randomization) as outlined in Figure 2. Calculations to determine eligibility will be performed automatically by IVWRS. For subjects with a three times weekly dialysis schedule, Hgb values must not be obtained on the first dialysis session of the week (e.g., if Monday-Wednesday-Friday schedule, the study visit cannot be on Monday). For subjects with a four to five times weekly dialysis schedule, Hgb values can be obtained on any hemodialysis session of the week.

Figure 2 Hemoglobin Stability Criteria



5.2. Inclusion Criteria

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

AGE
1. ≥18 years of age, at the time of signing the informed consent.
TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Hemoglobin**: Stable Hgb 9.0 - 11.5 g/dL (see Section 5.1).
3. **Dialysis frequency**: On hemodialysis (HD, hemofiltration or hemodiafiltration) three to five times weekly for at least 4 weeks prior to Day -28 Screening through Day 29.
4. **Dialysis adequacy**: A single pool Kt/V_{urea} of ≥1.2 based on a historical value obtained within the prior three months in order to ensure the adequacy of dialysis. If Kt/V_{urea} is not available, then an average of the last 2 values of urea reduction ratio (URR) of at least 65%. **NOTE**: Only needs confirming at Day -28.
5. **Stable ESA dose**: Treated with the same ESA (epoetins or their biosimilars, or darbepoetin or methoxy PEG-epoetin beta) with total weekly dose varying by no more than 50% from 4 weeks prior to Day -28 through Day 1 (randomization).
6. **Iron replacement therapy**: Subjects may be on maintenance oral or IV iron

supplementation. If subjects are on oral iron, then the type of iron and doses must not be changed for the 4 weeks prior to Day -28, during the screening phase, and through the 29 days of treatment. If subjects are on IV iron, then doses must be ≤100 mg/week, and doses must not be changed for the 4 weeks prior to Day -28, during the screening phase, and through the 29 days of treatment.
INFORMED CONSENT
7. 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.

5.3. Exclusion Criteria

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

CKD-RELATED CRITERIA
1. **Dialysis modality**: Planned change from HD to peritoneal dialysis within the study time period.
2. **Renal transplant**: Planned for living-related or living-unrelated kidney transplant.
3. **High ESA dose**: An epoetin dose of ≥360 IU/kg/week IV or ≥250 IU/kg/week subcutaneous (SC) or darbepoetin dose of ≥1.8 µg/kg/week IV or SC or methoxy PEG-epoetin beta dose of ≥2.2 µg/kg/week within the prior 8 weeks through Day 1 (randomization).
4. **Mircera**: Administration of Mircera (methoxy PEG-epoetin beta) within 2 weeks prior to Day 1 if subject is on a once-every-2-weeks schedule or within 4 weeks prior to Day 1 if subject is on a once-every-4-weeks schedule.
CARDIOVASCULAR DISEASE-RELATED CRITERIA
5. **Myocardial infarction or acute coronary syndrome:** Within the 8 weeks prior to Screening through Day 1 (randomization).
6. **Stroke or transient ischemic attack:** Within 8 weeks prior to Screening through Day 1 (randomization).
7. **Heart failure:** Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system diagnosed prior to Screening through Day 1 (randomization).
8. **QTcB:** QTcB >500 msec or QTcB >530 msec in subjects with Bundle Branch Block. There is no QTc exclusion for subjects with a predominantly paced rhythm.
OTHER DISEASE-RELATED CRITERIA
9. **Inflammatory disease:** Active chronic inflammatory disease that could impact erythropoiesis (e.g., scleroderma, systemic lupus erythematosis, rheumatoid arthritis, celiac disease) diagnosed prior to Screening through Day 1 (randomization).
10. **Hematological disease**: Any hematological disease including those affecting platelets, white or red blood cells (e.g., sickle cell anemia, myelodysplastic syndromes, hematological malignancy, myeloma, hemolytic anemia and thalassemia), coagulation disorders (e.g., antiphospholipid syndrome, Protein C or S deficiency), or

any other cause of anemia of chronic disease other than renal disease diagnosed prior to Screening through Day 1 (randomization).

11. **Liver disease:** Current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) or evidence at Screening of abnormal liver function tests [alanine transaminase (ALT) or aspartate transaminase (AST) >2x upper limit of normal (ULN) or total bilirubin >1.5xULN]; or other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participating in the study.
    NOTE: Those with Hepatitis B or Hepatitis C are eligible provided these exclusions are not met.
12. **Major surgery:** Major surgery (excluding vascular access surgery) within the 8 weeks prior to Screening, during the Screening phase, or planned during the study.
13. **Transfusion:** Blood transfusion within the 8 weeks prior to Screening, during the Screening phase or an anticipated need for blood transfusion during the study.
14. **GI Bleeding:** Evidence of actively bleeding peptic, duodenal, or esophageal ulcer disease **OR** clinically significant GI bleeding within the 8 weeks prior to Screening through Day 1 (randomization).
15. **Acute Infection:** Clinical evidence of acute infection or history of infection requiring intravenous (IV) antibiotic therapy within the 4 weeks prior to Screening through Day 1 (randomization). **NOTE:** IV antibiotics as prophylaxis are allowed.
16. **Malignancy:** History of malignancy within the two years prior to Day -28 through to Day 1 (randomization) or currently receiving treatment for cancer, or has a known complex kidney cyst (i.e. Bosniak Category II F, III of IV) > 3cm. **NOTE:** The ONLY exception is squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥ 8 weeks prior to Screening.

CONCOMITANT MEDICATIONS

17. **Severe allergic reactions:** History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product.
18. **Drugs and supplements:** Use of any prescription or non-prescription drugs or dietary supplements that are prohibited (see Section 6.9.2 for details) from Screening until the Follow-up Visit.
19. **Prior investigational product exposure**: The Subject has participated in a clinical trial and has received an experimental investigational product within the prior 30 days from Screening through Day 1 (randomization).

GENERAL HEALTH RELATED CRITERIA

20. **Other conditions:** Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study.
21. **Females ONLY:** Does not meet the female eligibility criteria (Section 12.6 Appendix 6), is pregnant [as confirmed by a positive serum human chorionic gonadotrophin (hCG) test for females of reproductive potential (FRP) only], breastfeeding, and if of reproductive potential does not agree to follow one of the options listed in Section 12.6.1.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA (To be verified on Day -28 only)
22. **Vitamin B_{12}:** At or below the lower limit of the reference range (may rescreen in a minimum of 8 weeks).
23. **Folate:** <2.0 ng/mL (4.5 nmol/L) (may rescreen in a minimum of 4 weeks).
24. **Ferritin:** <100 ng/mL (<100 µg/L).
25. **Transferrin saturation (TSAT):** <20%.

5.4. Other Eligibility Criteria Considerations

Laboratory eligibility criteria will be assessed according to the central laboratory results from the Screening visit samples. See Section 7.4.6 for a listing of Clinical Laboratory Assessments.

5.5. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In this study, a subject can become a screen failure at any time from the Day -28 visit to the Day 1 visit, prior to randomization. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.6).

Subjects who fail screening may be rescreened as soon as the investigator feels they may have become eligible. However, an individual subject may not rescreen more than twice. There is no predetermined amount of time that the investigator needs to wait to rescreen a previously ineligible subject, except those excluded for Hgb or folate who may only rescreen in 2 and 4 weeks, respectively, and those excluded for Vitamin B_{12} who may rescreen in 8 weeks.

5.6. Withdrawal/Stopping Criteria

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral 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 reason for discontinuation of study treatment and/or withdrawal from the study must be recorded in the eCRF.

Refer to the Time and Events Table (Section 7.1) for the assessments to complete in the event of discontinuation of study medication and early withdrawal.

5.6.1. Criteria for Permanent Discontinuation from Study Medication and Early Withdrawal

Subjects must **permanently discontinue study medication** for the following reasons:

- Meeting Hgb stopping criteria (Section 5.6.2).
- Receiving blood transfusions.
- Receiving kidney transplant.
- Subject becomes pregnant or intends to become pregnant during the study.
- Active GI bleeding.
- Diagnosis of cancer, with the exception of squamous cell and basal cell carcinoma.
- Liver chemistry abnormalities exceeding the threshold criteria (Section 5.6.4).
- Missing 2 consecutive dialysis sessions.
- Need for chronic (more than 14 days) use of prohibited medication (Section 6.9.2).

The subject should attend the clinic as soon as possible to complete the Early Withdrawal assessments and return for a Follow-up visit as described in Section 7.1, Time and Events.

The reason for discontinuation of study medication and date of last dose will be recorded in the eCRF.

5.6.2. Hemoglobin Stopping Criteria

GSK will supply a point-of-care Hgb analyzer (HemoCue) to each site for rapid and convenient monitoring of Hgb levels and to ensure consistency of Hgb measurements across sites participating in the study.

Blood samples for measurement of Hgb concentrations via HemoCue from the screening visits and throughout the treatment period will be collected as specified in Section 7 and recorded in the eCRF.

Subjects must permanently discontinue study medication if:

- Confirmed Hgb (2 measurements by HemoCue pre-dialysis) <7.5 g/dL
- Confirmed Hgb increases ≥ 1.0 g/dL over the previous 2 weeks

For Hgb ≥ 13.0 g/dL, withdrawal will be in consultation with the GSK Medical Monitor. The table below summarizes the Hgb values and corresponding action to be taken:

Hgb (g/dL) at visit	Action	
<7.5	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug.	
≥7.5-<13.0	≥2.0 decrease in Hgb over 2 weeks	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug.
	<1.0 increase or <2.0 decrease in Hgb over 2 weeks	Continue study drug.
	≥1.0 increase in Hgb over 2 weeks	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug.
≥13.0	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, consider permanently discontinuing study drug in consultation with GSK Medical Monitor.	

In cases where the Hgb values from the central laboratory meet any of the Hgb stopping criteria in the above table, but the Hgb values from the HemoCue device do not, then the Investigator and the GSK Medical Monitor should discuss this situation before potentially discontinuing study medication.

If a subject is permanently discontinued from study medication, then the subject should attend the clinic as soon as possible to complete the Early Withdrawal assessments and Follow-up visit (see Section 7.1, Time and Events) as described in Section 5.7.

The reason for discontinuation of study medication and date of last dose will be recorded in the eCRF.

5.6.3. Missed Clinic Visits/Lost to Follow-up

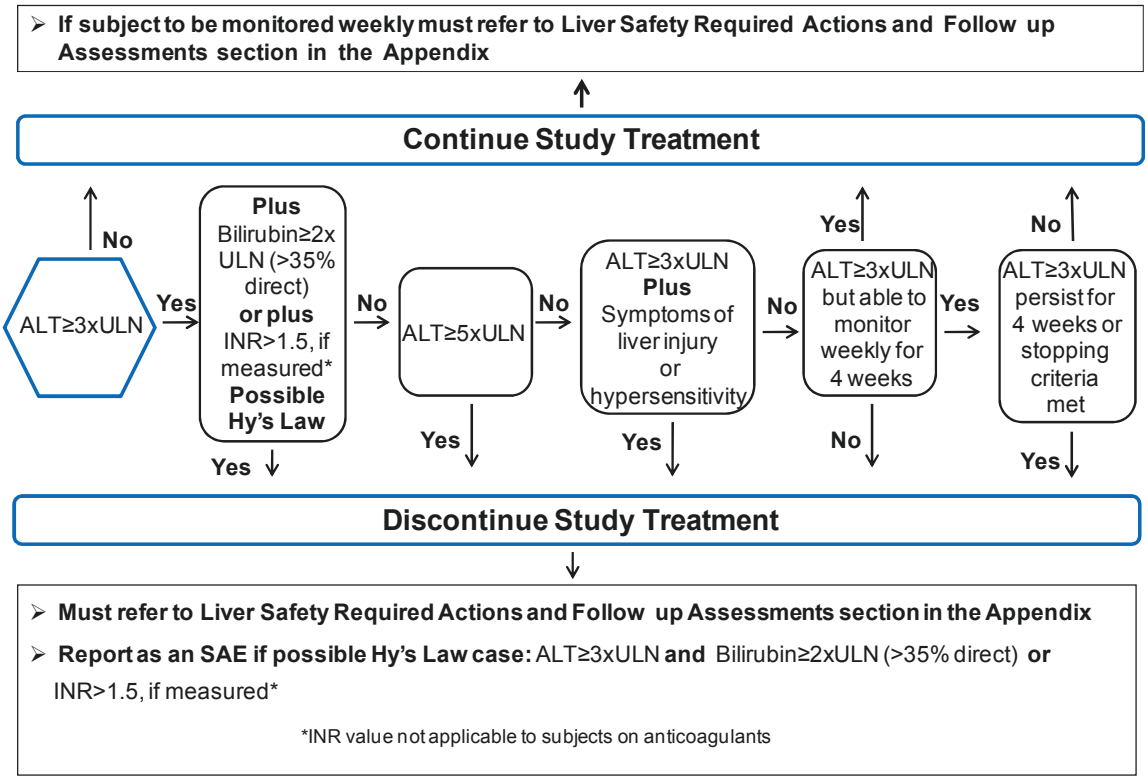
The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- 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”

5.6.4. 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). Drug-Induced Liver Injury Guidance

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



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

5.6.4.1. 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.

5.7. Early Withdrawal

If a subject is withdrawn from the study, for any reason, they will be considered to be an Early Withdrawal. The reason for the early withdrawal will be recorded in the eCRF. The Early Withdrawal assessments, as detailed in Section 7.1 Time and Events Table, should be performed as soon as possible following withdrawal. Subjects should also attend a Follow-up visit according to the timing and assessments in Section 7.1 Time and Events Table.

5.8. Subject and Study Completion

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

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

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:	GSK1278863	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	5 mg and 25 mg tablet strengths/10 mg, 15 mg, 25 mg, 30 mg dosage levels	0 mg
Route of Administration:	Oral	Oral
Physical description:	A round, biconvex, 10 mm white film coated tablet.	A round, biconvex, 10 mm white film coated tablet.

All eligible subjects will discontinue their current ESA therapy and will be randomized to receive either GSK1278863 or matching placebo on a dialysis day. This should be timed such that randomization (Day 1) occurs on the date that would have been the next scheduled dose of ESA (or as close as practicable). In addition, for subjects with a three times weekly dialysis schedule, Day 1 must not occur on the first dialysis session of the week (e.g., if Monday-Wednesday-Friday schedule, the study visit cannot be on Monday). For subjects with a four to five times weekly dialysis schedule, Day 1 can be on any hemodialysis session of the week. Examples of switching are provided in the SRM.

To maintain the blind, subjects will have study treatment dispensed from three bottles of study medication. This combination of tablets will provide the appropriate dose of study medication, and will include a combination of tablet strengths, active and placebo, to correspond to the appropriate dose.

Subjects will be dispensed one tablet from each bottle (all subjects will take three tablets in total) and take with a glass of water on a dialysis day, and this should be prior to dialysis; however, on Day 1 it is acceptable for the subject to take study medication after dialysis. All study medication should be taken in the clinic **EXCEPT** prior to the PK day (Day 15 study visit), or on other days only if the Investigator and GSK Medical Monitor agree that it will not interfere with the study procedures or affect the subject's compliance

with the protocol. The study site must ensure that the date and time the subject took each dose of study treatment is documented.

On the PK day, subjects will be instructed to take their dose of study medication at home and arrive for clinic visit approx. 6-10 hr post-dose. Subjects may take their Day 15 dose the evening prior to the study visit to accommodate the 6-10 hr PK/PD sampling window. Additional instructions can be found in the SRM.

Subjects can take their tablets without regard to food. For all study visits, it is recommended for subjects not to eat a heavy meal before coming to the clinic in order to avoid lipemia of the blood sample collected for the analysis of transferrin, iron and TIBC.

6.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

The randomization schedule will be computer generated by PPD using the randomization system Prism. Subjects will be stratified as outlined in Section 4.1 and assigned a randomization number by IVWRS managed by PPD. Once a randomization number has been assigned, it must not be reassigned.

6.3. Blinding

This will be double-blind study, with the subject, investigator and site staff, and GSK study team all unaware of the study treatment received. The following will apply concerning unblinding:

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the eCRF.

A subject may continue in the study if that subject's treatment assignment is unblinded.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

- Only subjects enrolled in the study may receive study treatment. Study medication is to be stored up to 30°C (86°F). **Maintenance of a temperature log (manual or automated) is required.**
- 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). Study treatment must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the study treatment will be limited to the investigator and authorized site staff.
- 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.
- 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.

6.6. Compliance with Study Treatment Administration

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee. The date and time of each dose administered in the clinic, as well as the bottle number will be recorded in the source documents.

When a subject self-administers study treatment at home, compliance with GSK1278863 will be documented in a subject-completed paper diary and assessed through querying the subject during the site visit, documented in the source document and recorded into the eCRF. A record of the number of GSK1278863/placebo tablets 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 eCRF.

6.7. Treatment of Study Treatment Overdose

There is no specific antidote for overdose with GSK1278863. The expected manifestations of GSK1278863 overdosage include signs and symptoms associated with an excessive and/or rapid increase in Hgb concentration. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted, as dictated by the subject's clinical status. Additionally, patients should be monitored closely for cardiovascular events, increased heart rate and hematologic abnormalities.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study.

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

6.9. Concomitant Medications and Non-Drug Therapies

Concomitant medications, including over-the-counter and supplements, taken during the study will be recorded in the eCRF. Start and stop dates will be recorded for general concomitant medications, while additional details of dose, route, and frequency will be recorded for supplemental iron. The potential for drug-drug interactions is described in Section 12.3 Appendix 3.

6.9.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.9.2, all concomitant prescription medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Regular multivitamins (at recommended daily allowance including for iron) and other vitamin supplements such as calcium and vitamin D are permitted at the discretion of the principal investigator or his/her designee.

GSK1278863 is a substrate of breast cancer resistance protein (BCRP). The potential for inhibitors of BCRP to increase the plasma exposure of GSK1278863 to any relevant extent is unknown. BCRP inhibitors are not excluded from safety/efficacy studies; Hemoglobin stopping criteria mitigate risk of increased pharmacology if co-administered. Co-administration of GSK1278863 with strong BCRP inhibitors [i.e., cyclosporine, HIV antivirals (atazanavir, lopinavir, ritonavir, tipranavir), lapatanib and curcumin] should be performed with caution.

6.9.2. Prohibited Medications and Non-Drug Therapies

Any herbal or dietary supplements, unless, in the opinion of the investigator (who should consult the Sponsor), the therapy will not interfere with the study, are prohibited from Screening to the Follow-up Visit.

New androgen therapy within the 12 weeks prior to Screening, at any time during the study, or changes to pre-existing androgen regimen during the study is prohibited.

Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of low dose (≤325 mg/day) aspirin/acetylsalicylic acid is prohibited. Occasional NSAID use is permitted.

Use of any of the following prescription drugs from Day 1 until seven days after the last dose of study treatment is prohibited and will constitute a protocol violation:

- Strong inhibitors of CYP2C8 (e.g., gemfibrozil)
- Strong inducers of CYP2C8 (e.g., rifampin/rifampicin)

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 (Section 7.1), are essential and required for study conduct.

Time and Events Tables are provided in Section 7.1 for the overall study and for the specific Pharmacokinetic/Pharmacodynamic assessments (Table 2).

Study visit days are based on the schedule for hemodialysis as follows:

- **Three times weekly:** Hgb levels may have the greatest variability around study visits at the beginning of the week; therefore, the Day 1, 15 and 29 study visit must not occur on the first dialysis session of the week (e.g., if Monday-Wednesday-Friday dialysis schedule, then the study visit cannot be on Monday).
- **Four to five times weekly:** Designated study visit can be on any hemodialysis session of the week.

To allow scheduling flexibility, study visits should occur within a window of ±2 days, **except for subjects on a three times weekly dialysis schedule for whom study visits must not be scheduled on the first dialysis session of the week**. Post-randomization visits should be referenced back to the Randomization visit (Day 1). In exceptional circumstances, minor changes to visit structure may be permitted after consultation with the GSK Medical Monitor.

The following points must be noted:

- If assessments are scheduled for the same nominal time, **THEN** the assessments should 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 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 Table

Protocol Activity [1, 2]	Screening		Day 1	Treatment Period				Follow-up
	Week -4	Week -2		Day 15	Day 29	Un-scheduled	Early Withdrawal	Day 43 ± 3 [6]
Informed Consent	X							
Entry Criteria	X		X					
Physical, Medical History, Demography	X							
HemoCue Hgb	X	X	X	X	X	X	X	
IVWRS Call	X	X	X	X	X	X	X	X
Females Only: Serum Pregnancy Test [3]		X					X	X
Females Only: Estradiol and FSH (if required) [3]		X						
ECG	X				X		X	
Vitals (Pre-dialysis and Post-dialysis) [4]		X	X	X	X	X	X	X
Clinical Chemistry		X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X
Folate and Vitamin B_{12}	X							
Ferritin, transferrin, total iron, UIBC	X		X		X		X	X
Pharmacokinetic/Pharmacodynamic Samples			X	X	X		X [5]	
Blood draw for PGx			X					
Adverse Events Assessment [7]			X	X	X	X	X	X
Review Concomitant Medications	X		X	X	X	X	X	X

1. All assessments should be done pre-dialysis except as noted.
2. Allowable time window of ± 2 days for all study visits, except the follow-up visit for which it is ± 3 days.
3. As detailed in Exclusion Criteria in Section 5.3.
4. Weight measured post-dialysis only & height measured at screening only.
5. Obtain samples as per the Day 29 visit in Table 2. If subject does not receive a dose of study medication at this early withdrawal visit, no post-dose PK/PD samples should be obtained.
6. Subjects who withdraw early from treatment should attend a follow-up visit 14 days ± 3 days after the last dose of study treatment.
7. Serious adverse events are assessed from the time of consent as stated in Section 7.4.1.1.

Table 2 Pharmacokinetic/Pharmacodynamic Time and Events Table

PK/PD Sample	Day 1 (dose study med at clinic)	Day 15 (dose study med at home[1])	Day 29 (dose study med at clinic)
Plasma PK[2]	Pre-dose	1st sample collected approx 6-10 hr post-dose on arrival. **Additional sampling:** 1, 2, and 3 h after this 1st sample	Pre-dose, 1, 2, and 3 h post dose
EPO & VEGF[2]	Pre-dose	1st sample collected approx 6-10 h post-dose on arrival. **Additional sampling:** 1, 2, and 3 h after this 1st sample	Pre-dose and 3 h post dose
Hepcidin[3]	Pre-dose	Single sample during visit	Single sample during visit

1. Subject to take their dose of study medication at home and arrive for clinic visit approx 6-10 h post-dose. Subjects may take their Day15 dose the evening prior to the Week 2 study visit to accommodate the 6-10 h PK/PD sampling window.
2. Sample to be collected within 30 minutes of planned collection time.
3. Sample can be pre- or post-GSK1278863 administration.

7.2. Screening and Critical Baseline Assessments

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

Entry into the study requires a stable Hgb of 9.0 - 11.5 g/dL. A stable Hgb value will be confirmed from three Hgb values taken during the screening period at Day -28, Day -14 and Day 1 (randomization) as outlined in Section 5.1.

7.3. Efficacy

Hgb values to be used in the determination of the primary endpoint (Hgb change from baseline at Day 29) will be measured by the central laboratory as part of the Clinical Safety Laboratory Assessments (Section 7.4.6). Day 1 measurement will serve as the baseline value.

7.4. Safety

Regular monitoring of hematology, blood chemistry and vital signs will occur throughout the study. Serum pregnancy tests will be performed in women of child-bearing potential at Screening and Follow-up.

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

The definitions of an AE or SAE can be found in Section 12.5.

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

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment (Day 1) until the Follow-up visit (see Section 7.4.1.4).
- 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 eCRF.
- All SAEs will be recorded and reported to PPD within 24 hours, as indicated in Section 12.5.4.
- 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 PPD.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to PPD are provided in Section 12.5.6.

7.4.1.2. Adverse Events of Special Interest

The following have been identified as adverse events of special interest (AESIs) for GSK1278863 based on nonclinical studies, the mechanism of action and pharmacological activity of GSK1278863, current information about hypoxia-associated pathophysiology, studies of genetically engineered animal models, and naturally occurring mutations in man:

- Thrombosis and tissue ischemia secondary to excessive erythropoiesis
- Death, MI, stroke, venous thromboembolism, thrombosis of vascular access
- Cardiomyopathy
- Pulmonary artery hypertension
- Cancer-related mortality and tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization

- Exacerbation of rheumatoid arthritis

The results of any investigation should be recorded in the relevant sections of the subject's eCRF

7.4.1.3. Method of Detecting AEs and SAEs

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

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

7.4.1.4. 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 7.4.1.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.6.3). Further information on follow-up procedures is given in Section 12.5.4.

7.4.1.5. Cardiovascular and Death Events

For any events that may represent the cardiovascular events detailed in Section 12.5.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK/PPD (or designee) of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that

legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, 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.

7.4.2. Pregnancy

- Details will be collected about all pregnancies reported after the start of dosing and until the Follow-up Visit.
- 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 Section 12.6.2.

Subjects must permanently discontinue study medication if pregnancy occurs (see Section 5.6.1).

7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, including vascular access, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.4. Vital Signs

Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), height and weight. Three measurements of SBP, DBP and HR will be recorded at each study-specified visit. Measurements will be taken from the subject while in a seated position or semi-supine in the dialysis chair. Vital signs will be recorded pre-dialysis (except weight) and post-dialysis as outlined in Section 7.1. Height will be measured during the Screening period (at Day -14) only. Additional details are provided in the SRM.

7.4.5. Electrocardiogram (ECG)

Full 12-lead ECGs will be recorded in subjects while in a supine position at the times as outlined in Section 7.1, Time and Events Table. The parameters to be measured include heart rate, PR interval, QRS duration, and QT (uncorrected) interval. QTcB is to be calculated.

While it is preferred that ECGs are performed pre-dialysis, it is acceptable for this to occur at any time during the dialysis session. However, it is requested that the timing of the ECGs be performed consistent with the Screening assessment.

At any study visit when ECGs are performed, two additional ECGs are required if initial ECG indicates prolonged QTcB using the manually-calculated QTcB value. The average QTcB value of three ECGs will be used to determine eligibility as provided in Section 5.3, Eligibility Criteria. Additional details are provided in the SRM.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 3, 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/center 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) the results must be recorded in the eCRF.

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

All study-required laboratory assessments will be performed by a central laboratory, apart from the HemoCue Hgb, with the results of each test entered into the eCRF.

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

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count	*RBC Indices:*	*WBC Count with Differential:*
	RBC Count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	MCHC	Monocytes
	WBC Count (absolute)	RDW	Eosinophils
	Reticulocyte Count	CHr	Basophils
Clinical Chemistry	Potassium	AST (SGOT)	Total and direct/indirect bilirubin
	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium (Albumin adjusted)	Alkaline Phosphatase
	Albumin	Phosphate	
Other laboratory Tests	Erythropoietin	Vascular Endothelial Growth Factor	Hepcidin
	Serum ferritin	Serum iron	Serum transferrin
	Transferrin saturation (% saturation)	Unbound iron binding capacity	Folate
	Vitamin B12		
Other Screening Tests[1]	FSH	Estradiol	Serum hCG Pregnancy test

NOTE: Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 12.2 Appendix 2
1 As required per Appendix 6

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.5. Pharmacokinetics/Pharmacodynamics

Blood samples for PK (GSK1278863 and metabolites) and PD (EPO, VEGF, hepcidin) will be collected from all subjects as outlined in Table 2.

7.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of parent GSK1278863 and metabolites (GSK2391220 [M2], GSK2531403 [M3], GSK2487818 [M4], GSK2506102 [M5], GSK2531398 [M6], and GSK2531401 [M13]) will be collected at the time points indicated in Section 7.1, Time and Events Table. 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.

For the PK/PD visits outlined in Table 2, sample times are approximate; however, it is imperative that **the actual date and time** of sampling is recorded in the eCRF.

- At the Day 1 Visit, pre-dose PK/PD samples will be obtained from all subjects. Record the date and time of the last ESA dose administered prior to PD sampling and the date and time of the GSK1278863 dose administered at this visit.
- At Day 15 Visit, post-dose PK/PD samples will be obtained. Initial PK/PD samples will be obtained from all subjects soon after arrival.
    - Record the date and time of the last **two** GSK1278863 doses taken prior to the Day 15 Visit (the last dose of GSK1278863 may be taken early on the day of the Day 15 Visit, or in the evening of the day before).
    - At Day 29 Visit, pre- and post-dose PK/PD samples will be obtained. Record the date and time of the last GSK1278863 dose taken prior to the Day 29 Visit, and the date and time of the dose taken at the Day 29 Visit.

Based on the time of dosing, samples may be obtained before, during, and after the hemodialysis procedure. **The start date/time and stop date/time of the hemodialysis procedure at the Day 15 and 29 Visits will be recorded**.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.5.2. Sample Analysis

Plasma PK analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, PTS DMPK, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of parent GSK1278863 and metabolites (GSK2391220 [M2], GSK2531403 [M3], GSK2487818 [M4], GSK2506102 [M5], GSK2531398 [M6], and GSK2531401 [M13]) will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Analysis of plasma EPO, VEGF and hepcidin are described in the SRM.

7.6. Genetics

A blood sample will be collected for Genetic research from consenting subjects. This sample should be collected on Day 1 (randomization) once written informed consent has been obtained.

Information regarding genetic research is included in Section 12.4 Appendix 4.

8. DATA MANAGEMENT

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Estimation

The primary objective of the study is to estimate the relationship between three-times weekly doses of GSK1278863 and Hgb response after 29 days of treatment. To achieve this, a model-based dose-response analysis is planned with the primary endpoint of change in Hgb from baseline at Day 29. It is anticipated that the data and the estimated parameters generated from this model will enable conversion of QD starting and maintenance dose regimens to three-times weekly doses/regimens.

Three-times weekly data from this study will be compared to the QD data from study PHI113633, which was a phase 2B dose-ranging study to evaluate the dose-response relationship of GSK1278863 over the first 4 weeks of treatment and evaluate the safety and efficacy of GSK1278863 over 24 weeks in hemodialysis-dependent subjects with anemia associated with CKD.

Although the primary analysis of dose-response relationship was estimated by a four parameter Emax model for study PHI113633, the estimated slope of 1.17 suggests that a simple, three parameter Emax model, which is a special case of the four parameter Emax model when the slope parameter has a value of one, is an appropriate option. For this study it is proposed to fit a three parameter Emax model to account for dose using Bayesian statistical methods (i.e. posterior Emax model), and the results will be compared back to QD dose-response data from study PHI113633 based on a similar three parameter Emax model. For this study, the prior distributions for each model parameter are informed by the QD dose-response from study PHI113633. For the purpose of estimating dose-ratio (three-times weekly:QD), a linear model will also be fitted if the dose-response data shows a linear trend within the three-times weekly dose range (see Section 9.4.1.1).

A posterior dose-response model, once fitted, will be used to make the following inferences to describe the dose response relationship:

- Estimation of the three-times weekly minimally effective dose (MED), defined as the smallest dose achieving a change of -0.5 g/dL over 29 days after being switched from ESA.

- Estimation of three-times weekly dose levels from the MED in +0.25 g/dL mean Hgb increments, including estimation of the target dose (TD), defined as the three-times weekly dose of GSK1278863 that achieves a 0 g/dL change over 4 weeks after being switched from ESA.

- Estimation of dose ratio between three-times weekly and QD doses that produce the same Hgb response.

9.2. Sample Size Considerations

No formal sample size and power calculations were performed because the focus of this study is on characterizing the Hgb-three-times weekly dose-response relationship and using the results to estimate the dose ratio between three-times weekly and QD doses that produce the same Hgb response, not on formal testing of hypotheses. A sample size of approximately 90 randomized subjects has been determined based on feasibility (18 per arm).

Assuming a maximum dropout rate of 15% between randomization and Day 29, it is anticipated that approximately 75 subjects will complete 29 days treatment.

Subjects will be stratified by prior ESA dose (low, high), and then randomized in equal proportions to receive placebo three-times weekly, or GSK1278863 dose of 10 mg three-times weekly, 15 mg three-times weekly, 25 mg three-times weekly, or 30 mg three-times weekly.

9.2.1. Sample Size Assumptions

For the three parameter Emax model, assuming that the sample size is 75, E0 = -0.666 and Emax = 5.258 (estimates based on PHI113633 Emax model), and SD for Hgb change = 1 g/dL (as assumed for study PHI113633 sample size calculation), the following table describes the precision for estimation of target dose (TD) and minimally effective dose (MED) based on different assumptions for the unknown parameter ED50. The relatively low precisions are at least partly due to the fact that the assumed ED50s lie outside the three-times weekly dose range for this study.

Table 4 Precision for Target Dose (TD) and Minimally Effective Dose (MED)

	Sample Size	ED50	Precision (Half-width of 95% CI) for target dose/MED
TD	75	37.28[1]	2.86
	75	78[2]	5.94
MED	75	37.28[1]	2.85
	75	78[2]	5.34

1. ED50 = 16 mg (assumed ED50 for PHI113633) x 2.33 (theoretical dose ratio).
2. ED50 = 33.41 mg (estimated ED50 from PHI113633) x 2.33 (theoretical dose ratio).

For the linear model described in Section 9.4.1.2, assuming the sample size is 75, the following table describes the precision for a range of estimated slopes from 0.03 to 0.07 and different standard deviations for three-times weekly dose (SDx) and Hgb change (SDy). Based on the dose-response curve of GSK study PHI113633 and the assumed theoretical dose ratio of 2.33 between three-times weekly and QD doses, it is estimated that the slope for the linear model with three-times weekly dose as the independent variable is about 0.05. The slopes of 0.03 and 0.07 are also explored as part of the sensitivity analysis.

Table 5 Precision for Linear Regression Slop (Actual distance from slope to limits)

Slope	SDx	SDy	Precision
0.03	9.0	1.0	0.025
0.03	9.0	1.5	0.038
0.03	10.0	1.0	0.022
0.03	10.0	1.5	0.034
0.03	11.0	1.0	0.020
0.03	11.0	1.5	0.031
0.05	9.0	1.0	0.023
0.05	9.0	1.5	0.037
0.05	10.0	1.0	0.020
0.05	10.0	1.5	0.033
0.05	11.0	1.0	0.018
0.05	11.0	1.5	0.030
0.07	9.0	1.0	0.020
0.07	9.0	1.5	0.035
0.07	10.0	1.0	0.017
0.07	10.0	1.5	0.031
0.07	11.0	1.0	0.014
0.07	11.0	1.5	0.027

9.2.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The analysis populations are:

- **All Randomized:** The All randomized population consists of all randomized subjects regardless of whether they took study drug. This population will be used for listings and to describe the breakdown of populations used for the trial. Subjects will be analyzed according to the treatment group they were randomized.
- **Intent-to-Treat (ITT):** The ITT population consists of all randomized subjects who received at least one dose of study drug, have a baseline and at least one corresponding on treatment assessment. This population will be used to summarize subject disposition, baseline and demographic data and will be the primary population used in the efficacy analyses. Subjects will be classified according to the treatment group to which they were randomized.
- **Per-Protocol (PP):** The PP population consists of all ITT subjects who are not major protocol violators with regards to inclusion/exclusion criteria, investigational product compliance and concomitant medication instructions. The PP population will not be analyzed if this population comprises more than 80% of the ITT population. Protocol violations that would exclude subjects from the PP population will be defined and documented in the RAP prior to unblinding.
- **Completers:** The Completers population consists of all ITT subjects who fully complete the Day 29 study assessments without prematurely discontinuing study drug.
- **Safety:** The Safety population consists of all subjects who received at least one dose of study drug. This population will be used for all assessments of safety and tolerability. Subjects will be analyzed according to actual dose of study drug taken.
- **Pharmacokinetic (PK):** The PK population consists of all subjects from whom a PK sample has been obtained and analyzed.

9.3.2. Analysis Datasets

Efficacy inference will be based on the ITT population using an observed case dataset, comprising of all non-missing data collected up to discontinuation of study drug and withdrawal from the trial.

The dose response dataset will be based on the ITT population using an observed case dataset, comprising of all non-missing data collected up to Day 29. In addition, for subjects who have a Day 15 Hgb measurement but a missing Day 29 Hgb measurement, a Day 29 value will be imputed based on the subject's Day 1 and Day 15 data. However, subjects with missing Hgb measurements at Day 15 and Day 29 will be excluded from the dose-response analysis.

9.3.3. Interim Analysis

No interim analysis is planned.

9.4. Key Elements of Analysis Plan

The analyses planned in this protocol will be expanded upon in the RAP, any subsequent deviations will be explained either in the RAP or the final study report as appropriate.

Demographics, all baseline characteristics and subject withdrawals (from IP and study) will be summarized.

The impact of key (pre-defined) baseline subject characteristics and covariates of specific clinical interest on the primary Hgb endpoint (and potentially other key PD endpoints) will be explored.

Baseline characteristics and clinical covariates include:

- Baseline Hgb
- Prior ESA dose (high, low)
- Weight
- Gender

9.4.1. Primary Analyses

9.4.1.1. Dose Response Model

The primary endpoint is change in Hgb from baseline at Day 29. To model the dose-response relationship a three-parameter Emax model is planned, where Emax is assumed an appropriate model based on the biology and QD-dose-response modeling completed to date for GSK1278863.

This model assumes the following form:

$$\Delta Hgb = E0 + \frac{(Emax - E0)}{1 + (\frac{ED50}{dose})} + \epsilon$$

Where:

- ΔHgb is the change in Hgb from baseline at Day 29
- E0 is the placebo response
- Emax is the maximum response
- ED50 is the dose that attains the intermediate response, i.e. where (E0+Emax) / 2, is attained

- ε is a random error assumed to be normally distributed with mean zero and constant variance (σ^2)

The observed change in Hgb from baseline at Day 29 will be used as the response variable in the Emax model. Subjects who have a Day 15 Hgb measurement but a missing Day 29 Hgb measurement will be included with a Day 29 value imputed (see Section 9.3.2). Any subject who prematurely discontinues dosing prior to Day 15 will be non-evaluable for the dose-response analysis.

The Emax model will be fitted using Bayesian statistical methods (i.e. a posterior Emax model). Prior distributions for the model parameters have been based on the estimates obtained from GSK study PHI113633. This modeling provides confidence in setting prior distributions for E0, however, there is greater uncertainty in the estimation of Emax and ED50 and this will be explored in sensitivity analyses that will apply alternative (weaker) prior distributions.

Table 6 Prior Distributions for the Primary Model

Emax Model Parameters	Bayesian Priors
E0	~Normal (-0.67, $(0.146)^2$)
Emax	~Normal (5.26, $(1.337)^2$)
ED50	~Uniform (10, 120)
Tau ($1/\sigma^2$)	~Gamma (1,1)

Once the dose response model has been fitted satisfactorily, the posterior distribution of the model parameters (E0, Emax, ED50, and variance) will be summarized through means, standard deviation, median, MCSE, MCSE/SD and equal-sided 95% credibility intervals. The predicted value at a series of doses (range of possible doses from 0 to 30 will be sectioned off into a sequence of 1 increments; i.e. dose levels of 0, 1.0, 2.0, …, 30.0.) will also be monitored and the median and 95% credibility values obtained at each dose. The Hgb dose response curve will be plotted as a line through these medians and 95% credibility bands, and overlaid on a scatter plot of the observed data. This estimated dose response curve is a composite best fit at each dose and is not in itself an Emax curve.

The dose response model will be used to make the primary efficacy inferences as described in Section 9.1.

To assess the robustness of the primary efficacy conclusions the dose-response analysis will be repeated using the following sensitivity approaches:

- excluding subjects who fail to complete 29 days of treatment (completers population)
- using alternative (weaker) prior distributions for the Emax model parameters (pre-specified in the RAP)
- fitting a Frequentist Emax model to the dose-response data (if possible to fit the model)

- fitting a linear model to the dose-response data, if a linear relationship looks plausible across the three-times weekly dose range

If problems are encountered fitting a three parameter Emax model or if the Emax shape is a poor fit for the data, alternative models will be investigated until an appropriate model can be chosen (i.e. power model, linear model, quadratic model, log-transformed dose *et al.*). Full details for model selection will be provided in the RAP.

9.4.1.2. Estimation of Dose Ratio

Both Emax model (if fitted well) and linear model (if the dose-response relationship is approximately linear over the three-times weekly dose range) will be explored to estimate the dose ratio between three-time weekly and QD doses. If the dose ratio is not dose-dependent, the ratio between two estimated ED50s from the QD Emax model (GSK study PHI113633) and three-times weekly Emax model (this study) and the ratio between two estimated slopes from the QD linear model (GSK study PHI113633) and three-times weekly linear model (this study) would be equivalent to the dose ratio.

If the linear model is appropriate across the three-times weekly dose range then it is anticipated that the dose ratio estimated using the slopes from the linear models will be more reliable than that estimated using the ED50s from the Emax models, since the ED50s lie outside the QD and three-times weekly dose ranges, and therefore are poorly estimated.

One way to investigate whether the dose ratio is dose-dependent is to calculate "point estimates" of the dose ratio at two or more three-times weekly dose levels. Specifically, for each of the selected three-times weekly doses, the observed Hgb response could be used to "read off" the equivalent QD dose with the same Hgb response, using the fitted dose-response curve from GSK study PHI113633, and then derive the point estimates of the dose ratio. If these dose ratios are not consistent with each other, it would suggest the dose ratio may be dose-dependent.

Further exploratory analysis, to investigate whether the dose ratio is consistent with the theoretical dose ratio of 2.33 will be performed. Details will be provided in the RAP.

Full details for estimating the dose ratio between three-times weekly and QD doses that produce the same Hgb response will be provided in the RAP.

9.4.2. Secondary Analyses

In general, all planned secondary analyses are descriptive and estimation based.

Summaries over time and change from baseline will be produced by treatment group for hematocrit, RBC count, reticulocyte count and reticulocyte Hgb (CHr).

EPO and change from baseline in EPO will be summarized at each time point within visit by treatment group. In addition, maximum observed change from baseline across all assessments will be summarized by treatment group.

VEGF and percent change from baseline in VEGF will be summarized at each time point within visit by treatment group (based on log-transformed data). In addition, maximum observed percent change from baseline across all assessments will be summarized by treatment group.

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling & Simulation department within GlaxoSmithKline. Plasma GSK1278863 and its major metabolite concentration-time pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. Data will be graphically compared with concentration-time simulations of the current population PK model to ensure that TIW PK from this population is within the model predictions.

Full details of planned analyses of secondary endpoints will be provided in the RAP.

9.4.3. Safety Analyses

Overall safety evaluations will be descriptive using the Safety Population (as described in Section 9.3.1). Graphical and tabular displays will be presented to facilitate safety data review.

9.4.3.1. Exposure

The complete dosing experience will be listed for all subjects. The total duration of exposure (number of days), final dose and cumulative dose will be summarized by treatment group.

9.4.3.2. Adverse Events

All AE data will be summarized, sorted by the system organ class and preferred term assigned by MedDRA, and presented by treatment group. The following summaries will be provided:

- All AEs (details for all AEs will be listed)
- Serious AEs
- AEs leading to discontinuation of study drug / withdrawal from study
- Treatment-related AEs
- AEs of special interest as defined in Section 7.4.1.2

Graphical displays will include incidence of most frequent AEs and AEs of special interest.

9.4.3.3. Other Safety Measures

Laboratory Evaluations

Laboratory values and change from baseline (or percentage change from baseline, where appropriate) will be summarized by visit and treatment group. In addition, the number and percentage of patients with values outside the potential clinical importance range at each visit, and separately for those who report at least one occurrence of laboratory values of potential clinical importance will be summarized. Criteria for potential clinical importance will be specified in the RAP. The number and percentage of subjects meeting Lab withdrawal criteria will be presented.

Laboratory data will be summarized graphically, as appropriate. Graphical displays of liver function tests (LFT) will include scatter plots of shifts from baseline to maximum values and scatter plots of maximum shifts comparing across LFTs.

Vital Signs

All vital sign data and change from baseline will be summarized by visit and treatment group. For systolic and diastolic blood pressure and heart rate, the number and percentage of subjects with values of potential clinical importance will be summarized by treatment group. Criteria for potential clinical importance will be specified in the RAP.

Graphical displays of vital signs data will include box plots and mean changes over time.

Pregnancy

A listing of subjects who become pregnant will be reported by treatment group.

Electrocardiographs

All ECG measures will be included in a subject listing. Data will not be summarized by treatment group, since the ECG will be read locally as opposed to being read by a central reader.

9.4.3.4. Pharmacokinetic/Pharmacodynamic Analyses

PK data (GSK1278863 and metabolites) and PD data (e.g., EPO, VEGF, hepcidin) will be listed and summarized by planned collection time, visit, and GSK1278863 dose level.

Exploratory modeling of the plasma EPO, VEGF and/or hepcidin concentrations also may be conducted, as a function of GSK1278863 dose or PK, and may be used to further characterize the effect of GSK1278863 on the Hgb profile. Other PD data such as iron parameters and RBC indices may also be included if relevant to characterize the PD response. Additional details will be provided in separate PK/PD RAP(s) and the results of these analyses will be reported in separate PK/PD report(s).

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

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

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

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
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK/PPD 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 (i.e., prior to performing any screening procedures).
- 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 PPD procedures, PPD 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 PPD requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

PPD 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, PPD 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 PPD monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and PPD 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/PPD 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/PPD will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK/PPD 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 PPD 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.
- PPD 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, PPD standards/procedures, and/or institutional requirements.
- The investigator must notify PPD 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.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

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.

11. REFERENCES

Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int 2015; 88: 905-914.

FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease. Safety Announcement issued June 24, 2011. Link: http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm#sa

GlaxoSmithKline Document Number 2015N266524_00 Investigator's Brochure Supplement, 17-DEC-2015.

GlaxoSmithKline Document Number 2015N266524_01 Investigator's Brochure Supplement, 08-APR-2016.

GlaxoSmithKline Document Number RM2008/00267/07 Investigator's Brochure, 14-OCT-2015.

Haase VH. Mechanisms of Hypoxia Responses in Renal Tissue. JASN 2013 24: 537-541.

McGowan T, Vaccaro NM, Beaver JS, Massarella J, Wolfson M. Pharmacokinetic and pharmacodynamics profiles of extended dosing of epoetin alfa in anemic patients who have chronic kidney disease and are not on dialysis. Clin J Am Soc Nephrol 2008; 3: 1006-1014.

Pfeffer MA, Burdmann EA, Chen C et al. for the TREAT Investigators. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. N Engl J Med 2009; 361: 2019-2032.

Provenzano R, Tumlin J, Zabaneh R, *et al*. Pharmacokinetics of oral FG-4592 to treat anemia in hemodialysis patients. National Kidney Foundation Conference, 2011 (Abstract #189).

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Curve
BP	Blood Pressure
CKD	Chronic Kidney Disease
CONSORT	Consolidated Standards of Reporting Trials
CV	Cardiovascular
DBP	Diastolic Blood Pressure
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EPO	Erythropoietin
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HD	Hemodialysis
HDF	Hemodiafiltration
HF	Hemofiltration
Hgb	Hemoglobin
HIF	Hypoxia-Inducible Factor
HR	Heart Rate
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MSDS	Material Safety Data Sheet
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
PD	Pharmacodynamic
pg	Picograms

PHD	Prolyl Hydroxylase Domain enzymes
PHI	Prolyl Hydroxylase Inhibitor
PK	Pharmacokinetics
pmol	Picomoles
QD	Once Daily
QT	Q-T Interval
QTcB	Bazett's Correction of Q-T Interval
rhEPO	Recombinant Human Erythropoietin
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard Deviation
SRM	Study Reference Manual
TIW	Three Times Weekly
TSAT	Transferrin Saturation
UF	Ultrafiltration
UIBC	Unsaturated Iron Binding Capacity
ULN	Upper Limit Normal
URR	Urea Reduction Ratio
VEGF	Vascular Endothelial Growth Factor

Trademark Information

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Epoetin
HemoCue
Mircera

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

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 5.6.4:

- Immediately withdraw the subject from study treatment
- Notify the Medical Monitor within 24 hr of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 12.5.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required
- Do not restart study treatment
- Refer to the Flow chart for a visual presentation of the procedures listed below.

Safety Follow-Up Procedures for subjects with ALT ≥ 3xULN:

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin); or ALT ≥ 3xULN and INR[1] > 1.5:

- This event is considered an SAE (see Section 7.4.1.) Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hr for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

[1] INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

In addition, for all subjects with ALT ≥ 3xULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - 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.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 24 h of last dose. 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 included in the SRM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

The following are required for subjects with ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) but are optional for other abnormal liver chemistries:

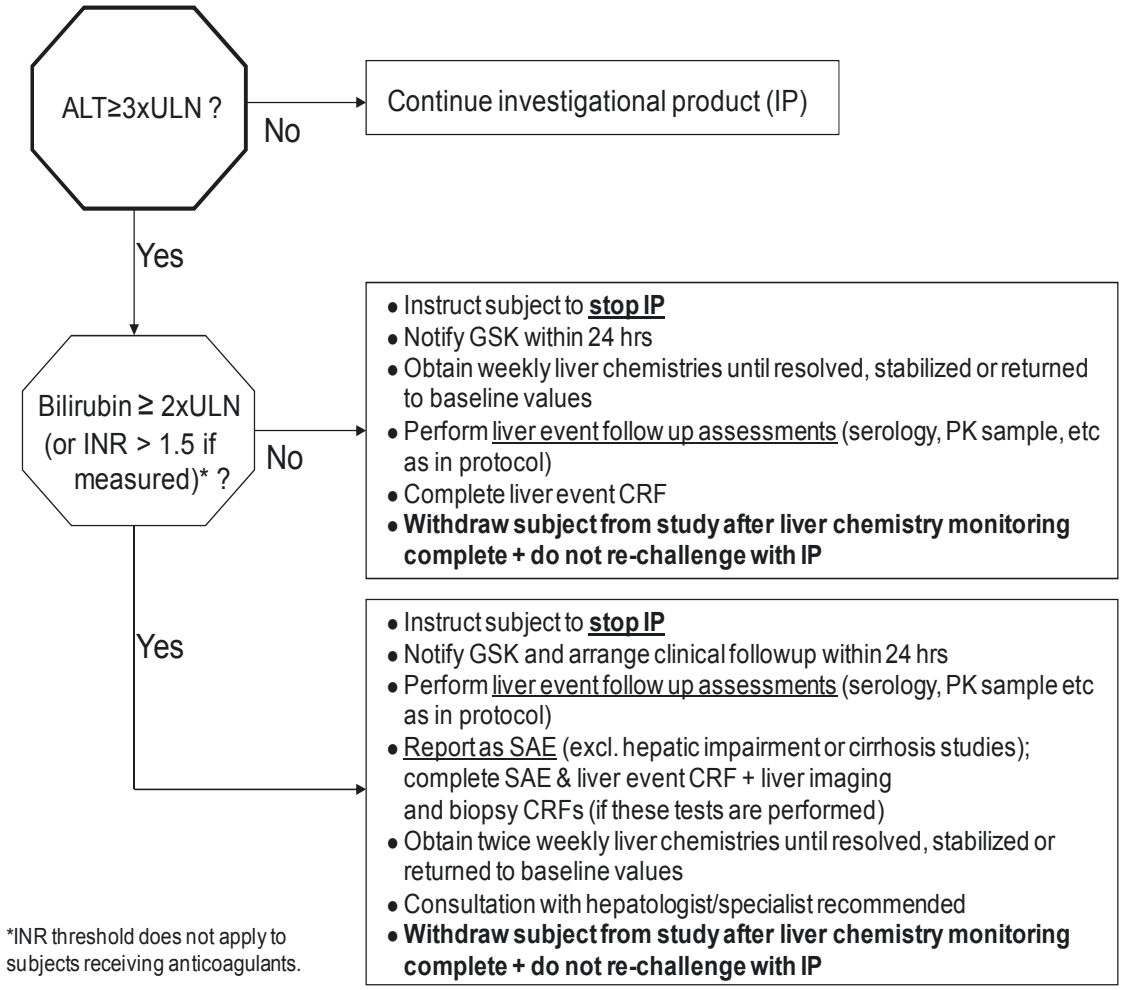
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.

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].

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

Refer to the diagram below for a visual presentation of the procedures listed above.



References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA Davern TJ Lee WM. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 2009; 37: 1779-1784.

12.3. Appendix 3: GSK1278863 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis attributed to GSK1278863 was associated with vascular congestion, microthrombi, and tissue ischemia in a number of organs. Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863. Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose levels, and dose adjustment scheme to optimize Hgb management.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 5 • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Section 7.1) • Specific guidance for discontinuation of GSK1278863 based on achieved Hgb is provided in Section 5.6.2 • Blinded monitoring of emerging safety data by an internal GSK Safety Review Team
Esophageal and gastric erosions	In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ ulcers with hemorrhage were observed. In rodents stomach erosions observed with intravenous and oral administration of GSK1278863. Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg). In clinical trials to date, mild-moderate GI signs and symptoms represent the most frequently reported adverse event, however	• Follow-up should be conducted (i.e., endoscopic examination) in subjects exhibiting symptoms of significant gastrointestinal distress as clinically appropriate • Blinded monitoring of emerging safety data by an internal GSK Safety Review Team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	causal association has not been established. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for GSK1278863.	
Death, MI, stroke, congestive heart failure, venous thromboembolism, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)	Marketed rhEPO/ESAs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD. Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863.	• Specific eligibility criteria related to CV risk are outlined in Section 5.3 • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Section 7.1) • Blinded monitoring of emerging safety data by an internal GSK Safety Review Team
Cancer-related mortality and tumor progression and recurrence	In clinical trials, use of rhEPO in patients with cancer has been associated with increased risk of cancer related morbidity and mortality. Administration of 60mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. In clinical studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations, an angiogenic factor that has been implicated in tumor growth, was observed at doses ranging from 10 to 150 mg. In clinical studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. Following review of clinical data received to date, this has not	• Specific eligibility criteria related to cancer risk are outlined in Section 5.3 • Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.6.1 • Blinded monitoring of emerging safety data by an internal GSK Safety Review Team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	been identified as a safety concern for GSK1278863.	
Pulmonary artery hypertension (PAH)	A role for HIF-regulated pathways in the pathophysiology of PAH has been suggested based on well established effects of acute and chronic hypoxia in man on the pulmonary vasculature (vasoconstriction), and by findings in patients with naturally occurring mutations that result in decreased HIF degradation [Smith, 2006; Formenti, 2011]. There have been no histopathologic findings suggestive of PAH in pre-clinical safety studies (up to 13-weeks duration in mice and dog, up to 26-weeks in rat, and up to 39-weeks in monkeys. Acute hypoxic challenge (rats): GSK1278863A produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. These hypoxia-induced PRVP changes fall within the range of PRVP differences noted among non-treated rats. Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with GSK1278863 5mg or 100mg has no clinically significant effect on echocardiographically estimated pulmonary artery systolic pressure (PASP) under either normoxic or hypoxic conditions. ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in sPAP in subjects not on dialysis. Further interrogation of sPAP data in dialysis subjects is ongoing. Following review of clinical data received to date, this has not	• Blinded monitoring of emerging safety data by an internal GSK Safety Review Team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	been identified as a safety concern for GSK1278863.	
Cardiomyopathy	Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized. Small increases in cardiac troponin in 6 month rat study were consistent with the background finding of spontaneous rodent cardiomyopathy. There were no elevations observed in cardiac troponin in 9 month monkey study. Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization. ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in LVEF. Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863.	• Blinded monitoring of emerging safety data by an internal GSK Safety Review Team
Proliferative retinopathy, macular edema, choroidal neovascularization	Increases in local (ocular) VEGF production with retinal neovascularization and macular edema observed in diabetic retinopathy and to choroidal leakage, edema and neovascularization seen in age-related macular degeneration [Nguyen, 2006]. Administration of 60 mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO	• Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted • Blinded monitoring of emerging safety

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	increases were observed. No ocular abnormalities were seen in non-clinical studies of up to 13 weeks duration in mice and dogs, 26 weeks in rats, and 39-weeks in monkeys. In clinical studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg. In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentrations were variable but similar relative to control. Ophthalmologic assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization. Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863.	data by an internal GSK Safety Review Team
Exacerbation of rheumatoid arthritis	In inflamed rheumatic joints, activation of HIF- related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra, 2010; Muz, 2009]. No abnormalities seen in non-clinical studies conducted to date. Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863.	• Blinded monitoring of emerging safety data by an internal GSK Safety Review Team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug-drug interactions	Co-administration of GSK1278863 with a strong CYP2C8 inhibitor increased the Cmax and AUC of GSK1278863, 4- and 19-fold, respectively, while co-administration of a weak inhibitor increased the Cmax and AUC of GSK1278863 by 1.3- and 1.5-fold, respectively. Population PK analysis from completed Phase 2 studies suggests that co-administration of GSK1278863 with a moderate CYP2C8 inhibitor, leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. GSK1278863 is an inhibitor of CYP2C8 *in vitro,* with an IC_{50} value of 21 µM. Population PK analysis from completed Phase 2 studies suggests that co-administration of GSK1278863 with clopidogrel (a moderate CYP2C8 inhibitor) leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Co-administration of GSK1278863 with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. Co-administration of GSK1278863 with potent BCRP inhibitors has the potential to increase exposure of GSK1278863. Use of BCRP inhibitors (mostly weak) was found to result in a small change in metabolite exposure (20% increase in AUC). GSK1278863 is an inhibitor of OATP1B1/1B3 *in vitro,* with IC_{50} values of 6 µM and 11 µM, respectively. A clinical drug interaction study between 25mg GSK1278863 with either a CYP2C8 substrate or an OATP1B1/1B3 substrate showed that there is no PK interaction at this dose of GSK1278863.	• Co-administration of GSK1278863 with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.9.2 • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.9. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Section 7.1) • Specific guidance for discontinuation of GSK1278863 based on achieved Hgb is provided in Section 5.6.2 • Blinded monitoring of emerging safety data by an internal GSK Safety Review Team

References

Formenti F, Beer PA, Croft QPP, Dorrington KL, Gale DP, Lappin TRJ, Lucas GS, Maher ER, Maxwell PH, McMullin MF, O'Connor DF, Percy MJ, Pugh CW, Ratcliffe PJ, Smith TG, Talbot NP, Robbins PA. Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2α gain-of-function mutation. FASEB J. 2011; 25:2001-2011.

Muz B, Khan MN, Kiriakidis S, Paleolog EM. The role of hypoxia and HIF-dependent signalling events in rheumatoid arthritis. Arthritis Research & Therapy 2009; 11:201-209.

Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J, Zimmer-Galler I, Do DV, Campochiaro PA. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. Amer J Ophthalmol 2006; 142:961-969.

Smith TG, Brooks JT, Balanos GM, Lappin TR, Layton DM, Leedham DL, Liu C, Maxwell PH, McMullin MF, McNamara CJ, Percy MJ, Pugh CW, Ratcliffe PJ, Talbot NP, Treacy M, Robbins PA. Mutation of von Hippel-Lindau tumour suppressor and human cardiopulmonary physiology. PLoS Med 2006;3:e290

Westra J, Molema G, Kallenberg CG. Hypoxia-inducible factor-1 as regulator of angiogenesis in rheumatoid arthritis - therapeutic implications. Curr Med Chem 2010; 17:254-63.

12.4. Appendix 4: Genetic Research

Genetics – Background

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

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK1278863 or any concomitant medicines;
- Susceptibility to anemia associated with chronic kidney disease; severity, and progression of disease(s) under study and related conditions

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

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

Study Population

Any subject who is enrolled in the study can participate in genetic research. 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. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, 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 sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

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

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

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

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

References

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

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

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

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • **NOTE:** An AE can therefore be any 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). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <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.

12.5.2. Definition of Serious Adverse Events

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

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or 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 Section 12.2 Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for events that represent the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension

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

12.5.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the eCRF
- 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 eCRF 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.

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

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

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

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool. • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the PPD Safety Hotline. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form and fax it to the PPD Safety Hotline or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Medical Monitor/Sponsor Information Page.

12.6. Appendix 6: Female Eligibility Criteria

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum hCG test for females of reproductive potential only), not breastfeeding, or at least one of the following conditions applies:

- Reproductive potential and agrees to follow one of the options listed in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (see below) from 30 days prior to the first dose of study treatment and until seven days after the last dose of study treatment and completion of the follow-up visit.

- Non-reproductive potential defined as either:

    - Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;

    - Postmenopausal defined as 12 months of spontaneous amenorrhea and age appropriate (i.e. >50 years). In questionable cases, a blood sample with simultaneous FSH and estradiol consistent with menopause is confirmatory (FSH 23.0-116.3 mIU/mL and estradiol ≤10 pg/mL (or ≤37 pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

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

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label.

- Intrauterine device or intrauterine system that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2011]

- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]

- Injectable progestogen [Hatcher, 2011]

- Contraceptive vaginal ring [Hatcher, 2011]

- Percutaneous contraceptive patches [Hatcher, 2011]

- Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on the male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label.

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

12.6.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.5 Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication and be withdrawn from the study

Reference

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

12.7. Appendix 7: Country Specific Requirements

No country-specific requirements exist.

12.8. Appendix 8: Protocol Changes

Protocol Amendment 01

Amendment 01 is applicable to all sites.

Brief Summary of Protocol Changes and Rationale for Revisions:

Inclusion criterion #5 was modified to include the complete timeframe in which this criterion is applicable. Other eligibility criteria have been clarified or updated for consistency with project level requirements. Minor clarifications were made throughout the protocol, including clarifications related to hemoglobin stopping criteria, wording of the AEs of special interest, visit windows and the Time and Events Table. References to IB Supplements 1 and 2 were added, and corresponding updates to the Risk Assessement Table were made. Flexible language was added to allow for subjects to be dosed outside of the study clinic in exceptional circumstances. The definition of the PK analysis population was added.

List of Specific Changes and Rationale:

1. Clarification of allowable window for study visits

Rationale: To clarify that the allowable window of ±2 days which was allowed for post-randomization visits is also applicable to the screening visits.

Section 1 Protocol Synopsis, Treatment Arms and Duration, and Section 4.2 Treatment Arms and Duration

Added Text: A window of ±2 days will be allowed for visits during the Screening period.

Added Text: A window of ±2 days will be allowed for visits during the Treatment period.

Section 7 Study Assessments and Procedures

Amended Text using revision marks: To allow scheduling flexibility, ~~post-randomization~~ study visits should occur within a window of ±2 days, **except~~ing~~ ~~that~~ for subjects on a three times weekly dialysis schedule ~~Day 15 or 19 is not~~ <u>for whom study visits must not be scheduled</u> on the first dialysis session of the week**.

2. Clarification that ESA therapy can restart after the follow-up visit

Rationale: To clarify the expectation that treatment with ESA, which was to be discontinued prior to Day 1, should be held through the follow-up period, and therapy with ESAs can resume after the follow-up visit. Flexibility is included in cases where there is clinical rationale to restart ESA after the last dose of study treatment.

Section 1 Protocol Synopsis, Treatment Arms and Duration, and Section 4.2 Treatment Arms and Duration

Added Text: At Day 29, all subjects will receive their last dose of study treatment and should not re-start ESA therapy until after the follow-up visit (Day 43). However, if the Investigator has a compelling clinical reason why a subject should restart ESA between Day 29 and Day 43, then ESA may be restarted prior to Day 43.

3. Correction of the timeframe in which ESA dosing must remain stable

Rationale: The timeframe in which the ESA dosing must remain stable was corrected to include the 28 day screening period. ESA dosing is required to remain stable from 4 weeks prior to the start of the screening period through to Day 1.

Section 1 Protocol Synopsis, Type and Number of Subjects, and Section 4.3 Type and Number of Subjects

Amended Text with revision marks: The range of Hgb values for study eligibility is 9.0 - 11.5 g/dL and the subjects must have received the same ESA product with total weekly doses that varied by no more than 50% ~~during the 4 weeks prior to the Screening visit~~ from 4 weeks prior to the Day -28 Screening visit through to Day 1.

Section 5.2 Inclusion Criteria

Amended Text with revision marks: **5. Stable ESA dose**: Treated with the same ESA (epoetins or their biosimilars, or darbepoetin or methoxy PEG-epoetin beta) with total weekly dose varying by no more than 50% ~~during the 4 weeks prior to Day -28~~from 4 weeks prior to Day -28 through Day 1 (randomization).

4. Clarification of the number of evaluable subjects expected in each treatment group

Section 1 Protocol Synopsis, Type and Number of Subjects, and Section 4.3 Type and Number of Subjects

Amended Text: Approximately 200 subjects will be screened to achieve approximately 90 randomized and 75 evaluable subjects ~~for a total of~~, with approximately 15 evaluable subjects per treatment group.

5. Update to references for the Investigator Brochure Supplements

Rationale: Added references for IB Supplement 1 and 2, which were published after the original protocol was published.

Section 2.1 Brief Background, Section 4.6 Benefit:Risk Assessment, Section 5 Selection of Study Population and Withdrawal Criteria, Section 5.3 Exclusion Criteria, Section 11 References

Added to applicable sections: IB Supplements [GlaxoSmithKline Document Number 2015N266524_00, GlaxoSmithKline Document Number 2015N266524_01]

Section 5.3 Exclusion Criteria

Rationale: For Exclusion Criterion #17, the reference to the IB was removed, rather than being updated, since the reference is not required to be included in the eligibility criterion text and it is understood that the list of excipients of the investigational product can be found in the IB and IB supplements.

Amended Text with revision marks:

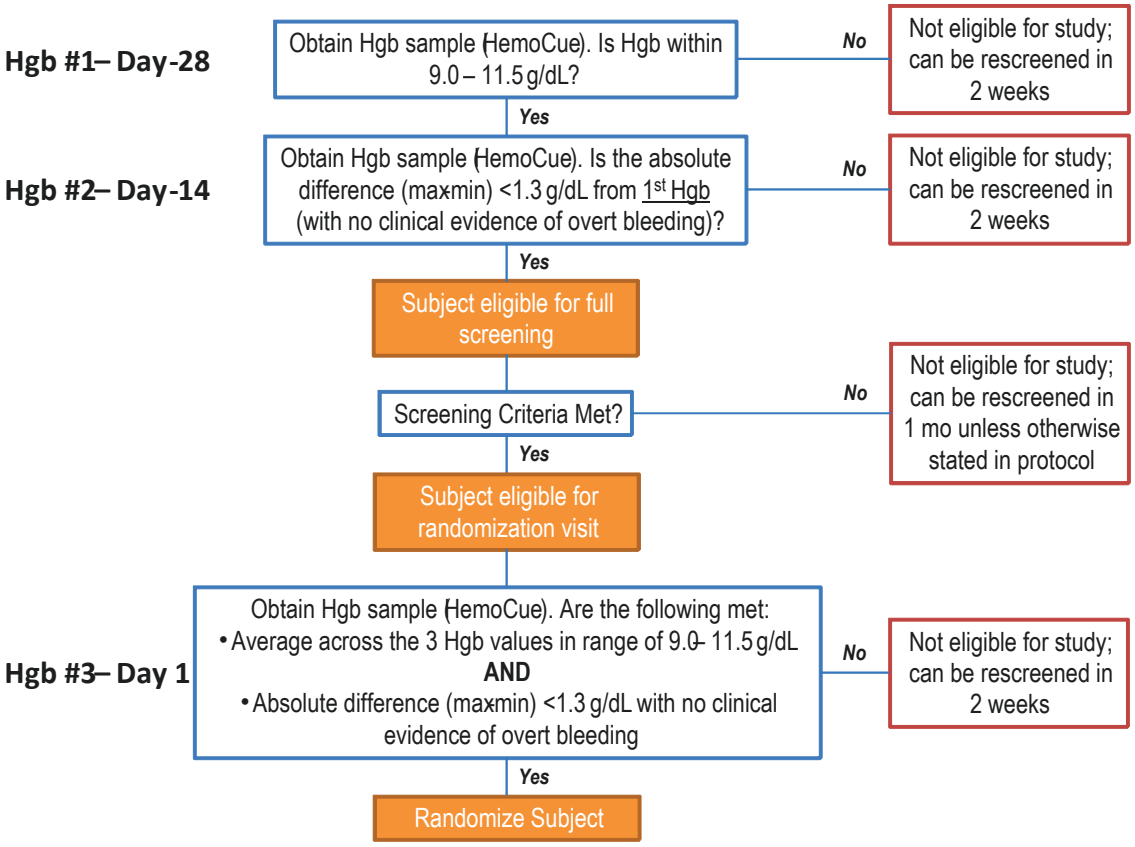
17. Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product ~~(see GSK1278863 IB for list of excipients [GlaxoSmithKline Document Number RM2008/00267/07])~~.

6. Clarification of the Hemoglobin Stability Criteria

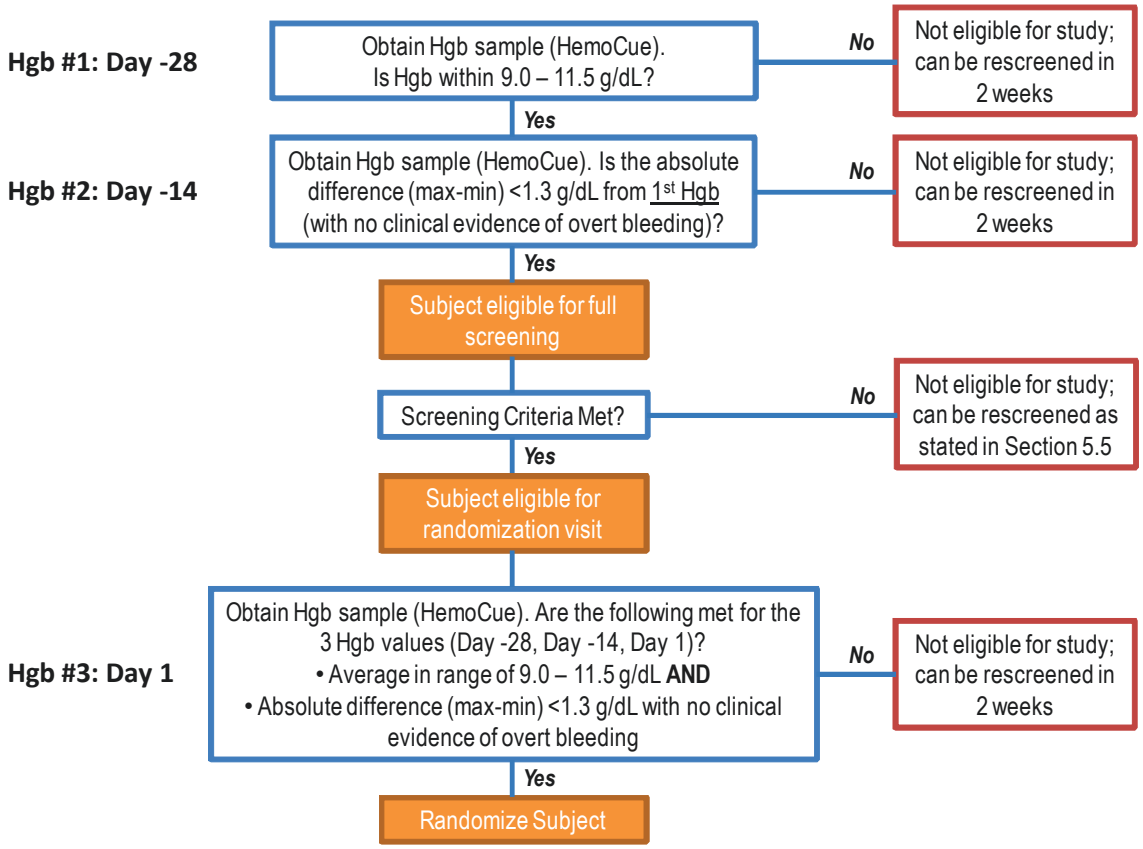
Rationale: Text was revised to remove any ambiguity to the hemoglobin stability criteria and the calculations that are to be made at the Day 1 visit. Text was also revised to clarify the timeframe in which subjects could be rescreened.

Section 5.1, Figure 2

Original Figure:



Amended Figure:



7. Clarification of the inclusion criterion for stable iron replacement therapy

Rationale: To clarify that the ≤100 mg/week limit relates to IV iron supplementation, and to clarify criterion by changing the term stable to state that the dose must not be changed.

Section 5.2 Inclusion Criteria

Amended Text with revision marks: **6. Iron replacement therapy**: Subjects may be on ~~stable~~ maintenance oral or IV ~~(≤100 mg/week)~~ iron supplementation. If subjects are on oral ~~or IV~~ iron, then the type of iron and doses must ~~be stable~~ not be changed for the 4 weeks prior to Day -28, during the screening phase, and through the 29 days of treatment. If subjects are on IV iron, then doses must be ≤100 mg/week, and doses must not be changed for the 4 weeks prior to Day -28, during the screening phase, and through the 29 days of treatment.

8. Clarification of the exclusion criterion for planned kidney transplant

Rationale: To clarify that any planned kidney transplant from a living donor is excluded, including a planned living-unrelated kidney transplant.

Section 5.3 Exclusion Criteria

Amended Text with revision marks: **2. Renal transplant**: Planned for living-related or living-unrelated kidney transplant

9. Clarification of the exclusion criterion for administration of Mircera

Rationale: To clarify that the timeframe for restriction of Mircera administration is dependent upon the dosing schedule of Mircera.

Section 5.3 Exclusion Criteria

Amended Text with revision marks: **4. Mircera**: Administration of Mircera (methoxy PEG-epoetin beta) within ~~the prior 4 weeks through Day 1 (randomization)~~ 2 weeks prior to Day 1 if subject is on a once-every-2-weeks schedule or within 4 weeks prior to Day 1 if subject is on a once-every-4-weeks schedule.

10. Update to the exclusion criterion for malignancy

Rationale: The exclusion criterion for malignancy was updated to be in alignment with the current requirements for the GSK1278863 program.

Section 5.3 Exclusion Criteria

Amended Text: **16. Malignancy:** History of malignancy within the two years prior to Day -28 through to Day 1 (randomization) or currently receiving treatment for cancer, or has a known ~~≥ 4 cm~~ complex kidney cyst (i.e. Bosniak Category II F, III of IV) > 3cm. **NOTE:** The ONLY exception is squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥ 8 weeks prior to Screening.

11. Clarification of the screening visit at which the diagnostic assessments should be verified for eligibility

Rationale: To clarify the screening visit during which the diagnostic assessments are required to be verified.

Section 5.3 Exclusion Criteria

Added Text under the heading "**DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA"**: (To be verified on Day -28 only)

12. Clarification of screen failures

Rationale: To clarify that after consent, a subject must attend at least the first screening visit before he/she can be considered a screen failure.

Section 5.5 Screening/Baseline/Run-in Failures

Added Text: In this study, a subject can become a screen failure at any time from the Day -28 visit to the Day 1 visit, prior to randomization.

13. Clarification of actions to be taken for subjects who are permanently discontinued from study medication

Rationale: To clarify that a subject who is permanently discontinued from study medication should return for an Early Withdrawal visit and a Follow-up Visit.

Section 5.6.1 Criteria for Permanent Discontinuation from Study Medication and Early Withdrawal

Amended Text with revision marks: Subjects must **permanently discontinue study medication** ~~and be withdrawn from the study~~ for the following reasons:

Added Text:

The subject should attend the clinic as soon as possible to complete the Early Withdrawal assessments and return for a Follow-up visit as described in Section 7.1, Time and Events.

The reason for discontinuation of study medication and date of last dose will be recorded in the eCRF.

14. Clarification of Hemoglobin Stopping Criteria

Rationale: Clarification of the hemoglobin stopping criteria by eliminating the discrepancy between the text and the figure.

Section 5.6.2 Hemoglobin Stopping Criteria

Amended Text with revision marks:

- Confirmed Hgb (2 measurements by HemoCue pre-dialysis) ≦ < 7.5 g/dL

Original Text within the figure:

Hgb (g/dL) at visit	Action	
<7.5	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug and withdraw subject from the study.	
≥7.5-<13.0	≥2.0 decrease in Hgb over 2 weeks	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug and withdraw subject from the study.
	<1.absolute change in Hgb over 2 weeks	Continue study drug
	≥1.0 increase in Hgb over 2 weeks	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug and withdraw subject from the study.

≥13.0	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, consider permanently discontinuing study drug and withdrawing subject from the study in consultation with GSK Medical Monitor.

Amended Text within the figure:

Hgb (g/dL) at visit	Action	
<7.5	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug.	
≥7.5-<13.0	≥2.0 decrease in Hgb over 2 weeks	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug.
	<1.0 increase or <2.0 decrease in Hgb over 2 weeks	Continue study drug
	≥1.0 increase in Hgb over 2 weeks	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study drug.
≥13.0	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, consider permanently discontinuing study drug in consultation with GSK Medical Monitor.	

Rationale: While the HemoCue values will be the primary values used to monitor hemoglobin for safety purposes, text was added to clarify how discrepancies in hemoglobin values between central laboratory and HemoCue device should be managed.

Added Text: In cases where the Hgb values from the central laboratory meet any of the Hgb stopping criteria in the above table, but the Hgb values from the HemoCue device do not, then the Investigator and the GSK Medical Monitor should discuss this situation before potentially discontinuing study medication.

Amended Text with revision marks: If a subject is permanently discontinued from study medication, then the subject should attend the clinic as soon as possible to complete the Early Withdrawal assessments and Follow-up visit (see Section 7.1, Time and Events) as described in Section ~~5.6~~ 5.7.

~~In all cases,~~ The reason for discontinuation of study medication and date of last dose will be recorded in the eCRF.

15. Revision to allow flexibility for subjects to self-administer study medication on additional days

Rationale: Currently the protocol only allows subjects to take the study medication home prior to the PK visit. This change will allow some flexibility for subjects to take medication home on additional occasions.

Section 6.1 Investigational Product and Other Study Treatment

Amended Text with revision marks: All study medication ~~will be taken~~ should be taken in the clinic **EXCEPT** prior to the PK day (Day 15 study visit), or on other days only if the Investigator and GSK Medical Monitor agree that it will not interfere with the study procedures or affect the subject's compliance with the protocol.

Added Text: The study site must ensure that the date and time the subject took each dose of study treatment is documented.

16. Clarification of Text

Rationale: GSK1278863 dose titrations were not allowed in this study. Non-applicable text was deleted.

Section 6.9.1 Permitted Medications and Non-Drug Therapies

Amended Text with revision marks: ~~GSK1278863 dose titrations and~~ Hemoglobin stopping criteria mitigate risk of increased pharmacology if co-administered.

17. Clarification of Time and Events Table

Rationale: Clarifications were made to the Time and Events table for consistency with changes made to other sections as well as to remove ambiguities in original table.

Original Table:

7.1 Time and Events Table

Protocol Activity[1]	Screening		Day 1	Treatment Period				Follow-up
	Week -4	Week -2		Day 15[2]	Day 29[2]	Un-scheduled	Early Withdrawal	Day 43 ± 3
Informed Consent	X							
Entry Criteria	X		X					
Physical, Medical History, Demography	X							
HemoCue Hgb	X	X	X	X	X	X	X	
IVWRS Call	X	X	X	X	X	X	X	X
Females Only: Serum Pregnancy Test		X					X	X
Females Only: Estradiol and FSH (if required)[3]		X						
ECG	X				X		X	
Vitals (Pre-dialysis and Post-dialysis)[4]		X	X	X	X	X	X	X
Clinical Chemistry		X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X
Folate	X							
Ferritin, transferrin, total iron, UIBC	X		X		X		X	X
Pharmacokinetic/Pharmacodynamic Samples			X	X	X		X[5]	
Blood draw for PGx			X					
Adverse Events Assessment			X	X	X	X	X	X
Review Concomitant Medications	X		X	X	X	X	X	X

1. All assessments should be done pre-dialysis except as noted.
2. Allowable time window ±2 days.
3. As detailed in Inclusion Criteria in Section 5.2.
4. Weight measured post-dialysis only & height measured at screening only.
5. Obtain samples as per the Day 29 visit in Table 2. If subject does not receive a dose of study medication at this early withdrawal visit, no post-dose PK/PD samples should be obtained.

Amended Table:

7.1 Time and Events Table

Protocol Activity [1, 2]	Screening		Day 1	Treatment Period				Follow-up
	Week -4	Week -2		Day 15	Day 29	Un-scheduled	Early Withdrawal	Day 43 ± 3 [6]
Informed Consent	X							
Entry Criteria	X		X					
Physical, Medical History, Demography	X							
HemoCue Hgb	X	X	X	X	X	X	X	
IVWRS Call	X	X	X	X	X	X	X	X
Females Only: Serum Pregnancy Test [3]		X					X	X
Females Only: Estradiol and FSH (if required) [3]		X						
ECG	X				X		X	
Vitals (Pre-dialysis and Post-dialysis) [4]		X	X	X	X	X	X	X
Clinical Chemistry		X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X
Folate and Vitamin B_{12}	X							
Ferritin, transferrin, total iron, UIBC	X		X		X		X	X
Pharmacokinetic/Pharmacodynamic Samples			X	X	X		X [5]	
Blood draw for PGx			X					
Adverse Events Assessment [7]			X	X	X	X	X	X
Review Concomitant Medications	X		X	X	X	X	X	X

1. All assessments should be done pre-dialysis except as noted.
2. Allowable time window of ± 2 days for all study visits, except the follow-up visit for which it is ± 3 days.
3. As detailed in Exclusion Criteria in Section 5.3.
4. Weight measured post-dialysis only & height measured at screening only.
5. Obtain samples as per the Day 29 visit in Table 2. If subject does not receive a dose of study medication at this early withdrawal visit, no post-dose PK/PD samples should be obtained.
6. Subjects who withdraw early from treatment should attend a follow-up visit 14 days ± 3 days after the last dose of study treatment.
7. Serious adverse events are assessed from the time of consent as stated in Section 7.4.1.1.

18. Update of Terms for Adverse Events of Special Interest

Rationale: Adverse events of special interest terms were updated to be consistent with current list of terms for the GSK1278863 project.

Section 7.4.1.2 Adverse Events of Special Interest

Amended Text:

- ~~Risk of~~ Death, MI, stroke, venous thromboembolism, thrombosis of vascular access

Amended Text:

- ~~Increased~~ Cancer-related mortality and tumor progression and recurrence

19. Clarification of Laboratory Assessments

Rationale: To clarify which subjects require the screening tests.

Section 7.4.6 Clinical Safety Laboratory Assessments, Table 3

Amended Footnote to table with revision marks: 1 ~~As needed in women of non-child bearing potential only.~~ As required per Appendix 6.

20. Inclusion of the PK Analysis Population

Rationale: The definition of the PK Analysis Population was added.

9.3.1 Analysis Populations

Added Text:

- **Pharmacokinetic (PK):** The PK population consists of all subjects from whom a PK sample has been obtained and analyzed.

21. Update to Risk Assessment Table

Rationale: The GSK1278863 Risk Assessment Table was updated to be consistent with the current risk assessment for the GSK1278863 project.

Section 12.3 Appendix 3

Amended Text with revision marks in "Potential Risk of Clinical Significance" Column:

~~Risk of~~ Death, MI, stroke, congestive heart failure, venous thromboembolism, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)

~~Increased~~ Cancer-related mortality and tumor progression and recurrence

Added text in “Mitigation Strategy” Column for the potential risk of “Proliferative retinopathy, macular edema, choroidal neovascularisation”:

Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted

22. Correction of Minor Typographical Errors

Rationale: Minor typographical errors were corrected.

Section 2.1 Brief Background

The original text “rick” was corrected to “risk”

Section 5.3 Exclusion Criteria

The original text in exclusion criteria #6 and #10 “though” was corrected to “through”