TITLE PAGE

Division : Worldwide Development

Information Type : Clinical Protocol

Title : A 52-week, Phase III, open-label, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese non-dialysis and peritoneal dialysis subjects with anemia associated with chronic kidney disease.

Compound Number : GSK1278863

Development Phase III

Effective Date : 03-JUL-2017

Protocol Amendment Number: 04

Author(s) :

PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N266248_00	2016-02-18	Original
2015N266248_01	2016-04-12	Amendment No. 1
Clarification of the method of administration of control, clarification of the withdrawal/dropout criteria, addition of medical devices, clarification of the time and events, clarification of procedures after occurrence of liver events		
2015N266248_02	2016-08-01	Amendment No. 2
Clarification of exclusion criteria, clarification of the procedure for the ophthalmology exam at the re-screening, clarification of analysis populations, updates of risk assessment, updates of the procedures for SAE reports		
2015N266248_03	2017-03-08	Amendment No. 3
Addition of Cohort3, change of the starting dose for ND subjects, ESA non-users, change of analysis population for efficacy analyses, addition of Week 2 visit, clarification of the timing of eligibility assessment regarding exclusion criteria, clarification of prohibited medications, correction of adverse events of special interest		
2015N266248_04	2017-07-03	Amendment No. 4
Addition of target number of ND subjects, change for definition of screen failures, clarification of the withdrawal/dropout criteria for prohibited medication, clarification of definition of overdose of GSK1278863, updates of adverse events of special interest, change of a dropout rate after the start of study treatment, addition of details of sensitivity analyses in primary efficacy analysis, updates and correction of erroneous description of risk assessment		

Sponsor Signatory:

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The IMMS document approved is as follows:

Unique ID：090033ec841233f5

System Version：2.0

Effective Date：3 Jul 2017

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and the rivision.
- 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 Signature	Date

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Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

Objective(s)/Endpoint(s)

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	• Number (%) of subjects with mean Hgb in the target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change from baseline in Hgb at Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category at Week 4
• To evaluate dose adjustment scheme of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustment scheme of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control of GSK1278863 in PD subjects	• Hgb and change from baseline at each assessment visit • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment visit • Time (%) in Hgb target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52) • Time (in days) to reach the lower Hgb target

Objective	Endpoint
	(11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks • Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes
• To evaluate the effect on iron use of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate effect on iron use of GSK1278863 in PD subjects	• Dose of oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To evaluate the effect on iron metabolism of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on iron metabolism of GSK1278863 in PD subjects	• Change from baseline in ferritin • Change from baseline in transferrin saturation (TSAT) • Changes from baseline in hepcidin, serum iron, and total iron binding capacity (TIBC)
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To evaluate the effect on progression of Chronic Kidney Disease (CKD) of GSK1278863 in ND subjects using epoetin beta pegol as control	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To evaluate the effect on health-related QoL (HR-QoL) of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on HR-QoL of GSK1278863 in PD subjects	SF-36 • Changes from baseline in SF-36 HR-QoL scores [Physical Component Summary (PCS), Mental Component Summary (MCS), and 8 subscales] EuroQol Health Utility Index (EQ-5D-5L) • Change from baseline in EQ-5D-5L score • Change from baseline in EQ-5D-5L Visual Analog Scale (VAS)
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest

Objective	Endpoint
	• Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

Study Design

This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (demonstration of non-inferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 286 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. Cohort 1 (ND subjects) and Cohort 2 (PD subjects) were set for target population of this study when the study was planned. Cohort 3 is newly added in Protocol amendment (Amendment No.3). ND subjects will be randomized not to Cohort 1 but to Cohort 3 after Protocol amendment No.3.

<table>
<tr><th>Patient population</th><th>Cohort</th><th>Treatment group</th><th colspan="2">Target number of subjects (randomized)</th></tr>
<tr><td rowspan="4">ND patient</td><td rowspan="2">Cohort 1[1]</td><td>GSK1278863 group (starting dose: 4 mg)</td><td rowspan="2">169 subjects[4)]</td><td rowspan="4">286 subjects[5)]</td></tr>
<tr><td>Epoetin beta pegol group</td></tr>
<tr><td rowspan="2">Cohort 3[2)]</td><td>GSK1278863 group (starting dose: 2 mg or 4 mg[3)])</td><td rowspan="2">117 subjects</td></tr>
<tr><td>Epoetin beta pegol group</td></tr>
<tr><td>PD patient</td><td>Cohort 2</td><td>GSK1278863 group (starting dose: 4 mg)</td><td colspan="2">50 subjects</td></tr>
</table>

1) At least 50 ESA users and at least 50 ESA non-users will be randomized to Cohort 1.

2) ND patients will be randomized to Cohort 3 and at least 80 ESA non-user will be randomized after Protocol Amendment No.3.

3) GSK 1278863 starting dose in Cohort 3 as below

- ESA non-user (baseline Hgb 8.0-<9.0 g/dL):4 mg
- ESA non-user (baseline Hgb 9.0-<11.0 g/dL):2 mg
- ESA user: 4 mg

4) The exact number of ND subjects randomized to Cohort 1

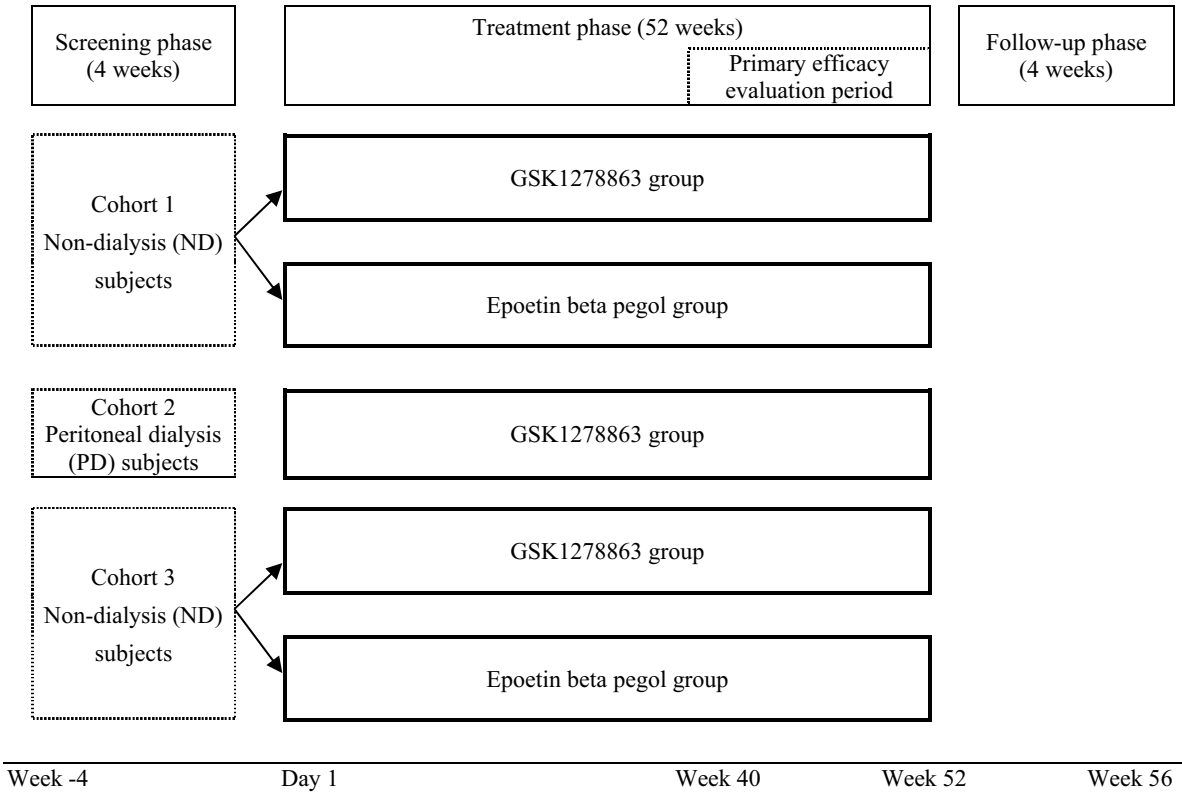
5) Subjects will be randomized in a 1:1 ratio to one of the two treatment groups

ESA: erythropoiesis-stimulating agent

For the patient populations in either cohort, the Hgb criteria are specified according to the presence or absence of prior ESA: ESA non-users with an Hgb level of ≥ 8.0 to <11.0 g/dL and ESA users with an Hgb level of 9.0 to 13.0 g/dL will be included in the study.

In Cohort 1 and Cohort 3, eligible ND subjects [total of 286 subjects (169 subjects in Cohort 1, 117 subjects in Cohort 3)] will be stratified by the current ESA therapy and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group.
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown below.



Method of Administration of Study Medication in Each Treatment Group

In each treatment group, study medication will be administered as follows:

GSK1278863 group:

- Cohort 1 (ND subjects) and Cohort 2 (PD subjects)
  Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1.
- Cohort 3 (ND subjects)
  - For ESA non-user with Baseline Hgb ≥8.0 and <9.0 g/dL, Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1.
  - For ESA non-user with Baseline Hgb ≥9.0 and <11.0 g/dL, Treatment with GSK1278863 will be started at a dose of 2 mg once daily on Day 1.
  - For ESA users, Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1.

After Week 4, dose adjustments will be made within the dose range of 1-24 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13 0 g/dL).

- Epoetin beta pegol group (ND subjects):
  - ESA non-users: Subcutaneous treatment with epoetin beta pegol will be started at a dose of 25 μg once every 2 weeks on Day 1. Subsequently, dose adjustments will be made within the dose range of 25-150 μg every 4 weeks according to the prespecified initial dose adjustment criteria to achieve the lower limit of the Hgb target (11.0 g/dL). Once Hgb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm. After it is confirmed that all of the criteria for dosing interval

change are met, dosing frequency will be changed to once every 4 weeks, and dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target Hgb range (11.0-13.0 g/dL).

- ESA users: Prior ESA therapy will be replaced with subcutaneous treatment with epoetin beta pegol at the equivalent dose once every 4 weeks according to prespecified dose conversion. Subsequently, dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL).

Analysis

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during in the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a two-sided significance level of 5% with a sample size of 100 subjects per group. Assuming a dropout rate of approximately 30%, 143 subjects will be randomized to each group. For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half the width of the 95% CI for mean Hgb during in the primary efficacy evaluation period is 0.493 g/dL. During this study, the protocol has been amended accordingto the change in starting dose for ND, ESA non-users in the GSK1278863 group; ESA non-users in Cohort 1 will be excluded from primary efficacy analysis according to this amendment. Additionally the protocol amendment has been made (Amendment No.4), in which the assumption of dropout rate after the start of study treatment was changed from 25% to 30% and 143 subjects per group (total 286 subjects) will be randomized. (see Section 9.2.1).

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects. A mixed model for repeated measurements (MMRM) will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. As a preliminary assessment, it will be confirmed if the lower and upper limit of 95% CI for mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL) In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in mean Hgb during the primary efficacy evaluation period will be estimated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e. lies fully within the range -1.0 to 0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimate in the GSK1278863 group is within the target range.

The primary efficacy population will be the ITT Population (excluding non-ESA users from Cohort 1), and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted.

Following sensitivity analyses will be conducted to assess robustness of the study result.

- If ND, ESA users whose dose level was decreased by one step at Week 2 exist in cohort 3, sensitivity analysis excluding these subjects from primary analysis will be conducted.

- Sensitivity analysis to primary efficacy analysis for all ND patients in Cohort 1 and Cohort 3 will be conducted.
- If there are Hgb considered to be impacted by blood transfusion or marketed ESAs, sensitivity analysis excluding the Hgb values from the analyses of primary endpoint will be conducted.
- Analysis of covariance (ANCOVA) will be conducted as sensitivity analysis to MMRM. This model includes treatment group and baseline Hgb level. The analysis population will be mITT population and the same analysis will be repeated in the PP population.
- A tipping point analysis based on multiple imputation will be conducted as sensitivity analysis to missing data assumption. This analysis explores a point where non-inferiority is not confirmed (tipping point) by changing assumption to missing data and repeating imputation. The analysis population will be ITT population and the same analysis will be repeated in the mITT and PP population.

Further details of sensitivity analyses will be provided in the Reporting and Analysis Plan (RAP).

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.
In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and the current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for the odds ratio is greater than 1.0.

2. INTRODUCTION

GSK1278863 is a hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitor (PHI) that stimulates erythropoiesis in the same manner as innate response to hypoxia and is currently being developed as a new treatment for renal anemia.

2.1. Study Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

2.2. Background

Renal anemia is diagnosed in many patients with CKD, and the prevalence of renal anemia increases with progression of CKD [Akizawa, 2011]. Causes of anemia in CKD patients include absolute or relative deficiency of erythropoietin (EPO), shortened erythrocyte survival, and reduced iron availability. Anemia is further exacerbated by chronic blood loss associated with hemodialysis procedure, infection, and functional hemolysis [Japanese Society for Dialysis Therapy, 2008].

GSK1278863 is a hypoxia-inducible factor-prolyl hydroxylase inhibitor that is currently being developed as a treatment for renal anemia. Data in Japanese patients have been collected from a Japanese Phase II 4-week treatment study in Japanese hemodialysis (HD) subjects (PHI116099: 97 Japanese subjects), an international multi-center Phase II 24-week treatment study in HD subjects (PHI113633: including 24 Japanese subjects), and an international multi-center Phase II 24-week treatment study in ND subjects (PHI113747: including 42 Japanese subjects). In these clinical studies, GSK1278863 increased endogenous EPO, reduced hepcidin, and increased Hgb in HD and ND subjects including Japanese subjects. In addition, GSK1278863 increased Hgb at lower blood EPO concentrations than existing erythropoiesis-stimulating agents (ESAs).

Data from completed clinical and clinical pharmacology studies and the preclinical data safety package are provided in the Development Core Safety Information found in the current GSK1278863 Investigator Brochure (IB). A benefit: risk assessment, including risk mitigation strategies, is outlined in Section 4.6.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of	• Number (%) of subjects with mean Hgb in the

Objective	Endpoint
GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change in Hgb from baseline to Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category to Week 4
• To evaluate dose adjustments of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustments of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control by GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control by GSK1278863 in PD subjects	• Hgb at each assessment time point and change in Hgb from baseline to each assessment time point • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment time point • Proportion (%) of time with Hgb within the target range (11.0-13.0 g/dL) in the primary efficacy evaluation period (Weeks 40 to 52) • Time (number of days) to the lower Hgb target (11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks before Week 52 • Number (%) of subjects who achieve an Hgb level of more than 13.0 g/dL and number of episodes
• To compare the effect of GSK1278863 versus epoetin beta pegol on iron use in ND subjects • To evaluate the effect of GSK1278863 on iron use in PD subjects	• Dose of oral iron in the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To compare the effect of GSK1278863	• Change in ferritin from baseline

Objective	Endpoint
versus epoetin beta pegol on iron metabolism in ND subjects • To evaluate the effect of GSK1278863 on iron metabolism in PD subjects	• Change in transferrin saturation (TSAT) from baseline • Changes in hepcidin, serum iron, and total iron binding capacity (TIBC) from baseline
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To compare the effect of GSK1278863 versus epoetin beta pegol on progression of CKD in ND subjects	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To compare the effect of GSK1278863 versus epoetin beta pegol on health-related QoL (HR-QoL) in ND subjects • To evaluate the effect of GSK1278863 on H-RQoL in PD subjects	SF-36 • Changes in SF-36 HR-QoL scores (PCS, MCS, and 8 subscales) from baseline EuroQol Health Utility Index (EQ-5D-5L) • Change in EQ-5D-5L score from baseline • Change in EQ-5D-5L Visual Analog Scale (VAS) from baseline
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest • Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

4. STUDY DESIGN

4.1. Overall Design

This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (verification of noninferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 286 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. Cohort 1 (ND subjects) and Cohort 2 (PD subjects) were set for target population of this study when the study was planned. Cohort 3 is newly added in amendment (Amendment No.3). ND subjects will be randomized not to Cohort 1 but to Cohort 3 after amendment No.3.

Table 1 Composition of each cohort

[Including target number of subjects (randomized)]

Patient population	Cohort	Treatment group	Target number of subjects (randomized)	
ND patient	Cohort 1[1)]	GSK1278863 group (starting dose: 4 mg)	169 subjects[4)]	286 subjects[5)]
		Epoetin beta pegol group		
	Cohort 3[2)]	GSK1278863 group (starting dose: 2 mg or 4 mg[3)])	117 subjects	
		Epoetin beta pegol group		
PD patient	Cohort 2	GSK1278863 group (starting dose: 4 mg)	50 subjects	

1) At least 50 ESA users and at least 50 ESA non-users will be randomized to Cohort 1.

2) ND patients will be randomized to cohort3 and at least 80 ESA non-user will be randomized after Protocol amendment (Amendment No.3).

3) GSK 1278863 starting dose in Cohort3 as below

- ESA non-user (baseline Hgb 8.0-<9.0 g/dL):4 mg
- ESA non-user (baseline Hgb 9.0-<11.0 g/dL):2 mg
- ESA user: 4 mg

4) The exact number of ND subjects randomized to cohort 1

5) Subjects will be randomized in a 1:1 ratio to one of the two treatment groups

ESA: erythropoiesis-stimulating agent

For the patient populations in either cohort, the Hgb criteria are specified according to the presence or absence of prior ESA: ESA non-users with an Hgb level of ≥8.0 to <11.0 g/dL and ESA users with an Hgb level of 9.0 to 13.0 g/dL will be included in the study.

In Cohort 1and Cohort 3, eligible ND subjects [total of 286 subjects (169 subjects in Cohort 1, 117 subjects in Cohort 3)] will be stratified by the current ESA therapy (ESA non-user or ESA user) and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group.
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown in Figure 1.

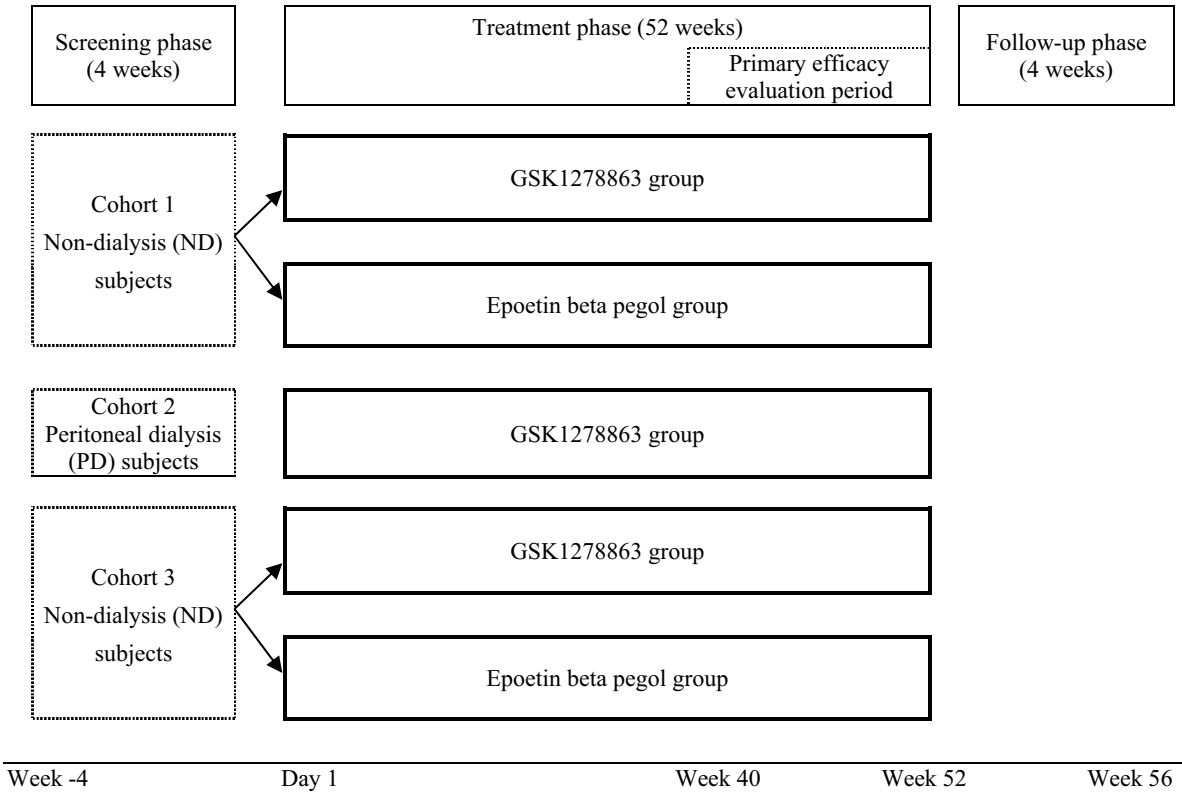


Figure 1 Study Design

4.2. Treatment Groups and Study Periods

Details for each study period and treatments are described below. In this study, a point-of-care Hgb analyzer (HemoCue®) will consistently be utilized for confirmation of subjects' eligibility, withdrawal criteria and dose adjustments of study medication.

Screening phase

Subjects who have provided informed consent and meet all of the eligibility criteria at screening (Week -4) (Sections 5.1 and 5.2) will be provisionally enrolled in the study. Subjects who have used ESA and/or oral iron since before the start of the study must remain on the same regimen throughout the screening phase (intravenous iron will not be allowed).

Treatment phase

Subjects who meet all of the eligibility criteria at the start of the treatment phase (Day 1) will be enrolled in the study. Study medication (either GSK1278863 or epoetin beta pegol group) will be administered for 52 weeks according to randomization in Cohort 1and Cohort 3. GSK1278863 will be administered in Cohort 2 for 52 weeks. For ESA users, prior ESA will be replaced with study medication on Day 1. GSK1278863 will be orally administered once daily, and epoetin beta pegol will be subcutaneously administered once every 2 or 4 weeks. In both groups, dose adjustments for study medication during the treatment phase will be made according to the administration schedule specified in Section 6.4. to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL). In addition,

supplemental iron therapy will be administered according to the standard initiation criteria as described in Section 6.12.. It should be noted that intravenous iron or dose change for oral iron will not be allowed from Day 1 to Week 4.

Follow-up phase

Subjects will visit the site for follow-up assessments and observations 4 weeks after the completion/discontinuation of study treatment. During the follow-up phase, treatment of renal anemia will be allowed as necessary at the discretion of the investigator (or subinvestigator).

4.3. Study Subjects and Number of Subjects

For ND subjects, a total of 286 subjects will be randomized (143 subjects in GSK1278863 group, 143 subjects in epoetin beta pegol group). The minimum target number of subjects is 50 ESA non-users and 50 ESA users to allow for evaluations by the current ESA therapy (ESA non-user or ESA user) in Cohort 1. At least 80 ESA non-user will be randomized to Cohort 3 defined in Protocol (Amendment No.3). Assuming a dropout rate of 35% during the screening phase, approximately 440 ND subjects need to be screened. Assuming a dropout rate of 30% after the start of study treatment, a total of 200 subjects are expected to complete the 52-week treatment. At planning the study, since a dropout rate after the start of study treatment was assumed to be approximately 25%, 135 subjects per group (total 270 subjects) were going to be randomized. After the start of study, however, the assumption of dropout rate after the start of study treatment was changed from 25% to 30% then the protocol amendment has been made (Amendment No.4). In the amended protocol, 143 subjects per group (total 286 subjects) will be randomized as mentioned above. If dropout rate is greater than the assumed, number of randomized subjects may be adjusted to ensure 100 subjects per group (total 200 subjects) to complete 52 week treatment.

In Cohort 2 involving PD subjects, 50 subjects will be enrolled (GSK1278863 group only). Since the number of PD patients is very limited in Japan, the target number of subjects is not set for either ESA non-users or users. Assuming a dropout rate of 35% during the screening phase, approximately 77 subjects need to be screened. Assuming a dropout rate of 25% after the start of study treatment, 38 subjects are expected to complete the 52-week treatment.

Table 2 Target Number of Subjects

	ND subjects		PD subjects
	Cohort 1	Cohort 3	Cohort 2
Screened	440		77
Randomized/enrolled	286		50
	169*1	117*2	
Expected tocomplete 52-week treatment	200		38

*1: In Cohort 1, at least 50 ESA non-users and at least 50 ESA users will be randomized.
*2: In Cohort 3, at least 80 ESA non-user will be randomized

4.4. Rationale for Study Design

Objectives and evaluations

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese ND and PD subjects with renal anemia. For Cohort 1 and Cohort 3, the study is designed as an active-controlled, parallel-group comparative study to meet the primary objective, that is, to demonstrate non-inferiority of GSK1278863 to the existing drug in ND, ESA user subjects in Cohort 1 or ND subjects in Cohort 3, depending on a change of the starting dose for ND, ESA non-users. For Cohort 2, the study is designed as an uncontrolled study because there are not many PD patients. The target Hgb range was set for study treatment in line with the Guidelines for Renal Anemia in Chronic Kidney Disease issued by the Japanese Society for Dialysis Therapy in 2008 [The Japanese Society for Dialysis Therapy, 2008] to demonstrate that treatment with GSK1278863 can result in achievement and/or maintenance of target Hgb in ND and PD subjects, and evaluate the appropriateness of the starting dose of GSK1278863.

Control

For the ND patient population (Cohort 1 and Cohort 3), epoetin beta pegol, which has been widely used in Japanese patients with renal anemia, primarily ND patients, since its approval in Japan in 2011, was selected as control.

Open-label

If the study is conducted as a double-blind study, it is necessary to not only administer GSK1278863 orally (once daily) or epoetin beta pegol subcutaneously (once every 2 or 4 weeks), but also administer the matching placebo subcutaneously or orally. It will be more stressful for subjects and complicate treatment procedures to use both active drug and matching placebo for two drugs with different routes and intervals of administration for the purpose of maintaining the blind, and make dose adjustments for individual subjects according to the change in Hgb over time. Accordingly, this study is designed as an open-label study rather than a double-blind study, which seems infeasible. Since Hgb used for efficacy evaluation is an objective measure, and dose adjustments for study medication will be made according to the prespecified Hgb-based dose adjustment method in both GSK1278863 and epoetin beta pegol groups, it is unlikely that the open-label design will create any bias in the primary evaluation.

4.5. Rationale for Dose Levels

Starting dose and dose adjustments of GSK1278863

The starting dose and the dose adjustment method (maintenance dose range: 1-24 mg) for GSK1278863 are described in Section 6.4..

The starting dose and the dose adjustment algorithm selected for Japanese ND subjects in the present study are based on the results from a review of the longitudinal model constructed using Hgb data from six Japanese or overseas Phase II studies (PHI112844, PHI116581, PHI116582, PHI113633, PHI113747, and PHI116099) as well as the results from clinical studies. The data set used in the model analyses was based on the data of GSK1278863 administered in a wide dose range (0-25 mg) and included a Japanese Phase II 4-week treatment study (PHI116099) and international multi-center late Phase II 24-week treatment studies (PHI113633 and PHI113747) in which subjects in Japan participated. For PD subjects, the starting dose and the dose adjustment algorithm for ND subjects will

be applied based on the PK/PD profiles in PD subjects determined from an interim analysis in an overseas 14-day treatment clinical pharmacology study (PHI200942).

Starting dose
Simulation results using the longitudinal model in ND subjects as well as the results from clinical studies indicated that GSK1278863 given at a dose of 4 mg may slowly increase Hgb (0.5-1.0 g/dL on average) without a rapid increase greater than 2 g/dL after 4 weeks of treatment in ESA non-users. 4 mg GSK1278863 may also maintain Hgb without a rapid increase greater than 2 g/dL for 4 weeks after switching from prior ESA in ESA users. Therefore, 4 mg was set as starting dose of GSK1278863 when study was planned.

As of Dec 2016 during this study, from the result of a review of blinded data, it was determined that the percentage of ND, ESA-non-user subjects with an Hgb increases of >2.0 g/dL from baseline to Week 4 was higher than expectation dedscribed above. This finding was not observed in ND, ESA-user subjects and PD subjects.

Therefore, in the protocol amendment No.3,

- For ND, ESA non-user subjects with baseline Hgb ≥9.0 g/dL and <11.0 g/dL, the starting dose of GSK1278863 is changed from 4 mg to 2 mg.
- For ND, ESA non-user subjects with baseline Hgb ≥8.0 g/dL and <9.0 g/dL, the starting dose remains at 4 mg.

For ND, ESA-user subjects and PD subjects, the starting dose of GSK1278863 were not changed and remains at 4 mg respectively.
In addition, Week 2 visit for additional Hgb monitoring in Cohort 3 was also included to allow earlier safety assessment of Hgb change at early phase of GSK1278863 treatment. (Refer to Section 6.4.1.)

Maintenance dose range and dose adjustment algorithm
Simulation results using the longitudinal model showed that drug response to GSK1278863 greatly varied among subjects, indicating that the dose range from 1 to 24 mg may be necessary to achieve and maintain target Hgb. Accordingly, a total of 8 dose levels (1, 2, 4, 6, 8, 12, 18, and 24 mg) were selected as the maintenance doses, with 4 mg intended for subjects with a standard drug response. The dose adjustment algorithm was defined so that target Hgb (11.0-13.0 g/dL) set for the present study according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] can be maintained. Since the upper limit of the Hgb target (13.0 g/dL) is equivalent to the interruption criterion for ESA, the dose level of GSK1278863 will be reduced by one step when Hgb increases to more than 12.5 g/dL, and the dose level will be maintained while Hgb is in the range of 11.5-<12.5 g/dL. Since the guidelines state that an Hgb increase of 0.5 g/dL or less per week is appropriate to prevent adverse reactions, the dose level will be reduced by one step when Hgb increases by more than 2 g/dL over 4 weeks (or when Hgb increases by more than 1 g/dL over 2 weeks at Week 4). For subjects whose anemia needs to be corrected (≥7.5 g/dL and <11.5 g/dL), the dose level will be maintained while the Hgb increase per 4 weeks is 0.5-2 g/dL, and the dose level will be increased by one step when the Hgb increase per 4 weeks is less than 0.5 g/dL.

Starting dose and dose adjustments of control (epoetin beta pegol)

The starting dose and the dose adjustment algorithm for epoetin beta pegol are described in Section 6.4..

The starting dose of epoetin beta pegol for subjects not using ESA or subjects on epoetin was selected based on the Prescribing Information in Japan. For subjects on darbepoetin alfa, darbepoetin alfa will be switched to epoetin beta pegol at a dose ratio of 6:5 according to overseas Prescribing Information, given no specification for dose conversion from darbepoetin currently approved in Japan to epoetin beta pegol.

The dose adjustment algorithm for epoetin beta pegol was determined based on the product information and previous Japanese clinical studies. In Cohort 3, a study visit at Week 2 for Hgb monitoring was also added for the control group. (Refer to Section 6.4.2.)

4.6. Benefit: Risk Assessment

Summaries of findings from clinical and nonclinical studies of GSK1278863 can be found in the IB and IB supplement. The risk assessment and risk minimization strategies for the present study are outlined in the following sections:

4.6.1. Risk Assessment

Based on the results of completed clinical and nonclinical studies of GSK1278863, the potential risks of clinical significance and the risk minimization strategies for the present study are outlined in Section 12.2. Appendix 2.

4.6.2. Benefit Assessment

Study PHI201753 is a Phase 3 study in Japanese ND and PD subjects with renal anemia. Previous clinical studies of GSK1278863 administered for up to 24 weeks in ND or HD subjects have demonstrated clinical efficacy (increase in and/or maintenance of Hgb) with serum EPO concentrations increased within the normal physiologic range in CKD subjects. Data obtained in Study PHI201753 will generate safety and efficacy data in Japanese ND and PD subjects with renal anemia for a 52-week treatment period. Study participants who will receive GSK1278863 may benefit from the expected clinical efficacy. Participants who will receive the control (epoetin beta pegol approved for the treatment of renal anemia in Japan) are also expected to benefit from the clinical efficacy.

GSK1278863 may have important advantages over existing ESAs. GSK1278863, which is orally administered and requires no cold chain management unlike ESAs, is more convenient to patients. GSK1278863 is shown to increase Hgb at lower EPO concentrations than ESAs. Since increased exposure to EPO following administration of ESAs may be associated with an increased cardiovascular risk [Szczech, 2008], GSK1278863 may increase Hgb without increasing the cardiovascular risk.

4.6.3. Overall Benefit: Risk Conclusion

GSK1278863 is shown to have a positive benefit-risk balance based on the following findings: in studies of GSK1278863 administered for up to 24 weeks, treatment with GSK1278863 resulted in

achievement of target Hgb, and no adverse events have been identified as related to treatment with GSK1278863.

The present study is intended to evaluate the efficacy and safety of GSK1278863 administered for 52 weeks in Japanese ND and PD subjects with renal anemia, and designed to administer GSK1278863 or epoetin beta pegol as control to all enrolled subjects; therefore, subjects randomized in either treatment group are expected to benefit from the treatment.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (Section 12.2. Appendix 2). Given these precautions, as well as the potential benefit that GSK1278863 holds for the treatment of renal anemia compared with the current standard treatment, the overall benefit risk balance is considered to be positive.

5. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) and/or other pertinent documents.

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

5.1. Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the inclusion criteria.
Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

1. Age (at the time of informed consent): ≥20 years of age
2. (Screening verification only) Stage of chronic kidney disease (CKD) (ND patients only): CKD stages 3, 4, and 5 defined by eGFR using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Dialysis:
   - Not on dialysis for at least 12 weeks prior to screening (ND patients)
   - On peritoneal dialysis (PD patients)
4. Use of erythropoiesis-stimulating agent (ESA):
   - ESA non-users: Have not used ESAs for at least 8 weeks prior to screening
   - ESA users: Have used the same ESA for at least 8 weeks prior to screening. However, in the ND patients, the dose of darbepoetin alfa or epoetin beta pegol must be stable (administered once every 4 weeks and up to one-step dose change during at least 8 weeks prior to screening).
5. Hemoglobin (Hgb): Determined at the site using an Hgb analyzer (HemoCue)
   - ESA non-users: ≥8.0 g/dL and <11.0 g/dL
   - ESA users: ≥9.0 g/dL and ≤13.0 g/dL

6. Iron parameters: Ferritin >100 ng/mL or transferrin saturation (TSAT) >20% (screening verification only)
7. Gender (screening verification only): Female or male
   Females: Not pregnant [demonstrated to be negative for human chorionic gonadotropin (hCG) in urine or serum], not breast-feeding, and meet at least one of the following:
   1) Females of non-childbearing potential are defined as follows:
   - Pre-menopausal with at least one of the following and no plans to utilise assisted reproductive techniques (e.g., in vitro fertilisation or donor embryo transfer):
     - History of bilateral tubal ligation or salpingectomy
     - History of hysteroscopic tubal occlusion and postoperatively documented bilateral tubal obstruction
     - History of hysterectomy
     - History of bilateral oophorectomy
   - Postmenopausal defined as 1) females 60 years of age or older or 2) In females < 60 years of age, 12 months of spontaneous amenorrhea [in questionable cases a blood sample with postmenopausal follicle stimulating hormone (FSH) and estradiol concentrations is confirmatory (see separately specified reference ranges)]. Females on hormone replacement therapy (HRT) whose menopausal status is in doubt will be required to use one of the most 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.

   2) Females of childbearing potential must agree to comply with one of the contraception methods listed as requirements in "GSK Listing of Most Effective Contraceptive Methods for Females of Childbearing Potential (Section 12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential)" from at least 28 days prior to the first dose of study medication until the completion of the follow-up visit (for subjects randomized to the GSK1278863 group) or 7 weeks after the last dose of study treatment (for subjects randomized to the Epoetin beta pegol group).
8. Informed consent: Written informed consent, including adherence to the requirements and conditions specified in the consent form and the protocol, must be obtained from each subject as specified in Section 10.2..

5.2. Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study.
Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

Chronic kidney disease (CKD)-related criteria

1. Dialysis
   - Cohort 1and Cohort 3: Start or plan to initiate dialysis during the study
   - Cohort 2: Plan to stop peritoneal dialysis or start hemodialysis during the study
2. Kidney transplant: Planned living-related kidney transplant during the study

Anemia-related criteria

3. Aplasia: History of bone-marrow hypoplasia or pure red cell aplasia
4. Other causes of anemia: pernicious anemia, thalassemia, sickle cell anemia, or myelodysplastic syndromes
5. Gastrointestinal (GI) bleeding: Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding within 8 weeks prior to screening or during a period from screening to Day 1.

Cardiovascular disease-related criteria

6. Myocardial infarction, acute coronary syndrome, stroke, or transient ischemic attack: Diagnosed within 8 weeks prior to screening or during a period from screening to Day 1.
7. Heart failure: Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system
8. QTc (screening verification only): QTc >500 msec or QTc >530 msec in subjects with bundle branch block

   Note: QT interval corrected using the Bazett's formula (QTcB) will be used, and ECG can be mechanically or manually read.

Other disease-related criteria

9. Liver disease (if any of the following occurs):
   - (Screening verification only): Alanine transaminase (ALT) >2×upper limit of normal (ULN)
   - (Screening verification only): Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
   - Current unstable active liver or biliary disease (generally defined by the onset of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal/gastric varices, persistent jaundice, or cirrhosis)

     Note: Stable liver disease (including asymptomatic gallstones, chronic hepatitis B/C, or Gilbert's syndrome) is acceptable if the subject otherwise meets entry criteria.
10. Malignancy: History of malignancy within 2 years prior to screening, or currently receiving treatment for cancer, (PD patients only) complex renal cystic >3 cm (II F, III or IV based on the Bosniak classification)

    Note (ND patients and PD patients): The only exception is squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥ 8 weeks before screening.
11. In the opinion of the investigator, Hgb increase to the target range (11.0-13.0 g/dL) is medically risky.

Concomitant medication and other study treatment-related criteria

12. Iron: Planned use of intravenous iron during the screening phase or during a period from Day 1 to Week 4

    Note: Oral iron is acceptable. However, the same dose regimen must be used throughout the screening phase and from Day 1 to Week 4. Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) are also acceptable only if used for at least 12 weeks prior to screening. However, they must be continued throughout the screening phase and from Day 1 to Week 4.

13. Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product [see the GSK1278863 IB (ND and PD patients) or epoetin beta pegol Prescribing Information (ND patients)]
14. Drugs and supplements: Use or planned use of any prescription or non-prescription drugs or dietary supplements that are prohibited during the study period (prohibited medications: strong inducers and inhibitor of CYP2C8, see Section 6.11.2.)
15. Prior investigational product exposure: Use of an investigational agent within 30 days or five half lives of the investigational agent (whichever is longer)
16. Prior treatment with GSK1278863: Any prior treatment with GSK1278863 for a treatment duration of >30 days

General health-related criteria

17. Other conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator (or subinvestigator) 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

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial, but are not subsequently randomized in the study. A minimum set of information is required from screen failure subjects including Demography, Screen Failure details, Eligibility Criteria, and SAEs in order to report screen failures in a reliable manner, satisfy the requirements for publication defined by the Consolidated Standards of Reporting Trials (CONSORT), and respond to requests of the regulatory authorities.

Subjects that fail screening are eligible to be rescreened up to 3 times as soon as the investigator (or subinvestigator) assesses they may meet study entry criteria. Re-screening subjects are allowed to use the results of the latest ophthalmology exam to replace the rescreening ophthalmology exam, at the discretion of the investigator (see Table 14).

5.4. Withdrawal/Dropout Criteria

If subjects meet one of the following criteria, study treatment should be permanently discontinued and subjects will be withdrawn from the study. The withdrawal reason should be recorded.

- Hgb <7.5 g/dL
  Note: HemoCue Hgb values will be employed. If an initial Hgb value meets the Hgb stopping criteria, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be discontinued.
- Subject needs for maintenance dialysis or changes dialysis modality (PD subjects only) during the study period.
- Kidney transplant
- Subject becomes pregnant or intends to become pregnant during the study.
- Diagnosis of new or recurrent cancer

- Liver chemistry abnormalities exceeding the threshold criteria (see Section 5.4.1.)
- Need for chronic (more than 14 days) use of prohibited medication (strong inhibitors/ inducers of CYP2C8 meet this criteria)
- When the investigator (or subinvestigator) considers necessary to withdraw the subject from the study for other reasons

Subjects who meet any of the withdrawal criteria or are withdrawn for other reasons during the treatment phase should be assessed at withdrawal visit after study treatment is discontinued, and will then enter the follow-up phase.
Should a subject fail to attend a required study visit, the investigator (or subinvestigator) should take the following measures:

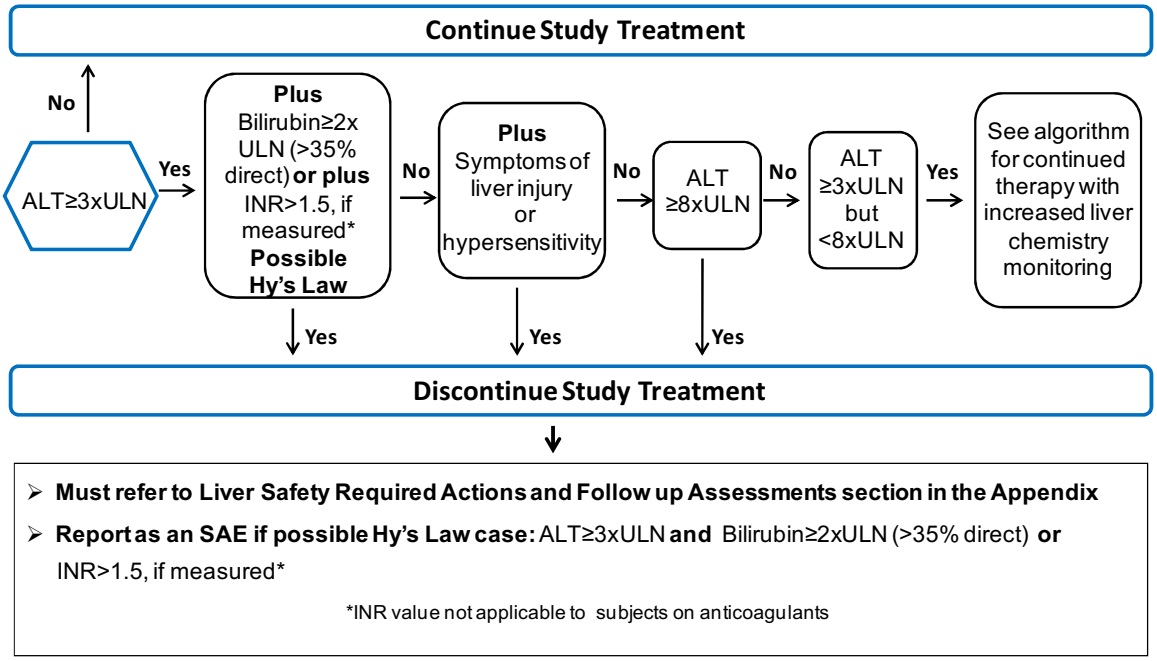
- The investigator (or subinvestigator) or designee should attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The investigator (or subinvestigator) should counsel the subject on the importance of maintaining the assigned visit schedule and determine whether the subject is willing to continue his/her participation in the study and/or whether the subject should remain in the study.
- The investigator (or subinvestigator) or designee should make every effort to regain contact with a subject who is deemed “Lost to Follow-up”. All efforts to contact the subject should be documented in the subject’s clinical charts.
- Should the subject continue to be unreachable, then and only then will he/she be considered “Lost to Follow-up.”

A subject may withdraw from the study at any time at his/her own request. The investigator (or subinvestigator) may withdraw a subject from the study at any time for safety or compliance reasons or study conduct considerations. If a subject withdraws from the study, he/she may request destruction of any clinical samples taken, and the investigator (or subinvestigator) must document this in the site study records.

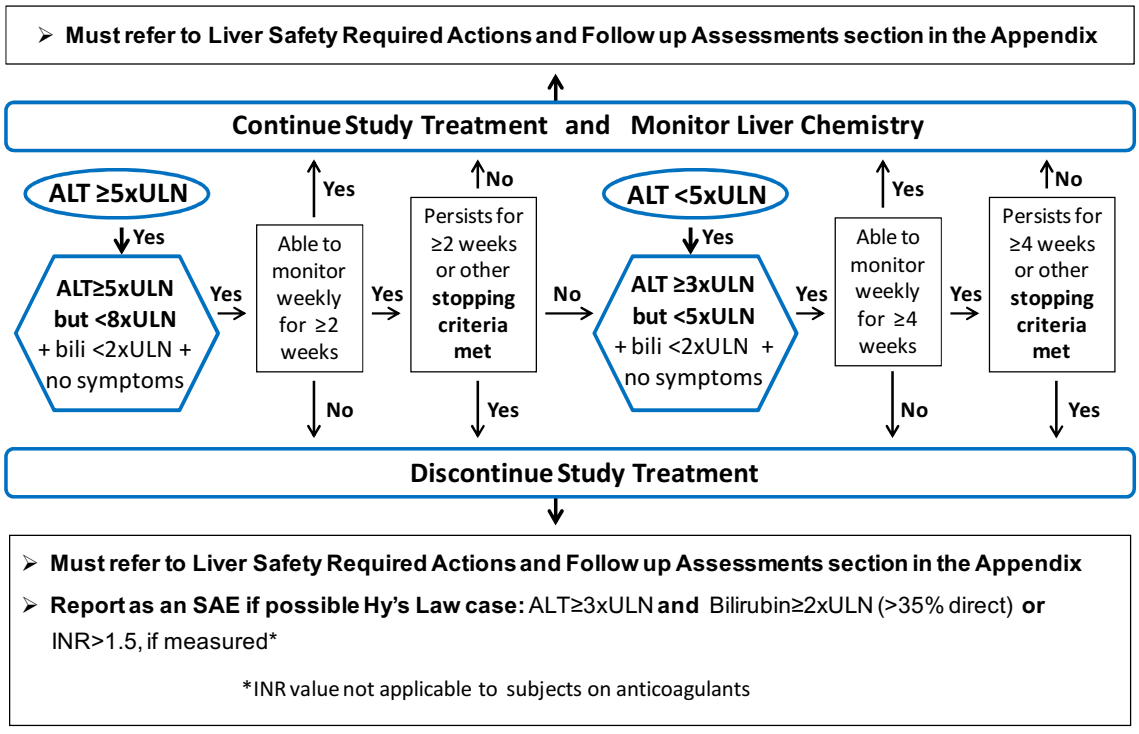
5.4.1. Liver Chemistry Stopping Criteria

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

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.5. Appendix 5

5.4.1.1. Study Treatment Restart or Rechallenge

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

5.5. Subject and Study Completion

A completed subject is one who has completed all periods of the study including the follow-up visit. The study will be completed with the last subject's last study visit.

6. STUDY TREATMENTS

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any products received by the subject as per the protocol design. Accordingly, 'study treatment' sometimes refers to each product and sometimes refers to multiple products.

GSK1278863 (study drug)

The study drug GSK1278863 will be supplied as fast-release film coated tablets for oral administration containing 1 mg, 2 mg, 4 mg, or 6 mg of GSK1278863 (Table 3). There are two sizes of GSK1278863 tablets.

Table 3 Description of GSK1278863 Tablets

GSK1278863 tablets of specific content	Description
1 mg tablets, 2 mg tablets, 4 mg tablets	7.0 mm round, standard biconvex, white film coated tablets containing 1 mg, 2 mg, or 4 mg of GSK1278863 as active ingredient
6 mg tablets	9.0 mm round, standard biconvex, white film coated tablets containing 6 mg of GSK1278863 as active ingredient

GSK1278863 tablets of specific content are packed in high density polyethylene (HDPE) bottles, with 35 tablets per bottle. Subjects are to take one to four tablets (Table 4) with water once daily according to the dose level indicated at each study visit. Subjects can take GSK1278863 tablets without regard to food or peritoneal dialysis. The administration schedule (starting dose and dose adjustment) described in Section 6.4.1. should be followed.

Table 4 Dose Levels of GSK1278863 and Number of Tablets Taken

Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Subjects should be instructed to bring GSK1278863 tablets with bottles at each study visit, and all unused GSK1278863 tablets will be collected from subjects at each study visit.

Epoetin beta pegol (control)

The control epoetin beta pegol (brand name: Mircera® Pre-filled Syringe) will be supplied by GSK. This product is an injectable formulation containing 25 µg, 50 µg, 75 µg, 100 µg, 150 µg, 200 µg, or 250 µg of epoetin beta pegol per syringe (0.3 mL) and is supplied as a glass syringe prefilled with epoetin beta pegol solution (clear colorless to pale yellow).
Subjects are to receive epoetin beta pegol subcutaneously once every 2 or 4 weeks at the site (Table 5). The administration schedule (starting dose and dose adjustment) described in Section 6.4.2. should be followed.

Table 5 Dose Levels of Epoetin Beta Pegol and Number of Subcutaneous Doses

Dose level of epoetin beta pegol (once every 2 or 4 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg
Number of subcutaneous doses of epoetin beta pegol	25 µg injection ×1	50 µg injection ×1	75 µg injection ×1	100 µg injection ×1	150 µg injection ×1	200 µg injection ×1	250 µg injection ×1

6.2. Medical Devices

The Epoetin beta pegol (Brand name :MIRCERA® Injection Syringe) marketed with the device (kit formulation which was filled liquid medication in glass syringe) provided for use in this study. Instructions for medical device are described in the Prescribing Infromation of MIRCERA® Injection Syringe.

The medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 7.4.4.

6.3. Treatment Assignment

The randomization schedule will be generated by GlaxoSmithKline (GSK) using the randomization system (Randall).

In Cohort 1 and Cohort 3 (ND subjects), subjects will be stratified by the current ESA therapy (ESA non-user or ESA user) and the Hgb level on Day 1 and randomized in a 1:1 ratio to one of the two treatment groups according to the randomization schedule. Randomization should precede the study treatment.

- GSK1278863 group
- Epoetin beta pegol group

In Cohort 2 (PD subjects), all eligible subjects will start treatment with GSK1278863 on Day 1.

Subjects will be assigned a randomization number by the Interactive Web Recognition System (IWRS). Once a randomization number has been assigned, it must not be re-assigned. Further details are provided in the Study Reference Manual (SRM).

6.4. Administration Schedule (Starting Dose, Dose Adjustment, and Dosing Frequency)

6.4.1. GSK1278863 (ND and PD Subjects)

6.4.1.1. Starting Dose

For ND subjects randmized to GSK1278863 group

(Cohort 1)

Both ESA non-users and users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.

(Cohort 3)

- ESA non-users
  - Baseline Hgb ≥8.0 g/dL and <9.0 g/dL: the subjects will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*.
  - Baseline Hgb ≥9.0 g/dL and <11.0 g/dL: the subjects will start oral treatment with GSK1278863 at the starting dose of 2 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*.
- ESA users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*.

*: The HemoCue Hgb value will be measured for safety confirmation at Week 2 in ND subjects. When Hgb > 1.0 g/dL increase over 2 weeks, the dose of GSK1278863 is decreased to the next lower dose.

For PD subjects randomized to the GSK1278863 group (Cohort 2)

- ESA non-users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.
- ESA users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.

ESA users should skip ESA on Day 1 when treatment with GSK1278863 is started.

6.4.1.2. Maintenance Dose

From Weeks 4 to 52, interruption of treatment or dose adjustments will be made within the maintenance dose range of 1-24 mg (Table 6) according to the dose adjustment algorithm (Table 7) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (1 mg), treatment should be interrupted; once the one-step dose increase criteria are met, treatment at 1 mg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (24 mg), treatment at 24 mg should be continued.

Table 6 Maintenance Dose of GSK1278863

Dose step	1	2	3	4	5	6	7	8
Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Table 7 Dose Adjustment Algorithm (GSK1278863)

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (If interrupted at 1 mg: resume treatment at 1 mg once the one-step dose increase criteria are met)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0[1)]	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0[1)]	One-step dose reduction
	0.5-2.0	Continue treatment at the current dose level
	<0.5	One-step dose increase
<7.5	NA	Discontinue treatment permanently [2)] and initiate another appropriate treatment

1) Cohort 3 only: At Week 4, if an Hgb increase of >1.0 g/dL over 2 weeks is observed, the dose of GSK1278863 will be reduced by one step; if an Hgb increase of ≤1.0 g/dL over 2 weeks is observed, treatment will be continued as specified in the dose adjustment algorithm other than one-step dose reduction for an Hgb increase of >2.0 g/dL over 4 weeks.
2): If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.4.2. Epoetin Beta Pegol (ND Subjects Only)

For ND subjects (Cohort 1 and Cohort 3) randomized to the epoetin beta pegol group, ESA non-users and users will receive epoetin beta pegol subcutaneously according to the treatment regimens described below.

6.4.2.1. Starting Dose for ESA Non-users

ESA non-users will start subcutaneous treatment with epoetin beta pegol at a dose of 25 μg once every 2 weeks (Day 1). Dose adjustments will be made within the initial dose range of 25-150 μg (Table 8) according to the dose adjustment criteria (Table 9) to increase Hgb to 11.0 g/dL (lower limit of the target) or more based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the dose reduction criteria shown in Table 9 is met during treatment with epoetin beta pegol at 25 μg, treatment should be interrupted; once the dose reduction criteria are not met any longer, treatment will be resumed at a dose of 25 μg.

At Week 2, HemoCue Hgb value will be measured for subjects' safety confirmation. If the measurement shows an Hgb increase of >1.0 g/dL over 2 weeks, the dose of epoetin beta pegol will be reduced by one step (or treatment interrupted) (Cohort 3 only).

Table 8 Initial Dose of Epoetin Beta Pegol (ESA Non-users)

Dose step	1	2	3	4	5
Dose level of epoetin beta pegol (once every 2 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg

Table 9 Initial Dose Adjustment Criteria for Epoetin Beta Pego (ESA Non-users)

Hgb	Treatment
Hgb increase <1.0 g/dL over past 4 weeks, OR Hgb <10.0 g/dL and Hgb increase ≤2.0 g/dL over past 4 weeks	One-step dose increase
Hgb increase >2.0 g/dL over past 4 weeks[1)]	One-step dose reduction
Otherwise	Continue treatment at the current dose level

1) Cohort 3 only: Hgb increaseof >1.0 g/dL over past 2 weeks at Week 2.

Once Hgb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm (Table 13). The dosing interval should be changed from once every 2 weeks to once every 4 weeks with dose conversion for dosing interval change (Table 10) after it is confirmed that all of the following criteria are met:

- Hgb in the target range (11.0-13.0 g/dL)
- Hgb change ≤2.0 g/dL over past 4 weeks
- Equivalent dose will be given twice (at least 4 weeks)

Table 10 Dose Conversion of Epoetin Beta Pegol for Dosing Interval Change (ESA Non-users)

Initial dose of epoetin beta pegol (given once every 2 weeks)		Dose conversion of epoetin beta pegol (given once every 4 weeks)
25 µg	→	50 µg
50 µg	→	100 µg
75 µg	→	150 µg
100 µg	→	200 µg
150 µg	→	250 µg

6.4.2.2. Dose Conversion for ESA Users

For ESA users, prior ESA will be replaced with epoetin beta pegol at the equivalent dose once every 4 weeks (Day 1).

At Week 2, HemoCue Hgb value will be measured for subjects' safety confirmation. If the measurement shows an Hgb increase of >1.0 g/dL over 2 weeks, the dose of GSK1278863 will be reduced by one step (or treatment interrupted) at Week 4 (Cohort 3 only).

Table 11 Replacement with Epoetin Beta Pegol-Initial Dose (ESA Users)

Prior ESA		Epoetin beta pegol
Epoetin	<4500 IU per week	100 µg once every 4 weeks
	≥4500 IU per week	150 µg once every 4 weeks
Darbepoetin alfa	30 µg once every 4 weeks *	25 µg once every 4 weeks
	60 µg once every 4 weeks *	50 µg once every 4 weeks
	90 µg once every 4 weeks *	75 µg once every 4 weeks
	120 µg once every 4 weeks *	100 µg once every 4 weeks
	180 µg once every 4 weeks *	150 µg once every 4 weeks
Epoetin beta pegol	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks *	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks

*: Allowance of ±1 week
Maintenance treatment will be started at Week 4 as described in Section 6.4.2.3.

6.4.2.3. Maintenance Dose (ESA Non-users and Users)

Epoetin beta pegol will be administered once every 4 weeks from dosing interval change (once every 4 weeks) with Hgb ≥11.0 g/dL to Week 52 in ESA non-users and from Weeks 4 to 52 in ESA users. Interruption of treatment or dose adjustments will be made within the maintenance dose range of 25-250 µg (Table 12) according to the dose adjustment algorithm (Table 13) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (25 µg), treatment should be interrupted; once the one-step dose reduction criteria are not met any longer, treatment at 25 µg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (250 µg), treatment at 250 µg should be continued.

Table 12 Maintenance Dose of Epoetin Beta Pegol

Dose step	1	2	3	4	5	6	7
Epoetin beta pegol (once every 4 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg

Table 13 Dose Adjustment Algorithm (Epoetin Beta Pegol)

Hgb	Hgb increase over 4 weeks	Treatment

(g/dL)	(g/dL)	
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (resume treatment at 25 μg if interrupted at 25 μg)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0	One-step dose reduction
	1.0-2.0	Continue treatment at the current dose level
	<1.0	One-step dose increase
<7.5	NA	Discontinue treatment permanently * and initiate another appropriate treatment

*: If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.5. Blinding

This is an open-label study.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

- No special preparation of study treatment is required.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study medications must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator (or subinvestigator) and authorized site staff.
- Subjects must bring all of supplied study medication bottles of GSK127886 at each study visit. Study staff will collect all of study medication bottles supplied at the previous study visit and supply new study medication bottles.
- The investigator (or subinvestigator), 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).
- Under normal conditions of handling and administration, study medication is not expected to pose significant safety risks to site staff. GSK will provide a document describing occupational hazards and recommended handling precautions either to the investigator (or subinvestigator) when necessary or upon request of the medical institution.
- Further details are provided in the SRM.

6.8. Compliance with Study Treatment Administration

GSK1278863

Since GSK1278863 is self-administered, compliance with GSK1278863 treatment will be assessed through an interview with subjects at each study visit and recorded in the source document and eCRF. A record of the number of GSK1278863 tablets dispensed to and taken by each subject will be maintained and reconciled with study treatment and compliance records. In addition, the number of GSK1278863 doses dispensed, used, and unused, as well as study treatment start and stop dates will be recorded in the eCRF (the number of doses returned and unreturned will also be recorded separately).

Epoetin beta pegol

Epoetin beta pegol will be subcutaneously administered to subjects at the site. Dosing details will be recorded in the source document and eCRF.

6.9. Treatment of Study Treatment Overdose

For the purposes of this study, an overdose of GSK1278863 is defined as any dose greater than the highest daily dose included in the protocol. 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. GSK1278863 is highly protein bound; thus, clearance of GSK1278863 by hemodialysis or peritoneal dialysis is very low and these are not effective methods to enhance the elimination of GSK1278863. GSK1278863 metabolites are, in part, cleared via hemodialysis. 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, subjects should be monitored closely for cardiovascular events, increased heart rate and hematologic abnormalities.

Consult the respective approved Prescribing Information for information on overdose for epoetin beta pegol.

6.10. Treatment after the End of the Study

Since the target disease studied is not life-threatening or severely debilitating and there is the alternative therapy, subjects will not receive any additional treatment from GSK after completion of the study. Regardless of whether the sponsor provides specific treatments at the completion of the study, the investigator (or subinvestigator) is responsible for ensuring that consideration has been given to post-study care of the subject's medical condition.

6.11. Concomitant Medications and Non-Drug Therapies

Concomitant medications, including over-the-counter medications and supplements, taken during the study will be recorded in the eCRF. Drug names and start/stop dates will be recorded for general concomitant medications, while additional details, including dose, route of administration, and dosing frequency, will be recorded for certain medications (e.g., ESAs, iron, anti-hypertensive medications). Further details are provided in the SRM.

6.11.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.11.2., all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned. Regular multivitamins (at recommended daily allowance) and other supplements such as calcium and vitamin D may be used if permitted by the investigator or his/her designee.

CYP2C8 is involved in the primary route of metabolism of GSK1278863. Accordingly, co-administration of GSK1278863 with moderate CYP2C8 inhibitors (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks using a point-of-care Hgb analyzer.

Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) may be started from Week 4 onwards unless any other antihyperphosphatemic agents are appropriate. Once started, iron-containing antihyperphosphatemic agents must be continued until the end of the study wherever possible.

6.11.2. Prohibited Medications and Non-Drug Therapies

Use of any of the following drugs from screening until 7 days after the last dose of study treatment is prohibited:

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

Use of the following drug from 8 weeks prior to screening until the last dose of study treatment in ESA non-users and during study treatment in ESA user is prohibited.

- Erythropoietin (e.g., epoetin/darbepoetin alfa/ epoetin beta pegol)

Note: excluding epoetin beta pegol (brand name: Mircera® Injection Syringe) supplied by GSK.

6.12. Supplemental Iron Therapy

Supplemental iron therapy will be administered according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] if ferritin is ≤100 ng/mL and TSAT is ≤20%. The investigator (or subinvestigator) can choose the route of administration and dose of prescription iron.

7. Study Assessments and Procedures

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

7.1. Time and Events Table

The time and events tables for the entire study and PK assessment are presented as Table 14 and Table 15, respectively. To allow scheduling flexibility, study visits may occur within a window of ±7 days on Day 1 scheduled 4 weeks after screening, within a window of ±3 days at Week 2 (Cohort 3 only) and Week 4, and within a window of ±5 days for the rest of the study. However, subjects receiving the control epoetin beta pegol every 2 weeks should attend study visits, including those only for study treatment, within a window of ±3 days. Visit days are counted from Day 1.

Table 14 Time and Events Table

Phase	Screening[9]	Treatment																Follow-up
Week	-4	Day 1	2[10]	4	8	12	16	20	24	28	32	36	40	44	48	52	Early withdrawal[11]	4 weeks after 52 or withdrawal
Permissible range (days)	±7	-	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-	±7
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Medical history, demography, height, weight	X																	
Registration with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication dispensing [1,2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Study treatment compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X		X			X			X			X			X	X	X
Ophthalmology [3]	◄►					◄►									◄►		◄►	
ECG	X								X							X		
HemoCue Hgb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	X	X
Clinical chemistry	X	X		X			X			X			X			X	X	X
Urinalysis (ND subjects only)	X	X							X							X		X
Pregnancy test (urine or serum hCG) [4]	X	X		X			X			X			X			X	X	X
Estradiol, FSH [5]	X																	
PK [6]						X			X									
Ferritin, TSAT	X	X		X			X			X			X			X	X	
Serum iron, TIBC, UIBC, serum transferrin, hepcidin		X		X			X			X			X			X	X	
iPTH		X								X						X		
HR-QoL		X				X				X						X	X	
Genetics sample [7]		X																
Adverse event assessment [8]		◄►																
Review Concomitant Medications	◄►																	

1. In Cohort 1 and Cohort 3, ESA non-users randomized to the epoetin beta pegol group will start treatment with epoetin beta pegol at a dose of 25 µg once every 2 weeks. For these subjects, specified examinations will be performed at Week 2 (Cohort 3 only) and every 4 weeks after Week 4, and no study-related assessments will be necessary at study visits only for study treatment [e.g., Week 2 (Cohort 1 only), Week 6, Week 10) (see Section 6.4.2). It should be noted that subjects receiving epoetin beta pegol once every 2 weeks should attend study visits within a window of ±3 days.
2. If a subject visit the study site only to receive study medication, only registration with the IWRS, study medication dispensing, and study medication compliance will be required.
3. Ophthalmology exams should be conducted at the following time points.

- Screening: anytime after consenting and prior to first dose of study medication (Day 1)
- Week 12: window from weeks 10-14 (inclusive)
- End of study: window from weeks 48-52 (inclusive)
- Early study medication discontinuation: withdrawal eye exam as close to the last dose as possible (the repeat exams are not required if one has been performed within the 2 prior weeks).

4. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.
5. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
6. See Table 15.
7. Informed consent for optional Genetic research should be obtained before collecting a sample (see Section 7.6.).
8. See Section 7.4.1.1..
9. Re-screening subjects who meet all the following conditions are allowed to use the results of the latest ophthalmonogy exam and not required to undergo the rescreening ophthalmonogy exam, at the discretion of the investigator.
   - Subjects had no findings that deem re-exams within 3 months at the latest screening ophthalmology exam.
   - Subjects had no new eye-related symptoms or complaints until the rescreening following the latest screening ophthalmology exam.
   - The latest screening ophthalmology exam was performed within 3 months prior to Day 1 scheduled at the rescreening.
10. All ND subjects randomized to Cohort 3 will undergo assessment scheduled for Week 2 visit.
11. For withdrawn subjects, specified assessments should be done wherever possible.

Table 15 Blood Sampling Schedule for Pharmacokinetics (Only Subjects in GSK1278863 Group)

PK sample	Week 12 [2]	Week 24 [2]
Blood sampling timing [1]	1, 2, 3, and 4 h after administration of GSK1278863	

Subjects must take the study medication with regard to blood sampling time. Subjects will record the date and time of the last two study medication doses taken prior to blood sampling in the medication diary. Preferably, there should be an interval of at least 12 h between these two doses.

1. Blood sampling should be completed within +/- 30 min of the planned collected time.
2. Blood sampling not performed at this visit may be postponed until the following visits.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed (documented in the eCRF) at baseline.
In addition, the following demographic information will be collected:

- Year of birth
- Gender
- Race and ethnic
- Medical history/treatment history/family history will be assessed in relation to the inclusion/exclusion criteria (Section 5.).

Full details of baseline assessments are provided in Table 14.

7.3. Efficacy

Efficacy will be assessed according to the Time and Event Table (Table 14).
Hgb concentrations measured by the central laboratory will be mainly used for efficacy assessment (see Section 7.4.7.).
GSK will supply a point-of-care Hgb analyzer (HemoCue) to each site for rapid and convenient measurement of Hgb and to ensure consistency of Hgb measurements across all sites participating in the study. Assessment for Hgb concentrations via HemoCue will be used for eligibility (Section 5.1.), withdrawal (Section 5.4.), and dose adjustment criteria (Section 6.4.).
In addition, assessments of iron metabolism parameters and measures of CKD progression (e.g., eGFR) used for efficacy assessment are outlined with specific procedures in Section 7.4.7..

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Table 14).
Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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

The definitions of an AE or SAE can be found in Section 12.6. Appendix 6.
The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3.), at the timepoints specified in the Time and Events Table (Table 14).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.6. Appendix 6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.6. Appendix 6.

7.4.1.2. Method of Detecting AEs and SAEs

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

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.2.) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.). Further information on follow-up procedures is given in Section 12.6. Appendix 6..

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.6. Appendix 6 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.

7.4.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.2. Adverse Events of Special Interest

The investigator (or subinvestigator) or designee will be responsible for detecting, documenting, and reporting any AEs of special interest listed below. These events have been identified based on the known safety profiles of ESAs, theoretical or potential risks based on the mechanism of action of GSK1278863, and findings from completed nonclinical studies of GSK1278863.

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Death, myocardial infarction, stroke, heart failure, thromboembolic events, 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

Any relevant AE should be recorded in the relevant section of the subject's eCRF.

7.4.3. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the follow-up contact.

- 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 12.4.. Appendix 4.

Note: Subjects randomized in the epoetin beta pegol group should be advised to inform the investigator if they discover pregnancy in 7 weeks after the last dose of study treatment.

7.4.4. Medical Device Incidents (Including Malfunctions)

The medical devices are being provided for use in this study. The investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 8 (Section 12.8.)

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 7.4.1. and Appendix 6 (Section 12.6.) of the Protocol.

7.4.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a medical device provided for the study, the investigator will promptly notify GSK.

NOTE: The method of documenting Medical Device Incidents is provided in Appendix 8 (Section 12.8.).

7.4.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE, will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.). This applies to all subjects, including those withdrawn prematurely.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form ”Medical Device Incident Report Form” with all changes signed and dated by the investigator.

7.4.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the SAE contact information.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.4.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator, or responsible person will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.4.5. Vital Signs/Height/Weight

Systolic and diastolic blood pressure and pulse rate will be measured in sitting or semi-supine position after at least 5 minutes rest prior to clinical examination at each visit blood pressure and pulse rate. One reading of blood pressure and pulse rate will be taken and recorded in the source document and the CRF. Height and weight will be measured at screening visit only.

7.4.6. Electrocardiogram (ECG)

12-lead ECGs will be recorded in supine position. The heart rate, PR, QRS, and QT (pre-corrected) intervals will be measured. QTcB should be calculated by machine or manually by designated staff at each site. The investigator determines whether the ECG data is assessable or not.
At screening, visit when an ECG is performed, two additional ECGs are required if initial ECG indicates prolonged QTc using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility.
QTc exclusion criteria can be found in Section 5.2. Refer to SRM for further details.

7.4.7. Clinical Laboratory Assessments

All study-required laboratory assessments will be performed by a central laboratory with the exception of HemoCue Hgb. The results of each HemoCue Hgb must be entered into the subject's eCRF. Details are provided in the SRM.
All laboratory assessments, as defined in Table 16, 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 labeled 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 central laboratory. Reference ranges for all parameters will be provided to the site by the central laboratory. Details of blood sampling (including the volume of blood to be collected) as well as procedures for processing, storage, and shipment of samples are provided in the SRM.
PK assessment of GSK1278863 is outlined in Section 7.5.

Table 16 Laboratory Assessments

Laboratory assessment	Parameter		
Hematology	Leukocyte count	RBC indices:	WBC count with Differential
	Platelet count	MCV	Neutrophils
	RBC count	MCH	Lymphocytes
	Reticulocyte count	MCHC	Monocytes
	Hemoglobin	RDW	Eosinophils
	Hematocrit		Basophils
Clinical chemistry	Sodium	AST	Bicarbonate
	Potassium	ALT	Inorganic phosphate
	Chloride	Creatinine	Glucose
	Calcium (total and albumin-corrected)	Total bilirubin	Direct/indirect bilirubin
	Albumin	Urea nitrogen	
	Total cholesterol	HDL cholesterol	LDL cholesterol
Iron parameters	Serum iron	Serum ferritin	Serum transferrin
	TIBC	UIBC	TSAT
	Hepcidin		
Urinalysis (ND subjects only)	Urine albumin	Urine creatinine	Urine albumin/creatinine ratio
Other laboratory tests	FSH [1]	Estradiol [1]	iPTH
	eGFR [2]	hCG (serum or urine) [3]	

1. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
2. Calculated from serum creatinine using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.

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 (or subinvestigator) (e.g., SAE or AE or dose modification), the results must be recorded in the eCRF.
Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study 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 (or subinvestigator), the etiology should be identified and the Sponsor notified.

7.4.8. Ophthalmology

Ophthalmology exams will be performed by a study-designated ophthalmology specialist. Each assessment will include a comprehensive eye exam with at least the following components: measurement of best corrected visual acuity, intraocular pressure, an anterior aqueous chamber exam, and a fundoscopic exam. These exams will be used for assessment of ocular adverse events. Assessment results will be captured on worksheets which will be transferred to the eCRF. Additional details on the process for completing these assessments are provided in the SRM.

7.5. Pharmacokinetics

Blood samples for PK analysis of GSK1278863 will be collected from only subjects in the GSK1278863 group as outlined in Table 15, and the date and time of the last two study medication doses taken prior to blood sampling as well as the date and time of sampling must be recorded in the eCRF.

Blood PK analysis will be performed under the control of GSK Platform Technologies and Science-Drug Metabolism and Pharmacokinetics (PTS-DMPK)/Scinovo and GSK-Japan Bioanalysis, the details of which will be included in the SPM. Concentrations of parent GSK1278863 will be determined in blood samples using the currently approved analytical methodology. Raw data will be archived at the bioanalytical site.

Procedures for processing, storage, and shipment of samples are provided in the SRM.

7.6. Genetics

A blood sample will be collected for genetic analysis from consenting subjects. This sample can be collected on Day 1 once written informed consent has been obtained. Information regarding genetic research is included in Section 12.7. Appendix 7.

7.7. Patient Reported Outcome (PRO)

The patient reported outcome (PRO) [e.g., symptoms, severity, health-related QOL (HR-QoL), health status] will be assessed using several rating scales.

All questionnaires used in this study have been translated into Japanese and validated.

Specific instructions on how the subject is to complete the scales and the process for data entry are provided in the SPM.

7.7.1. SF-36

The SF-36 acute version is a general health status questionnaire designed to elucidate the patient's perception of his/her health on several domains, including physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, and general health over the past seven days. The questionnaire contains 36 Likert type questions that ask the patient to recall how he/she felt during the past seven days.

7.7.2. EuroQol Health Utility Index (EQ-5D-5L)/EQ Visual Analogue Scale (EQ-VAS)

The EQ-5D-5L is intended to measure the general health status and health utility. The EQ-5D-5L consists of 2 concepts: self-reported health status consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses and self-rated health status on a visual analog scale (VAS), a thermometer-like line.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- 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

A detailed description of any planned analyses will be documented in a RAP..Any deviations from the analyses described in the protocol will be documented in the RAP or the final study report.

9.1. Hypotheses

The primary objective of the study is to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol based on mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52) in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users).

As a preliminary assessment, it will be confirmed whether the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-13.0 g/dL) at first. And then the following non-inferiority statistical hypotheses are to be tested at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%):

- H_0: Treatment difference in mean Hgb during the primary efficacy evaluation period is -1.0 g/dL or less.
- H_1: Treatment difference in mean Hgb during the primary efficacy evaluation period is greater than -1.0 g/dL.

Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority according to the step-down procedure. More specifically, the superiority of GSK1278863 to epoetin beta pegol in terms of target Hgb control in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users), is to be demonstrated at a two-sided significance level of 5% by testing the following statistical hypotheses:

- H_0: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is equal between the treatment groups.
- H_1: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is different between the treatment groups.

No hypothesis will be tested in PD subjects (Cohort 2).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%) with a sample size of 100 subjects per group. At planning the study, a dropout rate was assumed to be approximately 25%, 135 subjects were going to be randomized to each group. Given the results from previous non-inferiority studies of similar drugs (darbepoetin alfa, epoetin beta pegol, and peginesatide), the non-inferiority margin of -1.0 g/dL is set. Since an increase of 1.0 g/dL indicates improvement in anemia according to the guidelines for renal anemia in Japan, the non-inferiority margin of -1.0 g/dL may be the clinically acceptable largest difference in renal anemia.

While the present study is designed to ensure long-term safety data from 100 ND subjects, and the primary hypothesis test has at least 99% power to estimate the efficacy very precisely, non-inferiority can be statistically demonstrated with a minimum between-group difference of -0.582 g/dL.

During this study, the protocol has been amended (Amendment No.3) according to the change in starting dose for ND, ESA non-users. ESA non-users in Cohort 1 will be excluded from primary efficacy analysis according to this amendment. Additionally the protocol amendment has been made (Amendment No.4), in which the assumption of dropout rate after the start of study treatment was changed from 25% to 30% and 143 subjects per group (total 286 subjects) will be randomized.

Analysis populations for primary efficacy analysis and safety evaluation on ND subjects are illustrated below.

Table 17 Primary Efficacy and Safety Analyses Populations for ND Subjects

<table>
<tr><th colspan="2">ND Subjects</th><th>Treatment Group</th><th>Starting Dose</th><th colspan="2">Number of Randomized Subjects</th><th colspan="2">Analysis Population</th></tr>
<tr><td rowspan="4">Cohort 1</td><td rowspan="2">ESA non-users</td><td>GSK1278863</td><td>4 mg</td><td rowspan="2">82 subjects</td><td rowspan="4">169 subjects</td><td rowspan="6">204 subjects for primary efficacy analyses</td><td rowspan="8">286 subjects for safety analyses</td></tr>
<tr><td>Epoetin beta pegol</td><td>-</td></tr>
<tr><td rowspan="2">ESA users</td><td>GSK1278863</td><td>4 mg</td><td rowspan="2">87 subjects</td></tr>
<tr><td>Epoetin beta pegol</td><td>-</td></tr>
<tr><td rowspan="4">Cohort 3</td><td rowspan="2">ESA non-users</td><td>GSK1278863</td><td>2 mg or 4 mg</td><td rowspan="4">≥80 ESA non-users will be randomized</td><td rowspan="4">117 subjects</td></tr>
<tr><td>Epoetin beta pegol</td><td>-</td></tr>
<tr><td rowspan="2">ESA users</td><td>GSK1278863</td><td>4 mg</td></tr>
<tr><td>Epoetin beta pegol</td><td>-</td></tr>
</table>

Note: In Cohort 1, 169 ND subjects who met eligibility criteria were stratified by the current ESA therapy and baseline Hgb (ESA non-users: ≥9.5 g/dL, <9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group. The same randomization strategy is used in Cohort 3.

When non-inferiority is tested in 204 ND subjects, this number of subjects ensures an enough power. This is because a power of at least 97% will be achieved in a population consisting of 140 subjects,

who will complete study on the condition of a dropout rate of approximately 30%, by the same assumptions and non-inferiority margin stated as above. In order to allow a subgroup analysis of the primary endpoint by the use of ESA in subgroups the sizes of which are equal as much as possible, at least 80 ND, ESA non-users are to be enrolled in Cohort 3.

For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half width of the 95% CI for mean Hgb during the primary efficacy evaluation period is 0.493 g/dL.

9.2.2. Sample Size Sensitivity

The power for the primary endpoint is shown according to treatment difference and standard deviation in Table 18 based on a population consisting of 140 subjects (70 subjects per group) who will complete study on the condition of a dropout rate of approximately 30%. This population is derived from 204 ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users)

Table 18 Power Sensitivity (70 Subjects Evaluated Per Group, Noninferiority Margin of -1.0, One-Sided Significance Level of 2.5%)

Treatment Difference	Standard Deviation		
	1.25	1.5	1.75
0	99.7%	**97.5%**	91.2%
-0.1	98.8%	94.1%	85.6%
-0.2	96.4%	88.0%	76.6%
-0.3	90.8%	78.3%	65.2%

9.2.3. 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

- All Screening Population

The All Screening Population consists of all subjects who are given subject number and whose data are collected, including demographics at screening.

- Intent-to-Treat (ITT) Population

The Intention-To-Treat Population consists of Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users) who are given randomization number with Hgb measurement at both baseline and at least one scheduled visits following the baseline. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of non-inferiority.

- modified ITT (mITT) Population

The mITT Population consists of all ITT subjects who have at least one Hgb measurement during the efficacy evaluation period. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of superiority.

- Per-Protocol (PP) Population

The PP Population consists of all mITT subjects who are not major protocol violators. Details will be defined in the RAP. This population will be used for efficacy sensitivity analyses.

- Safety Population

The Safety Population consists of all subjects who receive at least one dose of study treatment. Subjects will be analyzed according to the treatment received. This population will be used for safety analyses.

- PK Population

The PK Population consists of all GSK1278863-treated subjects from whom PK samples are collected and analyzed.

Additional populations may be defined in the RAP.

9.3.2. Interim Analysis

No interim analysis is planned.

9.3.3. Adjustment for Multiplicity

Adjustment for multiplicity will be applied to maintain an overall type I error rate of 5%. After a preliminary assessment, the primary endpoint will be evaluated to demonstrate the non-inferiority at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%). Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority. Since the process will follow step-down manner, a multiplicity adjustment for a two-sided significance level of 5% will not be needed according to a closed test procedure.
Other secondary endpoints, which will be evaluated on a complementary or exploratory basis, will be compared at a two-sided significance level of 5% without multiplicity adjustment.
Since Cohort 2 is a single-arm cohort, no testing will be performed to evaluate the efficacy in PD subjects.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Efficacy Analysis

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects. MMRM will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. This model includes treatment groups, baseline Hgb, assessment visits, interaction terms between treatment groups and assessment visits, as well as interaction terms between baseline Hgb and assessment visit. As a preliminary assessment, it will be confirmed if the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-

13.0 g/dL) at first. This confirmation will be established if the lower and upper limit of 95% CI for the mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL). In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in the mean Hgb during the primary efficacy evaluation period will be estimated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e. lies fully within the range -1.0 to <0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimated in the GSK1278863 group is within the target range.

The primary efficacy population will be the ITT Population, and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted.

Following sensitivity analyses will be conducted to assess robustness of the study result.

- If ND, ESA users in cohort 3 whose dose level was decreased by one step at Week 2 exist, sensitivity analysis excluding these subjects from primary analysis will be conducted.
- Sensitivity analysis to primary efficacy analysis for all ND patients in Cohort 1 and Cohort 3 will be conducted.
- If there are Hgb considered to be impacted by blood transfusion or marketed ESAs, sensitivity analysis excluding the Hgb values from the analyses of primary endpoint will be conducted.
- Analysis of covariance (ANCOVA) will be conducted as sensitivity analysis to MMRM. This model includes treatment group and baseline Hgb. The analysis population will be mITT population and the same analysis will be repeated in the PP population.
- A tipping point analysis based on multiple imputation will be conducted as sensitivity analysis to missing data assumption. This analysis explores a point where non-inferiority is not confirmed (tipping point) by changing assumption to missing data and repeating imputation. The analysis population will be ITT population and the same analysis will be repeated in the mITT and PP population.

Further details of sensitivity analyses will be provided in the RAP.

9.4.2. Principal Secondary Efficacy Analysis

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.

In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for odds ratio is greater than 1.0.

9.4.3. Other Secondary Efficacy Analyses

Among the secondary efficacy endpoints, the time (%) in Hgb target range during the primary efficacy evaluation period , proportion of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks, and changes in iron metabolism parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC),

the point estimates and 95% CIs for the treatment difference (or odds ratio) in ND subjects will be calculated. Other secondary efficacy and exploratory endpoints will be summarized by each treatment group.
For PD subjects, the efficacy endpoints will be descriptively summarized.

9.4.4. Safety Analyses

In principle, safety data will be summarized by each treatment group in the Safety Population. ND subjects and PD subjects will be summarized separately.

9.4.4.1. Exposure

Exposure information will be listed for all subjects. The duration of treatment (number of days) and cumulative dose will be tabulated. In addition, distribution of the dose level at each assessment visit and final dosing visit will be tabulated. Frequency of dose adjustment and duration of treatment interruption due to Hgb >13 g/dL will be summarized.

9.4.4.2. Adverse Events

All AEs will be categorized by the MedDRA system organ class and preferred term to tabulate the number and incidence. All AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs of special interest will be summarized separately. Similar summary will be provided for study treatment-related AEs.

9.4.4.3. Other Safety Parameters

For laboratory tests, vital signs and ECG, parameters and/or changes from baseline will be summarized using summary statistics at each assessment visit. The number and percentage of subjects with values of the potential clinical importance values will be tabulated. The criteria for the potential clinical importance will be described in the RAP. For lipid parameters (total cholesterol, LDL cholesterol, and HDL cholesterol), percent changes will also be tabulated. The number (%) of subjects who have any change in anti-hypertensive medications (type and/or dose) due to increased blood pressure will be tabulated.

9.4.5. Pharmacokinetics Analyses

For plasma concentrations of GSK1278863 over time, individual data will be listed, and summary statistics at each time point will be calculated for each dose level. For PK parameters (AUC_{0-4} and Cmax), summary statistics will be calculated for each dose level, and scatter plots against the dose level will be generated.

9.4.6. PRO Data Analysis

Details of PRO data tabulation will be described in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and the Pharmaceutical Affairs Law.

GSK will submit the CTN to the regulatory authorities in accordance with with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- 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.

Informed Consent

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential subject and the subject's legally acceptable representative (as required) of the study including the written information. The investigator (or subinvestigator) should provide the subject and the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and the subject's legally acceptable representative should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home,

he/she may take the consent form home. The person who conducted the informed consent discussion and study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject and the subject's legally acceptable representative.

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

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

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

10.6. Records Retention

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

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

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

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

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

10.8. Study Period

See Exhibit 1

10.9. Study Administrative Structure

Sponsor information is included in Exhibit 2. List of Medical Institutions and Investigators is included in Exhibit 3.

11. REFERENCES

Akizawa Tadao, Makino Hirofumi, Matsuo Seiichi, et al. Management of anemia in chronic kidney disease patients: baseline findings from Chronic Kidney Disease Japan Cohort Study. Clin Exp Nephrol. 2011;15:248-57.

Szczech Lynda A, Barnhart Huiman X., Inrig Jula K., et al. Secondary analysis of the CHOIR trial epoetin-α dose and achieved hemoglobin outcomes. Kidney International. 2008;74:791-8.

Guidelines for Renal Anemia in Chronic Kidney Disease issued by the Japanese Society for Dialysis Therapy in 2008. Journal of Japanese Society for Dialysis Therapy. 2008;41(10):661-716

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Curve
CKD	Chronic Kidney Disease
Cmax	Maximum concentration
CPK	Creatine Phosphokinase
CYP	Cytochrome P450
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
EQ-5D-5L	EuroQol Health Utility Index
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotrophin
HD	Hemodialysis
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
Hgb	Hemoglobin
HIF	Hypoxia-Inducible Factor
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonization
INR	International Normalized Ratio
iPTH	Intact Parathyroid Hormone
ITT	Intent-to-Treat
IWRS	Interactive Web Recognition System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MCS	Mental Component Summary
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
ND	Non dialysis
NYHA	New York Heart Association
PCS	Physical Component Summary
PD	Peritoneal Dialysis
PHI	Prolyl Hydroxylase Inhibitor
PK	Pharmacokinetic
PP	Per-Protocol
PRO	Patient Reported Outcome
QT	Q-T Interval
QTc	Q-T Interval Corrected for Heart Rate

QTcB	Bazett's Correction of QT Interval
RAP	Reporting and Analysis Plan
RDW	Red Blood Cell Distribution Width
RNA	Ribonucleic Acid
rhEPO	Recombinant human erythropoietin
SAE	Serious Adverse Event
SRM	Study Reference Manual
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
UIBC	Unsaturated iron Binding Capacity
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Hemocue
Mircera®

12.2. Appendix 2: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK1278863		
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 5.1. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is provided in Section 6.4.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
Risk of death, MI, stroke, heart failure, thromboembolic events, 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 5.2. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Suspected GI bleeding or significant symptoms consistent with erosion should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 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.	period.
Cancer-related mortality, 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 60 mg/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 been identified as a safety concern for GSK1278863.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 5.2.. ♣ Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.4. ♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	noted among non-treated rats. ・Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term therapy with GSK1278863 5 mg or 100 mg 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. Changes in sPAP from baseline in dialysis patients were comparable between GSK1278863 group and Control group (median). The numbers of patients who met the potentially clinically significant sPAP criteria (increased from baseline by >20 mmHg) were disproportionate between the treatment groups [8 patients (7%) in GSK1278863 group and 0 patient in Control group]. This imbalance was associaited with some confounding factors, including the randomization scheme of 4.5:1 ratio and inconsistency in timings of ECHO assessment related to dialysis. Additionally, 2 of the 3 patients with sPAP improvement at the follow-up ECHO assessment had confounding factors that were potentially attributable for sPAP improvement other than study medication discontinuation. No dose relationship was seen in patients who met potentially clinically significant sPAP criteria. Overall, no sufficient evidence was obtained to conclude the relationship with GSK1278863. ・Following review of clinical data received to date, this has not 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	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	
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 (Campochiaro, 2006). Administration of 60 mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO 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 25 mg, 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.	• Ophthalmology exams will be performed during screening, at approximately Week 12 on-study, and at the end of treatment. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period. • Ophthalmology exams should be specified in Section 7.4.8. and monitored. • When proliferative retinopathy, macular edema or choroidal neovascularization is suggested, or symptoms that are consistent with these AEs are reported, patients should consult ophthalmologist as clinically necessary.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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.	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Co-administration of GSK1278863 with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.11.2. • Co-administration of GSK1278863 with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 6.11.1. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.11. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	provided in Section 6.4.1. • These risks will be monitored instreamly by the internal safety review team throughout the study period.
Other		
ESA risks (Control)	・See risks outlined in table for GSK1278863 for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia; Risk of MI, stroke, thromboembolic events, thrombosis of vascular access; and risk of cancer-related mortality and tumor progression. ・Non-controllable hypertension ・Pure red cell aplasia ・Hepatic function disorder with increase of AST, ALT and Gamma-glutamyltransferase, and jaundice have been reported as adverse drug reactions for other ESA according to the prescribing information of Epoetin beta pegol.	• The same mitigation strategies have been indentified in acoordance with the mitigation strategies for GSK1278863 • Blood pressure will be monitored throughout the dosing period as outlined in the Time and Events Table provided in Section 7.1.. • A criterion to exclude subjects with history of pure red cell aplasia is added to Section 5.2.. • Liver function will be monitored throughout the dosing period as outlined in the Time and Events Table provided in Section 7.1.

References

Campochiaro et al., Ocular versus Extraocular Neovascularization: Mirror Images or Vague Resemblances; Invest Ophthalmol & Vis Sci 2006. 47:462-474.

Formenti et al., Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2alpha gain-of-function mutation. FASEB J. 2011, 25(6): 2001-2011.

Muz et al., The role of hypoxia and HIF-dependent signaling events in rheumatoid arthritis, Arthritis Research & Therapy 2009. 11:201-210.

Smith et al., Mutation of von Hippel–Lindau Tumour Suppressor and Human Cardiopulmonary Physiology PLOS 2006. 3:1176-1186.

Westra et al., Hypoxia-Inducible Factor-1 as Regulator of Angiogenesis in Rheumatoid Arthritis - Therapeutic Implications. Current Medicinal Chemistry 2010. 17:254-263.

12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential

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.

1. Contraceptive subdermal implant that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information
2. Intrauterine device or intrauterine system that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information [Hatcher, 2011]
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011].

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

References

Trussell J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, and Policar M (editors). Contraceptive Technology: Twentieth Revised Edition. New York: Ardent Media, 2011.

12.4. Appendix 4: 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 12.6. Appendix 6. 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 or be withdrawn from the study

12.5. Appendix 5: Liver Safety Required Actions and Follow up Assessments

Phase III-IV 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).

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) and quantitative hepatitis B DNA • Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>**

hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, (for ND patients only) if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase,

<2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

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

12.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.6.1. 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 meeting 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.

12.6.2. 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 and 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; (for ND patients only) if

unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. 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.

12.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

12.6.4. Recording of AEs and SAEs

AEs and SAE Recording:

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

12.6.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.6.6. 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 SAE contact.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will confirm that causal relationship of SAE has been considered, by ticking the 'reviewed' box at the bottom of eCRF page within 72 hours following the submission of SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE contact by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.7. Appendix 7 - Genetic Research

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 objective of the genetic research is to understand the response to GSK1278863. To achieve this objective, the relationship between genetic variants and the followings may be investigated.

- Response to medicine, including GSK1278863, ESA, other study medicines or any concomitant medicines;
- Nephrogenic anemia and related conditions susceptibility, severity, and progression

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 which will be conducted for this study 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 related to GSK1278863 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 the 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, align with the purpose of the genetic research, 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

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

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

12.8. Appendix 8: Definition of and Procedures for Documenting Medical Device Incidents

12.8.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all medical devices provided for use in the study (see Section 6.2. for the list of the medical devices).

Medical Device Incident Definition:
• Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an incident associated with a device happened and
- the incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents
• a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse • a patient's treatment is interrupted or compromised by a medical device failure • misdiagnosis due to medical device failure leads to inappropriate treatment • a patient's health deteriorates due to medical device failure

12.8.1.1. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 12.6. (Appendix 6). • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK.

- It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

TITLE PAGE

Division : Worldwide Development

Information Type : Clinical Protocol

Title : A 52-week, Phase III, open-label, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese non-dialysis and peritoneal dialysis subjects with anemia associated with chronic kidney disease.

Compound Number : GSK1278863

Development Phase III

Effective Date : 08-MAR-2017

Protocol Amendment Number: 03

Author(s) :

PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N266248_00	2016-02-18	Original
2015N266248_01	2016-04-12	Amendment No. 1
Clarification of the method of administration of control, clarification of the withdrawal/dropout criteria, addition of medical devices, clarification of the time and events, clarification of procedures after occurrence of liver events		
2015N266248_02	2016-08-01	Amendment No. 2
Clarification of exclusion criteria, clarification of the procedure for the ophthalmology exam at the re-screening, clarification of analysis populations, updates of risk assessment, updates of the procedures for SAE reports		
2015N266248_03	2017-03-08	Amendment No. 3
Addition of Cohort 3, change of the starting dose for ND subjects, ESA non-users, change of analysis population for efficacy analyses, addition of Week 2 visit, clarification of the timing of eligibility assessment regarding exclusion criteria, clarification of prohibited medications, correction of adverse events of special interest		

Sponsor Signatory:

Kihito Takahashi Director, Japan Development and Medical Affairs (JDMA), GlaxoSmithKline K. K.	**Date**

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number	Fax Number	Site Address
Medical Monitor	PPD M.D., Ph.D.			GlaxoSmithKline K.K. 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN
SAE contact information	Person in charge of GSK1278863 Clinical Operations dept.	PPD		GlaxoSmithKline K.K. 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN

Emergency Contact

Emergency Contact (Mon to Fri 10am to 6pm, except for national holiday and year-end and New Year holidays)
Person in charge of GSK1278863, Clinical Operations dept. R&D, Glaxo Smith Kline K.K
TEL: PPD
FAX: PPD

Emergency Contact at night and holiday (Mon to Fri 6pm to 10am, Sat, Sun, national holiday and year-end and New Year holidays)
BI medical Inc.
Responsible Person: PPD
TEL: PPD (toll free)
FAX: PPD (toll free)

Sponsor Legal Registered Address:

6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and the rivision.
- 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 Signature	Date

TABLE OF CONTENTS

1. PROTOCOL SYNOPSIS FOR STUDY PHI201753

Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

Objective(s)/Endpoint(s)

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	• Number (%) of subjects with mean Hgb in the target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change from baseline in Hgb at Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category at Week 4
• To evaluate dose adjustment scheme of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustment scheme of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control of GSK1278863 in PD subjects	• Hgb and change from baseline at each assessment visit • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment visit • Time (%) in Hgb target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52) • Time (in days) to reach the lower Hgb target

Objective	Endpoint
	(11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks • Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes
• To evaluate the effect on iron use of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate effect on iron use of GSK1278863 in PD subjects	• Dose of oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To evaluate the effect on iron metabolism of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on iron metabolism of GSK1278863 in PD subjects	• Change from baseline in ferritin • Change from baseline in transferrin saturation (TSAT) • Changes from baseline in hepcidin, serum iron, and total iron binding capacity (TIBC)
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To evaluate the effect on progression of Chronic Kidney Disease (CKD) of GSK1278863 in ND subjects using epoetin beta pegol as control	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To evaluate the effect on health-related QoL (HR-QoL) of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on HR-QoL of GSK1278863 in PD subjects	SF-36 • Changes from baseline in SF-36 HR-QoL scores [Physical Component Summary (PCS), Mental Component Summary (MCS), and 8 subscales] EuroQol Health Utility Index (EQ-5D-5L) • Change from baseline in EQ-5D-5L score • Change from baseline in EQ-5D-5L Visual Analog Scale (VAS)
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest

Objective	Endpoint
	• Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

Study Design

This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (demonstration of non-inferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 270 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. Cohort 1 (ND subjects) and Cohort 2 (PD subjects) were set for target population of this study when the study was planned. Cohort 3 is newly added in Protocol amendment (Amendment No.3). ND subjects will be randomized not to Cohort 1 but to Cohort 3 after Protocol amendment:

<table>
<tr><th>Patient population</th><th>Cohort</th><th>Treatment group</th><th colspan="2">Target number of subjects (randomized)</th></tr>
<tr><td rowspan="4">ND patient</td><td rowspan="2">Cohort 1[1]</td><td>GSK1278863 group (starting dose: 4 mg)</td><td rowspan="2">169 subjects[4)]</td><td rowspan="4">270 subjects[5)]</td></tr>
<tr><td>Epoetin beta pegol group</td></tr>
<tr><td rowspan="2">Cohort 3[2)]</td><td>GSK1278863 group (starting dose: 2 mg or 4 mg[3)])</td><td rowspan="2">101 subjects</td></tr>
<tr><td>Epoetin beta pegol group</td></tr>
<tr><td>PD patient</td><td>Cohort 2</td><td>GSK1278863 group (starting dose: 4 mg)</td><td colspan="2">50 subjects</td></tr>
</table>

1) At least 50 ESA users and at least 50 ESA non-users will be randomized to Cohort 1.

2) ND patients will be randomized to Cohort 3 and at least 80 ESA non-user will be randomized after Protocol Amendment No.3.

3) GSK 1278863 starting dose in Cohort 3 as below

- ESA non-user (baseline Hgb 8.0-<9.0 g/dL):4 mg
- ESA non-user (baseline Hgb 9.0-<11.0 g/dL):2 mg
- ESA user: 4 mg

4) The exact number of ND subjects randomized to Cohort 1

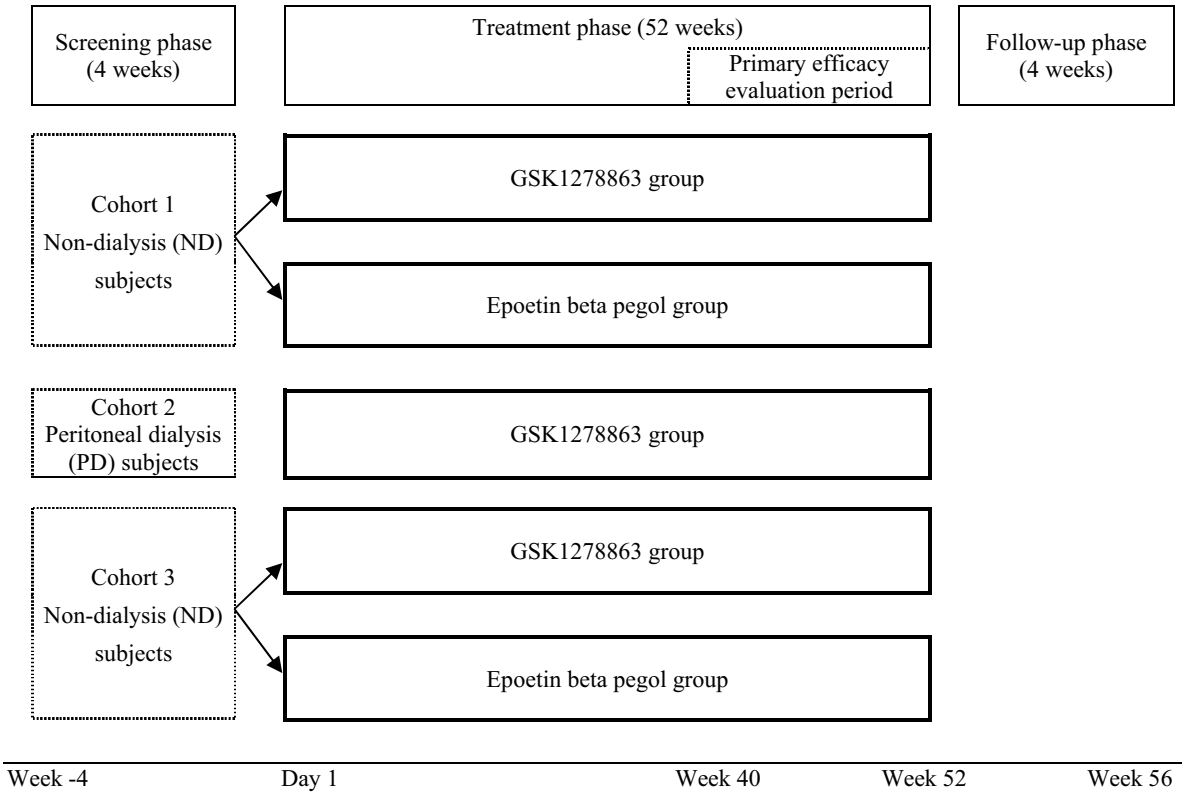
5) Subjects will be randomized in a 1:1 ratio to one of the two treatment groups

ESA: erythropoiesis-stimulating agent

For the patient populations in either cohort, the Hgb criteria are specified according to the presence or absence of prior ESA: ESA non-users with an Hgb level of ≥ 8.0 to <11.0 g/dL and ESA users with an Hgb level of 9.0 to 13.0 g/dL will be included in the study.

In Cohort 1 and Cohort 3, eligible ND subjects [total of 270 subjects (169 subjects in Cohort 1, 101 subjects in Cohort 3)] will be stratified by the current ESA therapy and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group.
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown below.



Method of Administration of Study Medication in Each Treatment Group

In each treatment group, study medication will be administered as follows:

GSK1278863 group:

- Cohort 1 (ND subjects) and Cohort 2 (PD subjects)
  Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1.
- Cohort 3 (ND subjects)
  - For ESA non-user with Baseline Hgb ≥8.0 and <9.0 g/dL, Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1.
  - For ESA non-user with Baseline Hgb ≥9.0 and <11.0 g/dL, Treatment with GSK1278863 will be started at a dose of 2 mg once daily on Day 1.
  - For ESA users, Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1.

After Week 4, dose adjustments will be made within the dose range of 1-24 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13 0 g/dL).

- Epoetin beta pegol group (ND subjects):
  - ESA non-users: Subcutaneous treatment with epoetin beta pegol will be started at a dose of 25 μg once every 2 weeks on Day 1. Subsequently, dose adjustments will be made within the dose range of 25-150 μg every 4 weeks according to the prespecified initial dose adjustment criteria to achieve the lower limit of the Hgb target (11.0 g/dL). Once Hgb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm. After it is confirmed that all of the criteria for dosing interval

change are met, dosing frequency will be changed to once every 4 weeks, and dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target Hgb range (11.0-13.0 g/dL).

- ESA users: Prior ESA therapy will be replaced with subcutaneous treatment with epoetin beta pegol at the equivalent dose once every 4 weeks according to prespecified dose conversion. Subsequently, dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL).

Analysis

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during in the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a two-sided significance level of 5% with a sample size of 100 subjects per group. Assuming a dropout rate of approximately 25%, 135 subjects will be randomized to each group. For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half the width of the 95% CI for mean Hgb during in the primary efficacy evaluation period is 0.493 g/dL. During this study, the protocol has been amended according to the change in starting dose for ND, ESA non-users in the GSK1278863 group; however, this amendment will need no change for the overall target sample size (see Section 9.2.).

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects. A mixed model for repeated measurements (MMRM) will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. As a preliminary assessment, it will be confirmed if the lower and upper limit of 95% CI for mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL) In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in mean Hgb during the primary efficacy evaluation period will be estimated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e. lies fully within the range -1.0 to 0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimate in the GSK1278863 group is within the target range.
The primary efficacy population will be the ITT Population (excluding non-ESA users from Cohort 1), and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted. Further details of sensitivity analyses will be provided in the Reporting and Analysis Plan (RAP).

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.

In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and the current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for the odds ratio is greater than 1.0.

2. INTRODUCTION

GSK1278863 is a hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitor (PHI) that stimulates erythropoiesis in the same manner as innate response to hypoxia and is currently being developed as a new treatment for renal anemia.

2.1. Study Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

2.2. Background

Renal anemia is diagnosed in many patients with CKD, and the prevalence of renal anemia increases with progression of CKD [Akizawa, 2011]. Causes of anemia in CKD patients include absolute or relative deficiency of erythropoietin (EPO), shortened erythrocyte survival, and reduced iron availability. Anemia is further exacerbated by chronic blood loss associated with hemodialysis procedure, infection, and functional hemolysis [Japanese Society for Dialysis Therapy, 2008].

GSK1278863 is a hypoxia-inducible factor-prolyl hydroxylase inhibitor that is currently being developed as a treatment for renal anemia. Data in Japanese patients have been collected from a Japanese Phase II 4-week treatment study in Japanese hemodialysis (HD) subjects (PHI116099: 97 Japanese subjects), an international multi-center Phase II 24-week treatment study in HD subjects (PHI113633: including 24 Japanese subjects), and an international multi-center Phase II 24-week treatment study in ND subjects (PHI113747: including 42 Japanese subjects). In these clinical studies, GSK1278863 increased endogenous EPO, reduced hepcidin, and increased Hgb in HD and ND subjects including Japanese subjects. In addition, GSK1278863 increased Hgb at lower blood EPO concentrations than existing erythropoiesis-stimulating agents (ESAs).

Data from completed clinical and clinical pharmacology studies and the preclinical data safety package are provided in the Development Core Safety Information found in the current GSK1278863 Investigator Brochure (IB). A benefit: risk assessment, including risk mitigation strategies, is outlined in Section 4.6.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of	• Number (%) of subjects with mean Hgb in the

Objective	Endpoint
GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change in Hgb from baseline to Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category to Week 4
• To evaluate dose adjustments of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustments of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control by GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control by GSK1278863 in PD subjects	• Hgb at each assessment time point and change in Hgb from baseline to each assessment time point • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment time point • Proportion (%) of time with Hgb within the target range (11.0-13.0 g/dL) in the primary efficacy evaluation period (Weeks 40 to 52) • Time (number of days) to the lower Hgb target (11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks before Week 52 • Number (%) of subjects who achieve an Hgb level of more than 13.0 g/dL and number of episodes
• To compare the effect of GSK1278863 versus epoetin beta pegol on iron use in ND subjects • To evaluate the effect of GSK1278863 on iron use in PD subjects	• Dose of oral iron in the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To compare the effect of GSK1278863	• Change in ferritin from baseline

Objective	Endpoint
versus epoetin beta pegol on iron metabolism in ND subjects • To evaluate the effect of GSK1278863 on iron metabolism in PD subjects	• Change in transferrin saturation (TSAT) from baseline • Changes in hepcidin, serum iron, and total iron binding capacity (TIBC) from baseline
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To compare the effect of GSK1278863 versus epoetin beta pegol on progression of CKD in ND subjects	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To compare the effect of GSK1278863 versus epoetin beta pegol on health-related QoL (HR-QoL) in ND subjects • To evaluate the effect of GSK1278863 on H-RQoL in PD subjects	SF-36 • Changes in SF-36 HR-QoL scores (PCS, MCS, and 8 subscales) from baseline EuroQol Health Utility Index (EQ-5D-5L) • Change in EQ-5D-5L score from baseline • Change in EQ-5D-5L Visual Analog Scale (VAS) from baseline
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest • Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

4. STUDY DESIGN

4.1. Overall Design

This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (verification of noninferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 270 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. Cohort 1 (ND subjects) and Cohort 2 (PD subjects) were set for target population of this study when the study was planned. Cohort 3 is newly added in amendment (Amendment No.3). ND subjects will be randomized not to Cohort 1 but to Cohort 3 after amendment No.3:

Table 1 Composition of each cohort

[Including target number of subjects (randomized)]

Patient population	Cohort	Treatment group	Target number of subjects (randomized)	
ND patient	Cohort 1[1)]	GSK1278863 group (starting dose: 4 mg)	169 subjects[4)]	270 subjects[5)]
		Epoetin beta pegol group		
	Cohort 3[2)]	GSK1278863 group (starting dose: 2 mg or 4 mg[3)])	101 subjects	
		Epoetin beta pegol group		
PD patient	Cohort 2	GSK1278863 group (starting dose: 4 mg)	50 subjects	

1) At least 50 ESA users and at least 50 ESA non-users will be randomized to Cohort 1.

2) ND patients will be randomized to cohort 3 and at least 80 ESA non-user will be randomized after Protocol amendment (Amendment No.3).

3) GSK 1278863 starting dose in Cohort 3 as below

- ESA non-user (baseline Hgb 8.0-<9.0 g/dL):4 mg
- ESA non-user (baseline Hgb 9.0-<11.0 g/dL):2 mg
- ESA user: 4 mg

4) The exact number of ND subjects randomized to cohort 1

5) Subjects will be randomized in a 1:1 ratio to one of the two treatment groups

ESA: erythropoiesis-stimulating agent

For the patient populations in either cohort, the Hgb criteria are specified according to the presence or absence of prior ESA: ESA non-users with an Hgb level of ≥8.0 to <11.0 g/dL and ESA users with an Hgb level of 9.0 to 13.0 g/dL will be included in the study.

In Cohort 1and Cohort 3, eligible ND subjects [total of 270 subjects (169 subjects in Cohort 1, 101 subjects in Cohort 3)] will be stratified by the current ESA therapy (ESA non-user or ESA user) and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group.
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown in Figure 1.

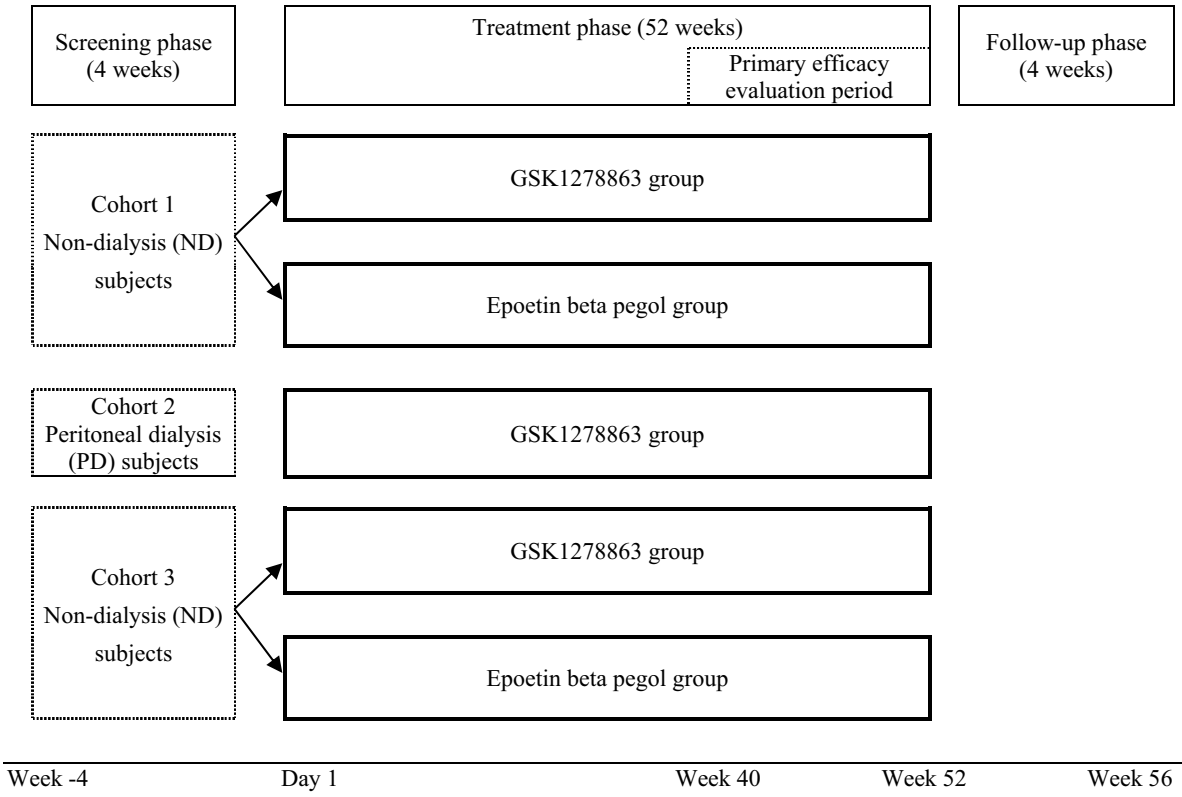


Figure 1 Study Design

4.2. Treatment Groups and Study Periods

Details for each study period and treatments are described below. In this study, a point-of-care Hgb analyzer (HemoCue®) will consistently be utilized for confirmation of subjects' eligibility, withdrawal criteria and dose adjustments of study medication.

Screening phase

Subjects who have provided informed consent and meet all of the eligibility criteria at screening (Week -4) (Sections 5.1 and 5.2) will be provisionally enrolled in the study. Subjects who have used ESA and/or oral iron since before the start of the study must remain on the same regimen throughout the screening phase (intravenous iron will not be allowed).

Treatment phase

Subjects who meet all of the eligibility criteria at the start of the treatment phase (Day 1) will be enrolled in the study. Study medication (either GSK1278863 or epoetin beta pegol group) will be administered for 52 weeks according to randomization in Cohort 1and Cohort 3. GSK1278863 will be administered in Cohort 2 for 52 weeks. For ESA users, prior ESA will be replaced with study medication on Day 1. GSK1278863 will be orally administered once daily, and epoetin beta pegol will be subcutaneously administered once every 2 or 4 weeks. In both groups, dose adjustments for study medication during the treatment phase will be made according to the administration schedule specified in Section 6.4. to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL). In addition,

supplemental iron therapy will be administered according to the standard initiation criteria as described in Section 6.12.. It should be noted that intravenous iron or dose change for oral iron will not be allowed from Day 1 to Week 4.

Follow-up phase

Subjects will visit the site for follow-up assessments and observations 4 weeks after the completion/discontinuation of study treatment. During the follow-up phase, treatment of renal anemia will be allowed as necessary at the discretion of the investigator (or subinvestigator).

4.3. Study Subjects and Number of Subjects

For ND subjects, a total of 270 subjects will be randomized (135 subjects in GSK1278863 group,135 subjects in epoetin beta pegol group). The minimum target number of subjects is 50 ESA non-users and 50 ESA users to allow for evaluations by the current ESA therapy (ESA non-user or ESA user) in Cohort 1. At least 80 ESA non-user will be randomized to Cohort 3 defined in Protocol (Amendment No.3). In protocol amendment No.3, each target number subjects are amended as Table 2, but total of target number of subjects is not changed.
Assuming a dropout rate of 35% during the screening phase, approximately 416 ND subjects need to be screened. Assuming a dropout rate of 25% after the start of study treatment, a total of 202 subjects are expected to complete the 52-week treatment.

In Cohort 2 involving PD subjects, 50 subjects will be enrolled (GSK1278863 group only). Since the number of PD patients is very limited in Japan, the target number of subjects is not set for either ESA non-users or users. Assuming a dropout rate of 35% during the screening phase, approximately 77 subjects need to be screened. Assuming a dropout rate of 25% after the start of study treatment, 38 subjects are expected to complete the 52-week treatment.

Table 2 Target Number of Subjects

	ND subjects		PD subjects
	Cohort 1	Cohort 3	Cohort 2
Screened	416		77
Randomized/enrolled	270		50
	169*1	101*2	
Completed 52-week treatment	202		38

*1: In Cohort 1, at least 50 ESA non-users and at least 50 ESA users will be randomized.
*2: In Cohort 3, at least 80 ESA non-user will be randomized

4.4. Rationale for Study Design

Objectives and evaluations

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese ND and PD subjects with renal anemia. For Cohort 1 and Cohort 3, the study is designed as an active-controlled, parallel-group comparative study to meet the primary objective, that is, to demonstrate non-inferiority of GSK1278863 to the existing drug in ND, ESA user subjects in Cohort 1 or ND subjects in Cohort 3, depending on a change of the starting dose for ND, ESA non-users. For Cohort 2, the study is designed as an uncontrolled study because there are not many PD patients. The target Hgb range was set for study treatment in line with the Guidelines for Renal Anemia in Chronic Kidney Disease issued

by the Japanese Society for Dialysis Therapy in 2008 [The Japanese Society for Dialysis Therapy, 2008] to demonstrate that treatment with GSK1278863 can result in achievement and/or maintenance of target Hgb in ND and PD subjects, and evaluate the appropriateness of the starting dose of GSK1278863.

Control

For the ND patient population (Cohort 1 and Cohort 3), epoetin beta pegol, which has been widely used in Japanese patients with renal anemia, primarily ND patients, since its approval in Japan in 2011, was selected as control.

Open-label

If the study is conducted as a double-blind study, it is necessary to not only administer GSK1278863 orally (once daily) or epoetin beta pegol subcutaneously (once every 2 or 4 weeks), but also administer the matching placebo subcutaneously or orally. It will be more stressful for subjects and complicate treatment procedures to use both active drug and matching placebo for two drugs with different routes and intervals of administration for the purpose of maintaining the blind, and make dose adjustments for individual subjects according to the change in Hgb over time. Accordingly, this study is designed as an open-label study rather than a double-blind study, which seems infeasible. Since Hgb used for efficacy evaluation is an objective measure, and dose adjustments for study medication will be made according to the prespecified Hgb-based dose adjustment method in both GSK1278863 and epoetin beta pegol groups, it is unlikely that the open-label design will create any bias in the primary evaluation.

4.5. Rationale for Dose Levels

Starting dose and dose adjustments of GSK1278863

The starting dose and the dose adjustment method (maintenance dose range: 1-24 mg) for GSK1278863 are described in Section 6.4..

The starting dose and the dose adjustment algorithm selected for Japanese ND subjects in the present study are based on the results from a review of the longitudinal model constructed using Hgb data from six Japanese or overseas Phase II studies (PHI112844, PHI116581, PHI116582, PHI113633, PHI113747, and PHI116099) as well as the results from clinical studies. The data set used in the model analyses was based on the data of GSK1278863 administered in a wide dose range (0-25 mg) and included a Japanese Phase II 4-week treatment study (PHI116099) and international multi-center late Phase II 24-week treatment studies (PHI113633 and PHI113747) in which subjects in Japan participated. For PD subjects, the starting dose and the dose adjustment algorithm for ND subjects will be applied based on the PK/PD profiles in PD subjects determined from an interim analysis in an overseas 14-day treatment clinical pharmacology study (PHI200942).

Starting dose

Simulation results using the longitudinal model in ND subjects as well as the results from clinical studies indicated that GSK1278863 given at a dose of 4 mg may slowly increase Hgb (0.5-1.0 g/dL on average) without a rapid increase greater than 2 g/dL after 4 weeks of treatment in ESA non-users. 4 mg GSK1278863 may also maintain Hgb without a rapid increase greater than 2 g/dL for 4 weeks

after switching from prior ESA in ESA users. Therefore, 4 mg was set as starting dose of GSK1278863 when study was planned.

As of Dec 2016 during this study, from the result of a review of blinded data, it was determined that the percentage of ND, ESA-non-user subjects with an Hgb increases of >2.0 g/dL from baseline to Week 4 was higher than expectaion dedscribed above. This finding was not observed in ND, ESA-user subjects and PD subjects.

Therefore, in the protocol amendment No 3,

- For ND, ESA non-user subjects with baseline Hgb ≥9.0 g/dL and <11.0 g/dL, the starting dose of GSK1278863 is changed from 4 mg to 2 mg.
- For ND, ESA non-user subjects with baseline Hgb ≥8.0 g/dL and <9.0 g/dL, the starting dose remains at 4 mg.

For ND, ESA-user subjects and PD subjects, the starting dose of GSK1278863 were not changed and remains at 4 mg respectively.
In addition, Week 2 visit for additional Hgb monitoring in Cohort 3 was also included to allow earlier safety assessment of Hgb change at early phase of GSK1278863 treatment. (Refer to Section 6.4.1.)

Maintenance dose range and dose adjustment algorithm
Simulation results using the longitudinal model showed that drug response to GSK1278863 greatly varied among subjects, indicating that the dose range from 1 to 24 mg may be necessary to achieve and maintain target Hgb. Accordingly, a total of 8 dose levels (1, 2, 4, 6, 8, 12, 18, and 24 mg) were selected as the maintenance doses, with 4 mg intended for subjects with a standard drug response. The dose adjustment algorithm was defined so that target Hgb (11.0-13.0 g/dL) set for the present study according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] can be maintained. Since the upper limit of the Hgb target (13.0 g/dL) is equivalent to the interruption criterion for ESA, the dose level of GSK1278863 will be reduced by one step when Hgb increases to more than 12.5 g/dL, and the dose level will be maintained while Hgb is in the range of 11.5-<12.5 g/dL. Since the guidelines state that an Hgb increase of 0.5 g/dL or less per week is appropriate to prevent adverse reactions, the dose level will be reduced by one step when Hgb increases by more than 2 g/dL over 4 weeks (or when Hgb increases by more than 1 g/dL over 2 weeks at Week 4). For subjects whose anemia needs to be corrected (≥7.5 g/dL and <11.5 g/dL), the dose level will be maintained while the Hgb increase per 4 weeks is 0.5-2 g/dL, and the dose level will be increased by one step when the Hgb increase per 4 weeks is less than 0.5 g/dL.

Starting dose and dose adjustments of control (epoetin beta pegol)
The starting dose and the dose adjustment algorithm for epoetin beta pegol are described in Section 6.4..
The starting dose of epoetin beta pegol for subjects not using ESA or subjects on epoetin was selected based on the Prescribing Information in Japan. For subjects on darbepoetin alfa, darbepoetin alfa will be switched to epoetin beta pegol at a dose ratio of 6:5 according to overseas Prescribing Information, given no specification for dose conversion from darbepoetin currently approved in Japan to epoetin beta pegol.

The dose adjustment algorithm for epoetin beta pegol was determined based on the product information and previous Japanese clinical studies. In Cohort 3, a study visit at Week 2 for Hgb monitoring was also added for the control group. (Refer to Section 6.4.2.)

4.6. Benefit: Risk Assessment

Summaries of findings from clinical and nonclinical studies of GSK1278863 can be found in the IB and IB supplement. The risk assessment and risk minimization strategies for the present study are outlined in the following sections:

4.6.1. Risk Assessment

Based on the results of completed clinical and nonclinical studies of GSK1278863, the potential risks of clinical significance and the risk minimization strategies for the present study are outlined in Section 12.2. Appendix 2.

4.6.2. Benefit Assessment

Study PHI201753 is a Phase 3 study in Japanese ND and PD subjects with renal anemia. Previous clinical studies of GSK1278863 administered for up to 24 weeks in ND or HD subjects have demonstrated clinical efficacy (increase in and/or maintenance of Hgb) with serum EPO concentrations increased within the normal physiologic range in CKD subjects. Data obtained in Study PHI201753 will generate safety and efficacy data in Japanese ND and PD subjects with renal anemia for a 52-week treatment period. Study participants who will receive GSK1278863 may benefit from the expected clinical efficacy. Participants who will receive the control (epoetin beta pegol approved for the treatment of renal anemia in Japan) are also expected to benefit from the clinical efficacy.

GSK1278863 may have important advantages over existing ESAs. GSK1278863, which is orally administered and requires no cold chain management unlike ESAs, is more convenient to patients. GSK1278863 is shown to increase Hgb at lower EPO concentrations than ESAs. Since increased exposure to EPO following administration of ESAs may be associated with an increased cardiovascular risk [Szczech, 2008], GSK1278863 may increase Hgb without increasing the cardiovascular risk.

4.6.3. Overall Benefit: Risk Conclusion

GSK1278863 is shown to have a positive benefit-risk balance based on the following findings: in studies of GSK1278863 administered for up to 24 weeks, treatment with GSK1278863 resulted in achievement of target Hgb, and no adverse events have been identified as related to treatment with GSK1278863.

The present study is intended to evaluate the efficacy and safety of GSK1278863 administered for 52 weeks in Japanese ND and PD subjects with renal anemia, and designed to administer GSK1278863 or epoetin beta pegol as control to all enrolled subjects; therefore, subjects randomized in either treatment group are expected to benefit from the treatment.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (Section 12.2. Appendix 2). Given these precautions, as well as the potential benefit that GSK1278863 holds for the treatment of renal anemia compared with the current standard treatment, the overall benefit risk balance is considered to be positive.

5. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) and/or other pertinent documents.

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

5.1. Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the inclusion criteria.
Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

1. Age (at the time of informed consent): ≥20 years of age
2. (Screening verification only) Stage of chronic kidney disease (CKD) (ND patients only): CKD stages 3, 4, and 5 defined by eGFR using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Dialysis:
   - Not on dialysis for at least 12 weeks prior to screening (ND patients)
   - On peritoneal dialysis (PD patients)
4. Use of erythropoiesis-stimulating agent (ESA):
   - ESA non-users: Have not used ESAs for at least 8 weeks prior to screening
   - ESA users: Have used the same ESA for at least 8 weeks prior to screening. However, in the ND patients, the dose of darbepoetin alfa or epoetin beta pegol must be stable (administered once every 4 weeks and up to one-step dose change during at least 8 weeks prior to screening).
5. Hemoglobin (Hgb): Determined at the site using an Hgb analyzer (HemoCue)
   - ESA non-users: ≥8.0 g/dL and <11.0 g/dL
   - ESA users: ≥9.0 g/dL and ≤13.0 g/dL
6. Iron parameters: Ferritin >100 ng/mL or transferrin saturation (TSAT) >20% (screening verification only)
7. Gender (screening verification only): Female or male

   Females: Not pregnant [demonstrated to be negative for human chorionic gonadotropin (hCG) in urine or serum], not breast-feeding, and meet at least one of the following:

   1) Females of non-childbearing potential are defined as follows:
   - Pre-menopausal with at least one of the following and no plans to utilise assisted reproductive techniques (e.g., in vitro fertilisation or donor embryo transfer):

- History of bilateral tubal ligation or salpingectomy
- History of hysteroscopic tubal occlusion and postoperatively documented bilateral tubal obstruction
- History of hysterectomy
- History of bilateral oophorectomy

- Postmenopausal defined as 1) females 60 years of age or older or 2) In females < 60 years of age, 12 months of spontaneous amenorrhea [in questionable cases a blood sample with postmenopausal follicle stimulating hormone (FSH) and estradiol concentrations is confirmatory (see separately specified reference ranges)]. Females on hormone replacement therapy (HRT) whose menopausal status is in doubt will be required to use one of the most 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.

2) Females of childbearing potential must agree to comply with one of the contraception methods listed as requirements in "GSK Listing of Most Effective Contraceptive Methods for Females of Childbearing Potential (Section 12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential)" from at least 28 days prior to the first dose of study medication until the completion of the follow-up visit (for subjects randomized to the GSK1278863 group) or 7 weeks after the last dose of study treatment (for subjects randomized to the Epoetin beta pegol group).

8. Informed consent: Written informed consent, including adherence to the requirements and conditions specified in the consent form and the protocol, must be obtained from each subject as specified in Section 10.2..

5.2. Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study.
Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

Chronic kidney disease (CKD)-related criteria

1. Dialysis
   - Cohort 1and Cohort 3: Start or plan to initiate dialysis during the study
   - Cohort 2: Plan to stop peritoneal dialysis or start hemodialysis during the study
2. Kidney transplant: Planned living-related kidney transplant during the study

Anemia-related criteria

3. Aplasia: History of bone-marrow hypoplasia or pure red cell aplasia
4. Other causes of anemia: pernicious anemia, thalassemia, sickle cell anemia, or myelodysplastic syndromes
5. Gastrointestinal (GI) bleeding: Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding within 8 weeks prior to screening or during a period from screening to Day 1.

Cardiovascular disease-related criteria

6. Myocardial infarction, acute coronary syndrome, stroke, or transient ischemic attack: Diagnosed within 8 weeks prior to screening or during a period from screening to Day 1.
7. Heart failure: Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system
8. QTc (screening verification only): QTc >500 msec or QTc >530 msec in subjects with bundle branch block

   Note: QT interval corrected using the Bazett's formula (QTcB) will be used, and ECG can be mechanically or manually read.

Other disease-related criteria

9. Liver disease (if any of the following occurs):
   - (Screening verification only): Alanine transaminase (ALT) >2×upper limit of normal (ULN)
   - (Screening verification only): Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
   - Current unstable active liver or biliary disease (generally defined by the onset of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal/gastric varices, persistent jaundice, or cirrhosis)

     Note: Stable liver disease (including asymptomatic gallstones, chronic hepatitis B/C, or Gilbert's syndrome) is acceptable if the subject otherwise meets entry criteria.
10. Malignancy: History of malignancy within 2 years prior to screening, or currently receiving treatment for cancer, (PD patients only) complex renal cystic >3 cm (II F, III or IV based on the Bosniak classification)

    Note (ND patients and PD patients): The only exception is squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥ 8 weeks before screening.
11. In the opinion of the investigator, Hgb increase to the target range (11.0-13.0 g/dL) is medically risky.

Concomitant medication and other study treatment-related criteria

12. Iron: Planned use of intravenous iron during the screening phase or during a period from Day 1 to Week 4

    Note: Oral iron is acceptable. However, the same dose regimen must be used throughout the screening phase and from Day 1 to Week 4. Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) are also acceptable only if used for at least 12 weeks prior to screening. However, they must be continued throughout the screening phase and from Day 1 to Week 4.
13. Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product [see the GSK1278863 IB (ND and PD patients) or epoetin beta pegol Prescribing Information (ND patients)]
14. Drugs and supplements: Use or planned use of any prescription or non-prescription drugs or dietary supplements that are prohibited during the study period (prohibited medications: strong inducers and inhibitor of CYP2C8, see Section 6.11.2.)
15. Prior investigational product exposure: Use of an investigational agent within 30 days or five half lives of the investigational agent (whichever is longer)

16. Prior treatment with GSK1278863: Any prior treatment with GSK1278863 for a treatment duration of >30 days

General health-related criteria

17. Other conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator (or subinvestigator) 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

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial and are screened, but are not subsequently randomized in the study. A minimum set of information is required from screen failure subjects including Demography, Screen Failure details, Eligibility Criteria, and SAEs in order to report screen failures in a reliable manner, satisfy the requirements for publication defined by the Consolidated Standards of Reporting Trials (CONSORT), and respond to requests of the regulatory authorities.

Subjects that fail screening are eligible to be rescreened up to 3 times as soon as the investigator (or subinvestigator) assesses they may meet study entry criteria. Re-screening subjects are allowed to use the results of the latest ophthalmology exam to replace the rescreening ophthalmology exam, at the discretion of the investigator (see Table 14).

5.4. Withdrawal/Dropout Criteria

If subjects meet one of the following criteria, study treatment should be permanently discontinued and subjects will be withdrawn from the study. The withdrawal reason should be recorded.

- Hgb <7.5 g/dL
  Note: HemoCue Hgb values will be employed. If an initial Hgb value meets the Hgb stopping criteria, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be discontinued.
- Subject needs for maintenance dialysis or changes dialysis modality (PD subjects only) during the study period.
- Kidney transplant
- Subject becomes pregnant or intends to become pregnant during the study.
- Diagnosis of new or recurrent cancer
- Liver chemistry abnormalities exceeding the threshold criteria (see Section 5.4.1.)
- Need for chronic (more than 14 days) use of prohibited medication
- When the investigator (or subinvestigator) considers necessary to withdraw the subject from the study for other reasons

Subjects who meet any of the withdrawal criteria or are withdrawn for other reasons during the treatment phase should be assessed at withdrawal visit after study treatment is discontinued, and will then enter the follow-up phase.

Should a subject fail to attend a required study visit, the investigator (or subinvestigator) should take the following measures:

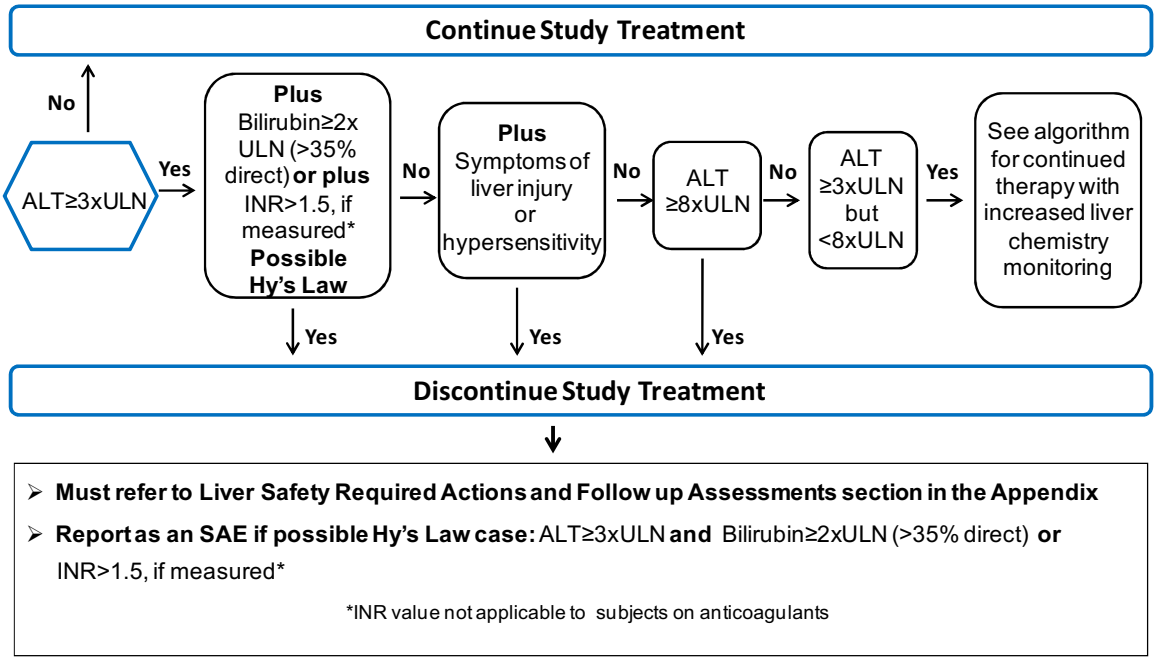
- The investigator (or subinvestigator) or designee should attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The investigator (or subinvestigator) should counsel the subject on the importance of maintaining the assigned visit schedule and determine whether the subject is willing to continue his/her participation in the study and/or whether the subject should remain in the study.
- The investigator (or subinvestigator) or designee should make every effort to regain contact with a subject who is deemed "Lost to Follow-up". All efforts to contact the subject should be documented in the subject's clinical charts.
- Should the subject continue to be unreachable, then and only then will he/she be considered "Lost to Follow-up."

A subject may withdraw from the study at any time at his/her own request. The investigator (or subinvestigator) may withdraw a subject from the study at any time for safety or compliance reasons or study conduct considerations. If a subject withdraws from the study, he/she may request destruction of any clinical samples taken, and the investigator (or subinvestigator) must document this in the site study records.

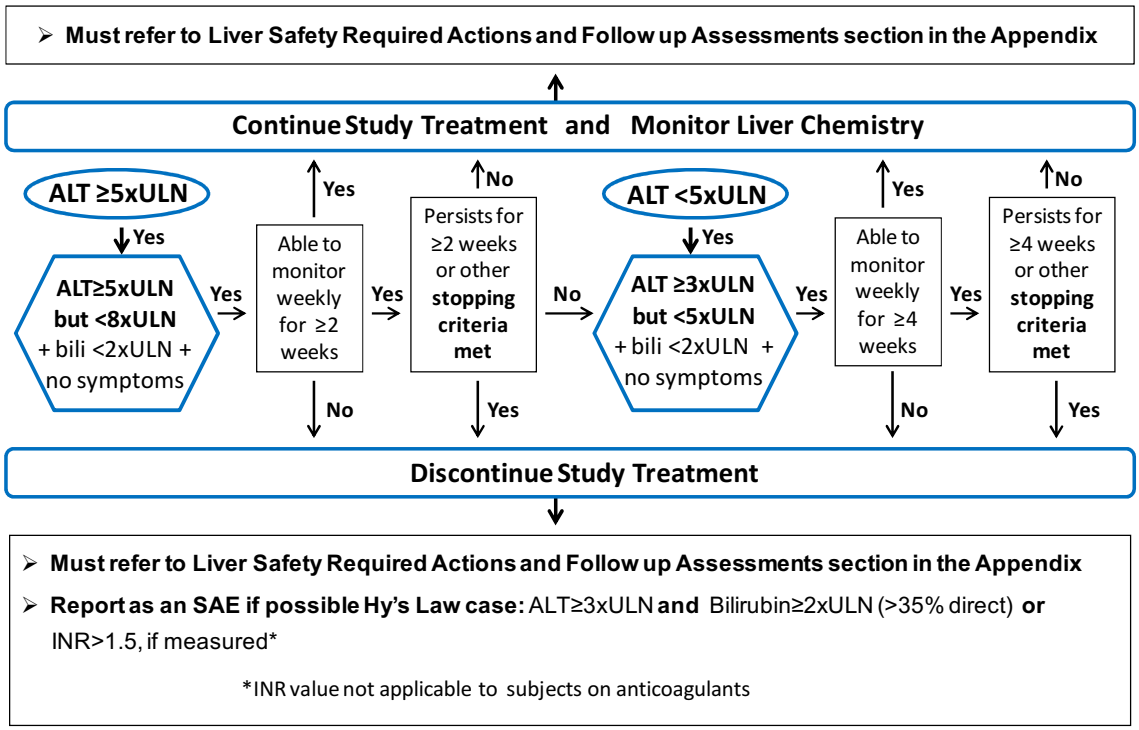
5.4.1. Liver Chemistry Stopping Criteria

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

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.5. Appendix 5

5.4.1.1. Study Treatment Restart or Rechallenge

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

5.5. Subject and Study Completion

A completed subject is one who has completed all periods of the study including the follow-up visit. The study will be completed with the last subject's last study visit.

6. STUDY TREATMENTS

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any products received by the subject as per the protocol design. Accordingly, 'study treatment' sometimes refers to each product and sometimes refers to multiple products.

GSK1278863 (study drug)

The study drug GSK1278863 will be supplied as fast-release film coated tablets for oral administration containing 1 mg, 2 mg, 4 mg, or 6 mg of GSK1278863 (Table 3). There are two sizes of GSK1278863 tablets.

Table 3 Description of GSK1278863 Tablets

GSK1278863 tablets of specific content	Description
1 mg tablets, 2 mg tablets, 4 mg tablets	7.0 mm round, standard biconvex, white film coated tablets containing 1 mg, 2 mg, or 4 mg of GSK1278863 as active ingredient
6 mg tablets	9.0 mm round, standard biconvex, white film coated tablets containing 6 mg of GSK1278863 as active ingredient

GSK1278863 tablets of specific content are packed in high density polyethylene (HDPE) bottles, with 35 tablets per bottle. Subjects are to take one to four tablets (Table 4) with water once daily according to the dose level indicated at each study visit. Subjects can take GSK1278863 tablets without regard to food or peritoneal dialysis. The administration schedule (starting dose and dose adjustment) described in Section 6.4.1. should be followed.

Table 4 Dose Levels of GSK1278863 and Number of Tablets Taken

Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Subjects should be instructed to bring GSK1278863 tablets with bottles at each study visit, and all unused GSK1278863 tablets will be collected from subjects at each study visit.

Epoetin beta pegol (control)

The control epoetin beta pegol (brand name: Mircera® Pre-filled Syringe) will be supplied by GSK. This product is an injectable formulation containing 25 µg, 50 µg, 75 µg, 100 µg, 150 µg, 200 µg, or 250 µg of epoetin beta pegol per syringe (0.3 mL) and is supplied as a glass syringe prefilled with epoetin beta pegol solution (clear colorless to pale yellow).
Subjects are to receive epoetin beta pegol subcutaneously once every 2 or 4 weeks at the site (Table 5). The administration schedule (starting dose and dose adjustment) described in Section 6.4.2. should be followed.

Table 5 Dose Levels of Epoetin Beta Pegol and Number of Subcutaneous Doses

Dose level of epoetin beta pegol (once every 2 or 4 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg
Number of subcutaneous doses of epoetin beta pegol	25 µg injection ×1	50 µg injection ×1	75 µg injection ×1	100 µg injection ×1	150 µg injection ×1	200 µg injection ×1	250 µg injection ×1

6.2. Medical Devices

The Epoetin beta pegol (Brand name :MIRCERA® Injection Syringe) marketed with the device (kit formulation which was filled liquid medication in glass syringe) provided for use in this study. Instructions for medical device are described in the Prescribing Infromation of MIRCERA® Injection Syringe.

The medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 7.4.4.

6.3. Treatment Assignment

The randomization schedule will be generated by GlaxoSmithKline (GSK) using the randomization system (Randall).

In Cohort 1 and Cohort 3 (ND subjects), subjects will be stratified by the current ESA therapy (ESA non-user or ESA user) and the Hgb level on Day 1 and randomized in a 1:1 ratio to one of the two treatment groups according to the randomization schedule. Randomization should precede the study treatment.

- GSK1278863 group
- Epoetin beta pegol group

In Cohort 2 (PD subjects), all eligible subjects will start treatment with GSK1278863 on Day 1.

Subjects will be assigned a randomization number by the Interactive Web Recognition System (IWRS). Once a randomization number has been assigned, it must not be re-assigned. Further details are provided in the Study Reference Manual (SRM).

6.4. Administration Schedule (Starting Dose, Dose Adjustment, and Dosing Frequency)

6.4.1. GSK1278863 (ND and PD Subjects)

6.4.1.1. Starting Dose

For ND subjects randmized to GSK1278863 group

(Cohort 1)

Both ESA non-users and users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.

(Cohort 3)

- ESA non-users
  - Baseline Hgb ≥8.0 g/dL and <9.0 g/dL: the subjects will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*.
  - Baseline Hgb ≥9.0 g/dL and <11.0 g/dL: the subjects will start oral treatment with GSK1278863 at the starting dose of 2 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*.
- ESA users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*.

*: The HemoCue Hgb value will be measured for safety confirmation at Week 2 in ND subjects. When Hgb > 1.0 g/dL increase over 2 weeks, the dose of GSK1278863 is decreased to the next lower dose.

For PD subjects randomized to the GSK1278863 group (Cohort 2)

- ESA non-users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.
- ESA users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.

ESA users should skip ESA on Day 1 when treatment with GSK1278863 is started.

6.4.1.2. Maintenance Dose

From Weeks 4 to 52, interruption of treatment or dose adjustments will be made within the maintenance dose range of 1-24 mg (Table 6) according to the dose adjustment algorithm (Table 7) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (1 mg), treatment should be interrupted; once the one-step dose increase criteria are met, treatment at 1 mg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (24 mg), treatment at 24 mg should be continued.

Table 6 Maintenance Dose of GSK1278863

Dose step	1	2	3	4	5	6	7	8
Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Table 7 Dose Adjustment Algorithm (GSK1278863)

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (If interrupted at 1 mg: resume treatment at 1 mg once the one-step dose increase criteria are met)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0[1)]	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0[1)]	One-step dose reduction
	0.5-2.0	Continue treatment at the current dose level
	<0.5	One-step dose increase
<7.5	NA	Discontinue treatment permanently [2)] and initiate another appropriate treatment

1) Cohort 3 only: At Week 4, if an Hgb increase of >1.0 g/dL over 2 weeks is observed, the dose of GSK1278863 will be reduced by one step; if an Hgb increase of ≤1.0 g/dL over 2 weeks is observed, treatment will be continued as specified in the dose adjustment algorithm other than one-step dose reduction for an Hgb increase of >2.0 g/dL over 4 weeks.
2): If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.4.2. Epoetin Beta Pegol (ND Subjects Only)

For ND subjects (Cohort 1 and Cohort 3) randomized to the epoetin beta pegol group, ESA non-users and users will receive epoetin beta pegol subcutaneously according to the treatment regimens described below.

6.4.2.1. Starting Dose for ESA Non-users

ESA non-users will start subcutaneous treatment with epoetin beta pegol at a dose of 25 μg once every 2 weeks (Day 1). Dose adjustments will be made within the initial dose range of 25-150 μg (Table 8) according to the dose adjustment criteria (Table 9) to increase Hgb to 11.0 g/dL (lower limit of the target) or more based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the dose reduction criteria shown in Table 9 is met during treatment with epoetin beta pegol at 25 μg, treatment should be interrupted; once the dose reduction criteria are not met any longer, treatment will be resumed at a dose of 25 μg.

At Week 2, HemoCue Hgb value will be measured for subjects' safety confirmation. If the measurement shows an Hgb increase of >1.0 g/dL over 2 weeks, the dose of epoetin beta pegol will be reduced by one step (or treatment interrupted) (Cohort 3 only).

Table 8 Initial Dose of Epoetin Beta Pegol (ESA Non-users)

Dose step	1	2	3	4	5
Dose level of epoetin beta pegol (once every 2 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg

Table 9 Initial Dose Adjustment Criteria for Epoetin Beta Pego (ESA Non-users)

Hgb	Treatment
Hgb increase <1.0 g/dL over past 4 weeks, OR Hgb <10.0 g/dL and Hgb increase ≤2.0 g/dL over past 4 weeks	One-step dose increase
Hgb increase >2.0 g/dL over past 4 weeks[1)]	One-step dose reduction
Otherwise	Continue treatment at the current dose level

1) Cohort 3 only: Hgb increase of >1.0 g/dL over past 2 weeks at Week 2.

Once Hgb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm (Table 13). The dosing interval should be changed from once every 2 weeks to once every 4 weeks with dose conversion for dosing interval change (Table 10) after it is confirmed that all of the following criteria are met:

- Hgb in the target range (11.0-13.0 g/dL)
- Hgb change ≤2.0 g/dL over past 4 weeks
- Equivalent dose will be given twice (at least 4 weeks)

Table 10 Dose Conversion of Epoetin Beta Pegol for Dosing Interval Change (ESA Non-users)

Initial dose of epoetin beta pegol (given once every 2 weeks)		Dose conversion of epoetin beta pegol (given once every 4 weeks)
25 µg	→	50 µg
50 µg	→	100 µg
75 µg	→	150 µg
100 µg	→	200 µg
150 µg	→	250 µg

6.4.2.2. Dose Conversion for ESA Users

For ESA users, prior ESA will be replaced with epoetin beta pegol at the equivalent dose once every 4 weeks (Day 1).

At Week 2, HemoCue Hgb value will be measured for subjects' safety confirmation. If the measurement shows an Hgb increase of >1.0 g/dL over 2 weeks, the dose of GSK1278863 will be reduced by one step (or treatment interrupted) at Week 4 (Cohort 3 only).

Table 11 Replacement with Epoetin Beta Pegol-Initial Dose (ESA Users)

Prior ESA		Epoetin beta pegol
Epoetin	<4500 IU per week	100 µg once every 4 weeks
	≥4500 IU per week	150 µg once every 4 weeks
Darbepoetin alfa	30 µg once every 4 weeks *	25 µg once every 4 weeks
	60 µg once every 4 weeks *	50 µg once every 4 weeks
	90 µg once every 4 weeks *	75 µg once every 4 weeks
	120 µg once every 4 weeks *	100 µg once every 4 weeks
	180 µg once every 4 weeks *	150 µg once every 4 weeks
Epoetin beta pegol	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks *	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks

*: Allowance of ±1 week
Maintenance treatment will be started at Week 4 as described in Section 6.4.2.3.

6.4.2.3. Maintenance Dose (ESA Non-users and Users)

Epoetin beta pegol will be administered once every 4 weeks from dosing interval change (once every 4 weeks) with Hgb ≥11.0 g/dL to Week 52 in ESA non-users and from Weeks 4 to 52 in ESA users. Interruption of treatment or dose adjustments will be made within the maintenance dose range of 25-250 µg (Table 12) according to the dose adjustment algorithm (Table 13) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (25 µg), treatment should be interrupted; once the one-step dose reduction criteria are not met any longer, treatment at 25 µg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (250 µg), treatment at 250 µg should be continued.

Table 12 Maintenance Dose of Epoetin Beta Pegol

Dose step	1	2	3	4	5	6	7
Epoetin beta pegol (once every 4 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg

Table 13 Dose Adjustment Algorithm (Epoetin Beta Pegol)

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (resume treatment at 25 μg if interrupted at 25 μg)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0	One-step dose reduction
	1.0-2.0	Continue treatment at the current dose level
	<1.0	One-step dose increase
<7.5	NA	Discontinue treatment permanently * and initiate another appropriate treatment

*: If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.5. Blinding

This is an open-label study.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

- No special preparation of study treatment is required.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study medications must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator (or subinvestigator) and authorized site staff.
- Subjects must bring all of supplied study medication bottles of GSK127886 at each study visit. Study staff will collect all of study medication bottles supplied at the previous study visit and supply new study medication bottles.
- The investigator (or subinvestigator), 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).
- Under normal conditions of handling and administration, study medication is not expected to pose significant safety risks to site staff. GSK will provide a document describing occupational hazards and recommended handling precautions either to the investigator (or subinvestigator) when necessary or upon request of the medical institution.
- Further details are provided in the SRM.

6.8. Compliance with Study Treatment Administration

GSK1278863

Since GSK1278863 is self-administered, compliance with GSK1278863 treatment will be assessed through an interview with subjects at each study visit and recorded in the source document and eCRF. A record of the number of GSK1278863 tablets dispensed to and taken by each subject will be maintained and reconciled with study treatment and compliance records. In addition, the number of GSK1278863 doses dispensed, used, and unused, as well as study treatment start and stop dates will be recorded in the eCRF (the number of doses returned and unreturned will also be recorded separately).

Epoetin beta pegol

Epoetin beta pegol will be subcutaneously administered to subjects at the site. Dosing details will be recorded in the source document and eCRF.

6.9. 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. GSK1278863 is highly protein bound; thus, clearance of GSK1278863 by hemodialysis or peritoneal dialysis is very low and these are not effective methods to enhance the elimination of GSK1278863. GSK1278863 metabolites are, in part, cleared via hemodialysis. 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, subjects should be monitored closely for cardiovascular events, increased heart rate and hematologic abnormalities.

Consult the respective approved Prescribing Information for information on overdose for epoetin beta pegol.

6.10. Treatment after the End of the Study

Since the target disease studied is not life-threatening or severely debilitating and there is the alternative therapy, subjects will not receive any additional treatment from GSK after completion of the study. Regardless of whether the sponsor provides specific treatments at the completion of the study, the investigator (or subinvestigator) is responsible for ensuring that consideration has been given to post-study care of the subject's medical condition.

6.11. Concomitant Medications and Non-Drug Therapies

Concomitant medications, including over-the-counter medications and supplements, taken during the study will be recorded in the eCRF. Drug names and start/stop dates will be recorded for general concomitant medications, while additional details, including dose, route of administration, and dosing frequency, will be recorded for certain medications (e.g., ESAs, iron, anti-hypertensive medications). Further details are provided in the SRM.

6.11.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.11.2., all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Regular multivitamins (at recommended daily allowance) and other supplements such as calcium and vitamin D may be used if permitted by the investigator or his/her designee.
CYP2C8 is involved in the primary route of metabolism of GSK1278863. Accordingly, co-administration of GSK1278863 with moderate CYP2C8 inhibitors (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks using a point-of-care Hgb analyzer.
Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) may be started from Week 4 onwards unless any other antihyperphosphatemic agents are appropriate. Once started, iron-containing antihyperphosphatemic agents must be continued until the end of the study wherever possible.

6.11.2. Prohibited Medications and Non-Drug Therapies

Use of any of the following drugs from screening until 7 days after the last dose of study treatment is prohibited:

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

Use of the following drug from 8 weeks prior to screening until the last dose of study treatment in ESA non-users and during study treatment in ESA user is prohibited.

- Erythropoietin (e.g., epoetin/darbepoetin alfa/ epoetin beta pegol)

Note: excluding epoetin beta pegol (brand name: Mircera® Injection Syringe) supplied by GSK.

6.12. Supplemental Iron Therapy

Supplemental iron therapy will be administered according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] if ferritin is ≤100 ng/mL and TSAT is ≤20%. The investigator (or subinvestigator) can choose the route of administration and dose of prescription iron.

7. Study Assessments and Procedures

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

7.1. Time and Events Table

The time and events tables for the entire study and PK assessment are presented as Table 14 and Table 15, respectively. To allow scheduling flexibility, study visits may occur within a window of ±7 days on Day 1 scheduled 4 weeks after screening, within a window of ±3 days at Week 2 (Cohort 3 only) and Week 4, and within a window of ±5 days for the rest of the study. However, subjects receiving the control epoetin beta pegol every 2 weeks should attend study visits, including those only for study treatment, within a window of ±3 days. Visit days are counted from Day 1.

Table 14 Time and Events Table

Phase	Screening[9]	Treatment															Follow-up
Week	-4	Day 1	2[10]	4	8	12	16	20	24	28	32	36	40	44	48	52	Early withdrawal[11]	4 weeks after 52 or withdrawal
Permissible range (days)	±7	-	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-	±7
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Medical history, demography, height, weight	X																	
Registration with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication dispensing [1,2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Study treatment compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X		X			X			X			X			X	X	X
Ophthalmology [3]	◄►					◄►									◄►		◄►	
ECG	X								X							X		
HemoCue Hgb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	X	X
Clinical chemistry	X	X		X			X			X			X			X	X	X
Urinalysis (ND subjects only)	X	X							X							X		X
Pregnancy test (urine or serum hCG) [4]	X	X		X			X			X			X			X	X	X
Estradiol, FSH [5]	X																	
PK [6]						X			X									
Ferritin, TSAT	X	X		X			X			X			X			X	X	
Serum iron, TIBC, UIBC, serum transferrin, hepcidin		X		X			X			X			X			X	X	
iPTH		X								X						X		
HR-QoL		X				X				X						X	X	
Genetics sample [7]		X																
Adverse event assessment [8]		◄►																
Review Concomitant Medications	◄	►																

1. In Cohort 1 and Cohort 3, ESA non-users randomized to the epoetin beta pegol group will start treatment with epoetin beta pegol at a dose of 25 µg once every 2 weeks. For these subjects, specified examinations will be performed at Week 2 (Cohort 3 only) and every 4 weeks after Week 4, and no study-related assessments will be necessary at study visits only for study treatment [e.g., Week 2 (Cohort 1 only), Week 6, Week 10) (see Section 6.4.2). It should be noted that subjects receiving epoetin beta pegol once every 2 weeks should attend study visits within a window of ±3 days.
2. If a subject visit the study site only to receive study medication, only registration with the IWRS, study medication dispensing, and study medication compliance will be required.
3. Ophthalmology exams should be conducted at the following time points.

- Screening: anytime after consenting and prior to first dose of study medication (Day 1)
- Week 12: window from weeks 10-14 (inclusive)
- End of study: window from weeks 48-52 (inclusive)
- Early study medication discontinuation: withdrawal eye exam as close to the last dose as possible (the repeat exams are not required if one has been performed within the 2 prior weeks).

4. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.
5. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
6. See Table 15.
7. Informed consent for optional Genetic research should be obtained before collecting a sample (see Section 7.6.).
8. See Section 7.4.1.1..
9. Re-screening subjects who meet all the following conditions are allowed to use the results of the latest ophthalmonogy exam and not required to undergo the rescreening ophthalmonogy exam, at the discretion of the investigator.
   - Subjects had no findings that deem re-exams within 3 months at the latest screening ophthalmology exam.
   - Subjects had no new eye-related symptoms or complaints until the rescreening following the latest screening ophthalmology exam.
   - The latest screening ophthalmology exam was performed within 3 months prior to Day 1 scheduled at the rescreening.
10. All ND subjects randomized to Cohort 3 will undergo assessment scheduled for Week 2 visit.
11. For withdrawn subjects, specified assessments should be done wherever possible.

Table 15 Blood Sampling Schedule for Pharmacokinetics (Only Subjects in GSK1278863 Group)

PK sample	Week 12 [2]	Week 24 [2]
Blood sampling timing [1]	1, 2, 3, and 4 h after administration of GSK1278863	

Subjects must take the study medication with regard to blood sampling time. Subjects will record the date and time of the last two study medication doses taken prior to blood sampling in the medication diary. Preferably, there should be an interval of at least 12 h between these two doses.

1. Blood sampling should be completed within +/- 30 min of the planned collected time.
2. Blood sampling not performed at this visit may be postponed until the following visits.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed (documented in the eCRF) at baseline.
In addition, the following demographic information will be collected:

- Year of birth
- Gender
- Race and ethnic
- Medical history/treatment history/family history will be assessed in relation to the inclusion/exclusion criteria (Section 5.).

Full details of baseline assessments are provided in Table 14.

7.3. Efficacy

Efficacy will be assessed according to the Time and Event Table (Table 14).
Hgb concentrations measured by the central laboratory will be mainly used for efficacy assessment (see Section 7.4.7.).
GSK will supply a point-of-care Hgb analyzer (HemoCue) to each site for rapid and convenient measurement of Hgb and to ensure consistency of Hgb measurements across all sites participating in the study. Assessment for Hgb concentrations via HemoCue will be used for eligibility (Section 5.1.), withdrawal (Section 5.4.), and dose adjustment criteria (Section 6.4.).
In addition, assessments of iron metabolism parameters and measures of CKD progression (e.g., eGFR) used for efficacy assessment are outlined with specific procedures in Section 7.4.7..

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Table 14).
Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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

The definitions of an AE or SAE can be found in Section 12.6. Appendix 6.
The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3.), at the timepoints specified in the Time and Events Table (Table 14).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.6. Appendix 6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.6. Appendix 6.

7.4.1.2. Method of Detecting AEs and SAEs

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

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.2.) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.). Further information on follow-up procedures is given in Section 12.6. Appendix 6..

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.6. Appendix 6 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.

7.4.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.2. Adverse Events of Special Interest

The investigator (or subinvestigator) or designee will be responsible for detecting, documenting, and reporting any AEs of special interest listed below. These events have been identified based on the known safety profiles of ESAs, theoretical or potential risks based on the mechanism of action of GSK1278863, and findings from completed nonclinical studies of GSK1278863.

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Death, myocardial infarction, stroke, congestive heart failure, 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

Any relevant AE should be recorded in the relevant section of the subject's eCRF.

7.4.3. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the follow-up contact.

- 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 12.4.. Appendix 4.

Note: Subjects randomized in the epoetin beta pegol group should be advised to inform the investigator if they discover pregnancy in 7 weeks after the last dose of study treatment.

7.4.4. Medical Device Incidents (Including Malfunctions)

The medical devices are being provided for use in this study. The investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 8 (Section 12.8.)

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 7.4.1. and Appendix 6 (Section 12.6.) of the Protocol.

7.4.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a medical device provided for the study, the investigator will promptly notify GSK.

NOTE: The method of documenting Medical Device Incidents is provided in Appendix 8 (Section 12.8.).

7.4.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE, will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.). This applies to all subjects, including those withdrawn prematurely.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form ”Medical Device Incident Report Form” with all changes signed and dated by the investigator.

7.4.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the SAE contact information.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.4.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator, or responsible person will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.4.5. Vital Signs/Height/Weight

Systolic and diastolic blood pressure and pulse rate will be measured in sitting or semi-supine position after at least 5 minutes rest prior to clinical examination at each visit blood pressure and pulse rate. One reading of blood pressure and pulse rate will be taken and recorded in the source document and the CRF. Height and weight will be measured at screening visit only.

7.4.6. Electrocardiogram (ECG)

12-lead ECGs will be recorded in supine position. The heart rate, PR, QRS, and QT (pre-corrected) intervals will be measured. QTcB should be calculated by machine or manually by designated staff at each site. The investigator determines whether the ECG data is assessable or not.
At screening, visit when an ECG is performed, two additional ECGs are required if initial ECG indicates prolonged QTc using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility.
QTc exclusion criteria can be found in Section 5.2. Refer to SRM for further details.

7.4.7. Clinical Laboratory Assessments

All study-required laboratory assessments will be performed by a central laboratory with the exception of HemoCue Hgb. The results of each HemoCue Hgb must be entered into the subject's eCRF. Details are provided in the SRM.
All laboratory assessments, as defined in Table 16, 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 labeled 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 central laboratory. Reference ranges for all parameters will be provided to the site by the central laboratory. Details of blood sampling (including the volume of blood to be collected) as well as procedures for processing, storage, and shipment of samples are provided in the SRM.
PK assessment of GSK1278863 is outlined in Section 7.5.

Table 16 Laboratory Assessments

Laboratory assessment	Parameter		
Hematology	Leukocyte count	RBC indices:	WBC count with Differential
	Platelet count	MCV	Neutrophils
	RBC count	MCH	Lymphocytes
	Reticulocyte count	MCHC	Monocytes
	Hemoglobin	RDW	Eosinophils
	Hematocrit		Basophils
Clinical chemistry	Sodium	AST	Bicarbonate
	Potassium	ALT	Inorganic phosphate
	Chloride	Creatinine	Glucose
	Calcium (total and albumin-corrected)	Total bilirubin	Direct/indirect bilirubin
	Albumin	Urea nitrogen	
	Total cholesterol	HDL cholesterol	LDL cholesterol
Iron parameters	Serum iron	Serum ferritin	Serum transferrin
	TIBC	UIBC	TSAT
	Hepcidin		
Urinalysis (ND subjects only)	Urine albumin	Urine creatinine	Urine albumin/creatinine ratio
Other laboratory tests	FSH [1]	Estradiol [1]	iPTH
	eGFR [2]	hCG (serum or urine) [3]	

1. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
2. Calculated from serum creatinine using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.

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 (or subinvestigator) (e.g., SAE or AE or dose modification), the results must be recorded in the eCRF.
Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study 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 (or subinvestigator), the etiology should be identified and the Sponsor notified.

7.4.8. Ophthalmology

Ophthalmology exams will be performed by a study-designated ophthalmology specialist. Each assessment will include a comprehensive eye exam with at least the following components: measurement of best corrected visual acuity, intraocular pressure, an anterior aqueous chamber exam, and a fundoscopic exam. These exams will be used for assessment of ocular adverse events. Assessment results will be captured on worksheets which will be transferred to the eCRF. Additional details on the process for completing these assessments are provided in the SRM.

7.5. Pharmacokinetics

Blood samples for PK analysis of GSK1278863 will be collected from only subjects in the GSK1278863 group as outlined in Table 15, and the date and time of the last two study medication doses taken prior to blood sampling as well as the date and time of sampling must be recorded in the eCRF.

Blood PK analysis will be performed under the control of GSK Platform Technologies and Science-Drug Metabolism and Pharmacokinetics (PTS-DMPK)/Scinovo and GSK-Japan Bioanalysis, the details of which will be included in the SPM. Concentrations of parent GSK1278863 will be determined in blood samples using the currently approved analytical methodology. Raw data will be archived at the bioanalytical site.

Procedures for processing, storage, and shipment of samples are provided in the SRM.

7.6. Genetics

A blood sample will be collected for genetic analysis from consenting subjects. This sample can be collected on Day 1 once written informed consent has been obtained. Information regarding genetic research is included in Section 12.7. Appendix 7.

7.7. Patient Reported Outcome (PRO)

The patient reported outcome (PRO) [e.g., symptoms, severity, health-related QOL (HR-QoL), health status] will be assessed using several rating scales.

All questionnaires used in this study have been translated into Japanese and validated.

Specific instructions on how the subject is to complete the scales and the process for data entry are provided in the SPM.

7.7.1. SF-36

The SF-36 acute version is a general health status questionnaire designed to elucidate the patient's perception of his/her health on several domains, including physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, and general health over the past seven days. The questionnaire contains 36 Likert type questions that ask the patient to recall how he/she felt during the past seven days.

7.7.2. EuroQol Health Utility Index (EQ-5D-5L)/EQ Visual Analogue Scale (EQ-VAS)

The EQ-5D-5L is intended to measure the general health status and health utility. The EQ-5D-5L consists of 2 concepts: self-reported health status consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses and self-rated health status on a visual analog scale (VAS), a thermometer-like line.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- 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

A detailed description of any planned analyses will be documented in a RAP..Any deviations from the analyses described in the protocol will be documented in the RAP or the final study report.

9.1. Hypotheses

The primary objective of the study is to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol based on mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52) in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users).

As a preliminary assessment, it will be confirmed whether the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-13.0 g/dL) at first. And then the following non-inferiority statistical hypotheses are to be tested at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%):

- H_0: Treatment difference in mean Hgb during the primary efficacy evaluation period is -1.0 g/dL or less.
- H_1: Treatment difference in mean Hgb during the primary efficacy evaluation period is greater than -1.0 g/dL.

Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority according to the step-down procedure. More specifically, the superiority of GSK1278863 to epoetin beta pegol in terms of target Hgb control in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users), is to be demonstrated at a two-sided significance level of 5% by testing the following statistical hypotheses:

- H_0: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is equal between the treatment groups.
- H_1: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is different between the treatment groups.

No hypothesis will be tested in PD subjects (Cohort 2).

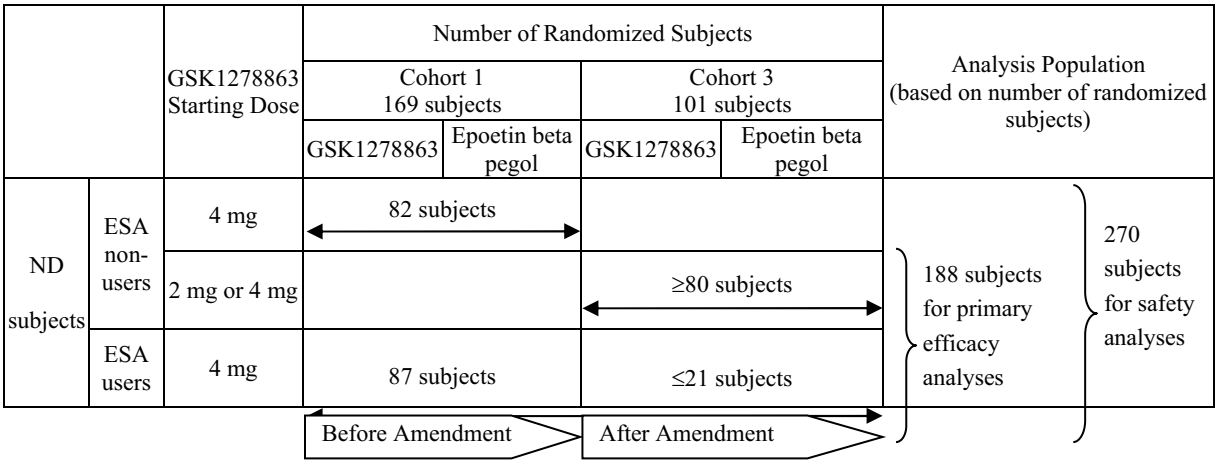
9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%) with a sample size of 100 subjects per group. Assuming a dropout rate of approximately 25%, 135 subjects will be randomized to each group. Given the results from previous non-inferiority studies of similar drugs (darbepoetin alfa, epoetin beta pegol, and peginesatide), the non-inferiority margin of -1.0 g/dL is set. Since an increase of 1.0 g/dL indicates improvement in anemia according to the guidelines for renal anemia in Japan, the non-inferiority margin of -1.0 g/dL may be the clinically acceptable largest difference in renal anemia.

While the present study is designed to ensure long-term safety data from 100 ND subjects, and the primary hypothesis test has at least 99% power to estimate the efficacy very precisely, non-inferiority can be statistically demonstrated with a minimum between-group difference of -0.582 g/dL.

During this study, the protocol has been amended (Amendment No.3) according to the change in starting dose for ND, ESA non-users, however, this amendment will need no change for the overall target sample size. Analysis populations for non-inferiority assessment and safety evaluation on ND subjects are amended as illustrated below.



Note: In Cohort 1, 169 ND subjects who met eligibility criteria were stratified by the current ESA therapy and baseline Hgb (ESA non-users: ≥9.5 g/dL, <9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group. The same randomization strategy is used in Cohort 3.

Figure 2 Primary Efficacy and Safety Analyses Populations for ND Subjects

When non-inferiority is tested, as shown in Figure 2, in 188 ND subjects, this number of subjects ensures an enough power. This is because a power of at least 97% will be achieved in a population consisting of 140 subjects, who will complete study on the condition of a dropout rate of approximately 25%, by the same assumptions and non-inferiority margin stated as above. In order to

allow a subgroup analysis of the primary endpoint by the use of ESA in subgroups the sizes of which are equal as much as possible, at least 80 ND, ESA non-users are to be enrolled in Cohort 3.

For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half width of the 95% CI for mean Hgb during the primary efficacy evaluation period is 0.493 g/dL.

9.2.2. Sample Size Sensitivity

The power for the primary endpoint is shown according to treatment difference and standard deviation in Table 17 based on a population consisting of 140 subjects (70 subjects per group) who will complete study on the condition of a dropout rate of approximately 25%. This population is derived from 188 ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users)

Table 17 Power Sensitivity (70 Subjects Evaluated Per Group, Noninferiority Margin of -1.0, One-Sided Significance Level of 2.5%)

Treatment Difference	Standard Deviation		
	1.25	1.5	1.75
0	99.7%	**97.5%**	91.2%
-0.1	98.8%	94.1%	85.6%
-0.2	96.4%	88.0%	76.6%
-0.3	90.8%	78.3%	65.2%

9.2.3. 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

- All Screening Population

The All Screening Population consists of all subjects who are given subject number and whose data are collected, including demographics at screening.

- Intent-to-Treat (ITT) Population

The Intention-To-Treat Population consists of Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users) who are given randomization number with Hgb measurement at both baseline and at least one scheduled visits following the baseline. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of non-inferiority.

- modified ITT (mITT) Population

The mITT Population consists of all ITT subjects who have at least one Hgb measurement during the efficacy evaluation period. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of superiority.

- Per-Protocol (PP) Population

The PP Population consists of all mITT subjects who are not major protocol violators. Details will be defined in the RAP. This population will be used for efficacy sensitivity analyses.

- Safety Population

The Safety Population consists of all subjects who receive at least one dose of study treatment. Subjects will be analyzed according to the treatment received. This population will be used for safety analyses.

- PK Population

The PK Population consists of all GSK1278863-treated subjects from whom PK samples are collected and analyzed.

Additional populations may be defined in the RAP.

9.3.2. Interim Analysis

No interim analysis is planned.

9.3.3. Adjustment for Multiplicity

Adjustment for multiplicity will be applied to maintain an overall type I error rate of 5%. After a preliminary assessment, the primary endpoint will be evaluated to demonstrate the non-inferiority at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%). Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority. Since the process will follow step-down manner, a multiplicity adjustment for a two-sided significance level of 5% will not be needed according to a closed test procedure.
Other secondary endpoints, which will be evaluated on a complementary or exploratory basis, will be compared at a two-sided significance level of 5% without multiplicity adjustment.
Since Cohort 2 is a single-arm cohort, no testing will be performed to evaluate the efficacy in PD subjects.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Efficacy Analysis

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects. MMRM will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. This model includes treatment groups, baseline Hgb, assessment visits, interaction terms between treatment groups and assessment visits, as well as interaction terms between baseline Hgb and assessment visit. As a preliminary assessment, it will be confirmed if the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-13.0 g/dL) at first. This confirmation will be established if the lower and upper limit of 95% CI for the mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL). In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in the mean

Hgb during the primary efficacy evaluation period will be estimated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e. lies fully within the range -1.0 to <0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimated in the GSK1278863 group is within the target range.
The primary efficacy population will be the ITT Population, and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted. If ND, ESA users in cohort 3 whose dose level was decreased by one step at Week 2 exist, sensitivity analysis excluding the subjects from primary analysis will be conducted. In addition, sensitivity analysis to primary efficacy analysis for all ND patients in Cohort 1 and Cohort 3 will be conducted. Further details of sensitivity analyses will be provided in the RAP.

9.4.2. Principal Secondary Efficacy Analysis

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.
In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for odds ratio is greater than 1.0.

9.4.3. Other Secondary Efficacy Analyses

Among the secondary efficacy endpoints, the time (%) in Hgb target range during the primary efficacy evaluation period , proportion of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks, and changes in iron metabolism parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC), the point estimates and 95% CIs for the treatment difference (or odds ratio) in ND subjects will be calculated. Other secondary efficacy and exploratory endpoints will be summarized by each treatment group.
For PD subjects, the efficacy endpoints will be descriptively summarized.

9.4.4. Safety Analyses

In principle, safety data will be summarized by each treatment group in the Safety Population. ND subjects and PD subjects will be summarized separately.

9.4.4.1. Exposure

Exposure information will be listed for all subjects. The duration of treatment (number of days) and cumulative dose will be tabulated. In addition, distribution of the dose level at each assessment visit and final dosing visit will be tabulated. Frequency of dose adjustment and duration of treatment interruption due to Hgb >13 g/dL will be summarized.

9.4.4.2. Adverse Events

All AEs will be categorized by the MedDRA system organ class and preferred term to tabulate the number and incidence. All AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs of special interest will be summarized separately. Similar summary will be provided for study treatment-related AEs.

9.4.4.3. Other Safety Parameters

For laboratory tests, vital signs and ECG, parameters and/or changes from baseline will be summarized using summary statistics at each assessment visit. The number and percentage of subjects with values of the potential clinical importance values will be tabulated. The criteria for the potential clinical importance will be described in the RAP. For lipid parameters (total cholesterol, LDL cholesterol, and HDL cholesterol), percent changes will also be tabulated. The number (%) of subjects who have any change in anti-hypertensive medications (type and/or dose) due to increased blood pressure will be tabulated.

9.4.5. Pharmacokinetics Analyses

For plasma concentrations of GSK1278863 over time, individual data will be listed, and summary statistics at each time point will be calculated for each dose level. For PK parameters (AUC_{0-4} and Cmax), summary statistics will be calculated for each dose level, and scatter plots against the dose level will be generated.

9.4.6. PRO Data Analysis

Details of PRO data tabulation will be described in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and the Pharmaceutical Affairs Law.

GSK will submit the CTN to the regulatory authorities in accordance with with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- 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.

Informed Consent

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential subject and the subject's legally acceptable representative (as required) of the study including the written information. The investigator (or subinvestigator) should provide the subject and the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and the subject's legally acceptable representative should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home,

he/she may take the consent form home. The person who conducted the informed consent discussion and study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject and the subject's legally acceptable representative.

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

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

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

10.6. Records Retention

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

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

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

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

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

10.8. Study Period

See Exhibit 1

10.9. Study Administrative Structure

Sponsor information is included in Exhibit 2. List of Medical Institutions and Investigators is included in Exhibit 3.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Curve
CKD	Chronic Kidney Disease
Cmax	Maximum concentration
CPK	Creatine Phosphokinase
CYP	Cytochrome P450
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
EQ-5D-5L	EuroQol Health Utility Index
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotrophin
HD	Hemodialysis
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
Hgb	Hemoglobin
HIF	Hypoxia-Inducible Factor
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonization
INR	International Normalized Ratio
iPTH	Intact Parathyroid Hormone
ITT	Intent-to-Treat
IWRS	Interactive Web Recognition System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MCS	Mental Component Summary
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
ND	Non dialysis
NYHA	New York Heart Association
PCS	Physical Component Summary
PD	Peritoneal Dialysis
PHI	Prolyl Hydroxylase Inhibitor
PK	Pharmacokinetic
PP	Per-Protocol
PRO	Patient Reported Outcome
QT	Q-T Interval
QTc	Q-T Interval Corrected for Heart Rate

QTcB	Bazett's Correction of QT Interval
RAP	Reporting and Analysis Plan
RDW	Red Blood Cell Distribution Width
RNA	Ribonucleic Acid
rhEPO	Recombinant human erythropoietin
SAE	Serious Adverse Event
SRM	Study Reference Manual
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
UIBC	Unsaturated iron Binding Capacity
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Hemocue
Mircera®

12.2. Appendix 2: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK1278863		
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 5.1. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is provided in Section 6.4.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
Risk of death, MI, stroke, 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 5.2. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Suspected GI bleeding or significant symptoms consistent with erosion should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 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.	period.
Cancer-related mortality, 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 60 mg/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 been identified as a safety concern for GSK1278863.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 5.2.. ♣ Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.4. ♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	noted among non-treated rats. ・Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term therapy with GSK1278863 5 mg or 10 mg 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. Changes in sPAP from baseline in dialysis patients were comparable between GSK1278863 group and Control group (median). The numbers of patients who met the potentially clinically significant sPAP criteria (increased from baseline by >20 mmHg) were disproportionate between the treatment groups [8 patients (7%) in GSK1278863 group and 0 patient in Control group]. This imbalance was associaited with some confounding factors, including the randomization scheme of 4.5:1 ratio and inconsistency in timings of ECHO assessment related to dialysis. Additionally, 2 of the 3 patients with sPAP improvement at the follow-up ECHO assessment had confounding factors that were potentially attributable for sPAP improvement other than study medication discontinuation. No dose relationship was seen in patients who met potentially clinically significant sPAP criteria. Overall, no sufficient evidence was obtained to conclude the relationship with GSK1278863. ・Following review of clinical data received to date, this has not 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	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	
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 (Campochiaro, 2006). Administration of 60 mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO 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 25 mg, 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.	• Ophthalmology exams will be performed during screening, at approximately Week 12 on-study, and at the end of treatment. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period. • Ophthalmology exams should be specified in Section 7.4.8. and monitored. • When proliferative retinopathy, macular edema or choroidal neovascularization is suggested, or symptoms that are consistent with these AEs are reported, patients should consult ophthalmologist as clinically necessary.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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.	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Co-administration of GSK1278863 with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.11.2. • Co-administration of GSK1278863 with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 6.11.1. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.11. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	provided in Section 6.4.1. • These risks will be monitored instreamly by the internal safety review team throughout the study period.
Other		
ESA risks (Control)	・See risks outlined in table for GSK1278863 for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia; Risk of MI, stroke, venous thromboembolism, thrombosis of vascular access; and risk of cancer-related mortality and tumor progression. ・Non-controllable hypertension ・Pure red cell aplasia ・Hepatic function disorder with increase of AST, ALT and Gamma-glutamyltransferase, and jaundice have been reported as adverse drug reactions for other ESA according to the prescribing information of Epoetin beta pegol.	• The same mitigation strategies have been indentified in acoordance with the mitigation strategies for GSK1278863 • Blood pressure will be monitored throughout the dosing period as outlined in the Time and Events Table provided in Section 7.1.. • A criterion to exclude subjects with history of pure red cell aplasia is added to Section 5.2.. • Liver function will be monitored throughout the dosing period as outlined in the Time and Events Table provided in Section 7.1.

References

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Formenti et al., Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2alpha gain-of-function mutation. FASEB J. 2011, 25(6): 2001-2011.

Muz et al., The role of hypoxia and HIF-dependent signaling events in rheumatoid arthritis, Arthritis Research & Therapy 2009. 11:201-210.

Smith et al., Mutation of von Hippel–Lindau Tumour Suppressor and Human Cardiopulmonary Physiology PLOS 2006. 3:1176-1186.

Westra et al., Hypoxia-Inducible Factor-1 as Regulator of Angiogenesis in Rheumatoid Arthritis - Therapeutic Implications. Current Medicinal Chemistry 2010. 17:254-263.

12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential

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.

1. Contraceptive subdermal implant that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information
2. Intrauterine device or intrauterine system that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information [Hatcher, 2011]
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011].

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

References

Trussell J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, and Policar M (editors). Contraceptive Technology: Twentieth Revised Edition. New York: Ardent Media, 2011.

12.4. Appendix 4: 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 12.6. Appendix 6. 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 or be withdrawn from the study

12.5. Appendix 5: Liver Safety Required Actions and Follow up Assessments

Phase III-IV 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).

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) and quantitative hepatitis B DNA • Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>**

hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, (for ND patients only) if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase,

<2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

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

12.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.6.1. 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 meeting 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.

12.6.2. 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 and 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; (for ND patients only) if

unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. 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.

12.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

12.6.4. Recording of AEs and SAEs

AEs and SAE Recording:

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

12.6.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.6.6. 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 SAE contact.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will confirm that causal relationship of SAE has been considered, by ticking the 'reviewed' box at the bottom of eCRF page within 72 hours following the submission of SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE contact by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.7. Appendix 7 - Genetic Research

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 objective of the genetic research is to understand the response to GSK1278863. To achieve this objective, the relationship between genetic variants and the followings may be investigated.

- Response to medicine, including GSK1278863, ESA, other study medicines or any concomitant medicines;
- Nephrogenic anemia and related conditions susceptibility, severity, and progression

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 which will be conducted for this study 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 related to GSK1278863 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 the 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, align with the purpose of the genetic research, 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

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

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

12.8. Appendix 8: Definition of and Procedures for Documenting Medical Device Incidents

12.8.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all medical devices provided for use in the study (see Section 6.2. for the list of the medical devices).

Medical Device Incident Definition:
• Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an incident associated with a device happened and
- the incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents
• a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse • a patient's treatment is interrupted or compromised by a medical device failure • misdiagnosis due to medical device failure leads to inappropriate treatment • a patient's health deteriorates due to medical device failure

12.8.1.1. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 12.6. (Appendix 6). • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK.

- It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

TITLE PAGE

Division : Worldwide Development

Information Type : Clinical Protocol

Title : A 52-week, Phase III, open-label, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese non-dialysis and peritoneal dialysis subjects with anemia associated with chronic kidney disease.

Compound Number : GSK1278863

Development Phase III

Effective Date : 12-APR-2016

Protocol Amendment Number: 01

Author(s) :

PPD

Sponsor Signatory:

Hiromu Nakajima Head, Medicines Development, Japan Development and Medical Affairs (JDMA), GlaxoSmithKline K. K.	**Date**

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number	Fax Number	Site Address
Medical Monitor	PPD M.D., Ph.D.			GlaxoSmithKline K.K. 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN
SAE contact information	Person in charge of GSK1278863 Clinical Operations dept.	PPD		GlaxoSmithKline K.K. 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN

Emergency Contact

Emergency Contact (Mon to Fri 10am to 6pm, except for national holiday and year-end and New Year holidays)
Person in charge of GSK1278863, Clinical Operations dept. R&D, Glaxo Smith Kline K.K
TEL: PPD
FAX: PPD

Emergency Contact at night and holiday (Mon to Fri 6pm to 10am, Sat, Sun, national holiday and year-end and New Year holidays)
Bell Medical Solutions Inc.
Responsible Person: PPD
TEL: PPD (toll free)
FAX: PPD (toll free)

Sponsor Legal Registered Address:

6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- 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 Signature	Date

TABLE OF CONTENTS

1. PROTOCOL SYNOPSIS FOR STUDY PHI201753

Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

Objective(s)/Endpoint(s)

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	• Number (%) of subjects with mean Hgb in the target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change from baseline in Hgb at Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category at Week 4
• To evaluate dose adjustment scheme of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustment scheme of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control of GSK1278863 in PD subjects	• Hgb and change from baseline at each assessment visit • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment visit • Time (%) in Hgb target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52) • Time (in days) to reach the lower Hgb target

Objective	Endpoint
	(11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks • Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes
• To evaluate the effect on iron use of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate effect on iron use of GSK1278863 in PD subjects	• Dose of oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To evaluate the effect on iron metabolism of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on iron metabolism of GSK1278863 in PD subjects	• Change from baseline in ferritin • Change from baseline in transferrin saturation (TSAT) • Changes from baseline in hepcidin, serum iron, and total iron binding capacity (TIBC)
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To evaluate the effect on progression of Chronic Kidney Disease (CKD) of GSK1278863 in ND subjects using epoetin beta pegol as control	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To evaluate the effect on health-related QoL (HR-QoL) of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on HR-QoL of GSK1278863 in PD subjects	SF-36 • Changes from baseline in SF-36 HR-QoL scores [Physical Component Summary (PCS), Mental Component Summary (MCS), and 8 subscales] EuroQol Health Utility Index (EQ-5D-5L) • Change from baseline in EQ-5D-5L score • Change from baseline in EQ-5D-5L Visual Analog Scale (VAS)
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest

Objective	Endpoint
	• Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

Study Design

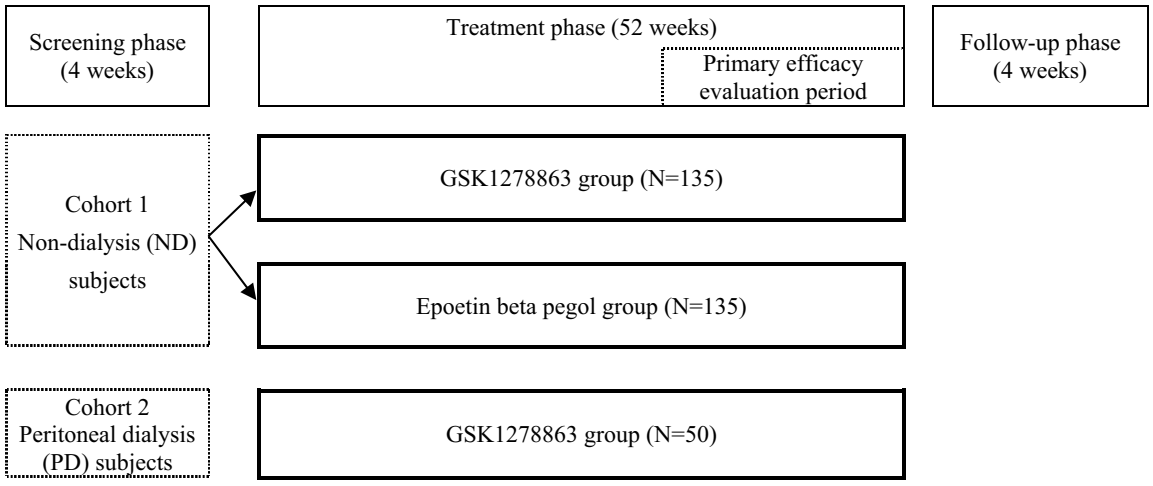
This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (demonstration of non-inferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 270 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. The study consists of the following 2 cohorts of different patient populations:

	Patient population	Presence or absence of ESA therapy (Hgb in subjects)	Treatment group	Target number of subjects (randomized/enrolled)
Cohort 1	ND patient	ESA non-user (Hgb 8.0-<11.0 g/dL) ESA user (Hgb 9.0-13.0 g/dL)	GSK1278863 group	135 subjects*
			Epoetin beta pegol group	135 subjects*
Cohort 2	PD patient	ESA non-user (Hgb 8.0-<11.0 g/dL) ESA user (Hgb 9.0-13.0 g/dL)	GSK1278863 group	50 subjects

*: At least 50 ESA users and at least 50 ESA non-users will be randomized to Cohort 1.
ESA: erythropoiesis-stimulating agent

In Cohort 1, 270 eligible ND subjects will be stratified by the current ESA therapy and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group (135 subjects per group).
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown below.



Method of Administration of Study Medication in Each Treatment Group

In each treatment group, study medication will be administered as follows:

- GSK1278863 group (ND and PD subjects): Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1. From Week 4 onwards, dose adjustments will be made within the dose range of 1-24 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13 0 g/dL).
- Epoetin beta pegol group (ND subjects):
  - ESA non-users: Subcutaneous treatment with epoetin beta pegol will be started at a dose of 25 μg once every 2 weeks on Day 1. Subsequently, dose adjustments will be made within the dose range of 25-150 μg every 4 weeks according to the prespecified initial dose adjustment criteria to achieve the lower limit of the Hgb target (11.0 g/dL). Once Hgb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm. After it is confirmed that all of the criteria for dosing interval change are met, dosing frequency will be changed to once every 4 weeks, and dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target Hgb range (11.0-13.0 g/dL).
  - ESA users: Prior ESA therapy will be replaced with subcutaneous treatment with epoetin beta pegol at the equivalent dose once every 4 weeks according to prespecified dose conversion. Subsequently, dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL).

Analysis

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during in the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a two-sided significance level of 5% with a sample size of 100 subjects per group. Assuming a dropout rate of approximately 25%, 135 subjects will be randomized to each group. For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half the width of the 95% CI for mean Hgb during in the primary efficacy evaluation period is 0.493 g/dL.

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects. A mixed model for repeated measurements (MMRM) will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. As a preliminary assessment, it will be confirmed if the lower and upper limit of 95% CI for mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL) In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in mean Hgb during the primary efficacy evaluation period will be estimated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e.

lies fully within the range -0.75 to <0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimate in the GSK1278863 group is within the target range.
The primary efficacy population will be the ITT Population, and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted. Further details of sensitivity analyses will be provided in the Reporting and Analysis Plan (RAP).

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.
In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and the current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for the odds ratio is greater than 1.0.

2. INTRODUCTION

GSK1278863 is a hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitor (PHI) that stimulates erythropoiesis in the same manner as innate response to hypoxia and is currently being developed as a new treatment for renal anemia.

2.1. Study Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

2.2. Background

Renal anemia is diagnosed in many patients with CKD, and the prevalence of renal anemia increases with progression of CKD [Akizawa, 2011]. Causes of anemia in CKD patients include absolute or relative deficiency of erythropoietin (EPO), shortened erythrocyte survival, and reduced iron availability. Anemia is further exacerbated by chronic blood loss associated with hemodialysis procedure, infection, and functional hemolysis [Japanese Society for Dialysis Therapy, 2008].

GSK1278863 is a hypoxia-inducible factor-prolyl hydroxylase inhibitor that is currently being developed as a treatment for renal anemia. Data in Japanese patients have been collected from a Japanese Phase II 4-week treatment study in Japanese hemodialysis (HD) subjects (PHI116099: 97 Japanese subjects), an international multi-center Phase II 24-week treatment study in HD subjects (PHI113633: including 24 Japanese subjects), and an international multi-center Phase II 24-week treatment study in ND subjects (PHI113747: including 42 Japanese subjects). In these clinical studies, GSK1278863 increased endogenous EPO, reduced hepcidin, and increased Hgb in HD and ND subjects including Japanese subjects. In addition, GSK1278863 increased Hgb at lower blood EPO concentrations than existing erythropoiesis-stimulating agents (ESAs).

Data from completed clinical and clinical pharmacology studies and the preclinical data safety package are provided in the Development Core Safety Information found in the current GSK1278863 Investigator Brochure (IB). A benefit: risk assessment, including risk mitigation strategies, is outlined in Section 4.6.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of	• Number (%) of subjects with mean Hgb in the

Objective	Endpoint
GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change in Hgb from baseline to Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category to Week 4
• To evaluate dose adjustments of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustments of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control by GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control by GSK1278863 in PD subjects	• Hgb at each assessment time point and change in Hgb from baseline to each assessment time point • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment time point • Proportion (%) of time with Hgb within the target range (11.0-13.0 g/dL) in the primary efficacy evaluation period (Weeks 40 to 52) • Time (number of days) to the lower Hgb target (11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks before Week 52 • Number (%) of subjects who achieve an Hgb level of more than 13.0 g/dL and number of episodes
• To compare the effect of GSK1278863 versus epoetin beta pegol on iron use in ND subjects • To evaluate the effect of GSK1278863 on iron use in PD subjects	• Dose of oral iron in the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To compare the effect of GSK1278863	• Change in ferritin from baseline

Objective	Endpoint
versus epoetin beta pegol on iron metabolism in ND subjects • To evaluate the effect of GSK1278863 on iron metabolism in PD subjects	• Change in transferrin saturation (TSAT) from baseline • Changes in hepcidin, serum iron, and total iron binding capacity (TIBC) from baseline
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To compare the effect of GSK1278863 versus epoetin beta pegol on progression of CKD in ND subjects	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To compare the effect of GSK1278863 versus epoetin beta pegol on health-related QoL (HR-QoL) in ND subjects • To evaluate the effect of GSK1278863 on H-RQoL in PD subjects	SF-36 • Changes in SF-36 HR-QoL scores (PCS, MCS, and 8 subscales) from baseline EuroQol Health Utility Index (EQ-5D-5L) • Change in EQ-5D-5L score from baseline • Change in EQ-5D-5L Visual Analog Scale (VAS) from baseline
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest • Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

4. STUDY DESIGN

4.1. Overall Design

This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (verification of noninferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 270 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. The study consists of the following 2 cohorts of different patient populations. At least 50 ESA users and at least 50 ESA non-users will be randomized to evaluate by current ESA therapy(ESA user or ESA non-user).

- Cohort 1: ND subjects (GSK1278863 and epoetin beta pegol groups)
- Cohort 2: PD subjects (GSK1278863 group)

For both patient populations, the Hgb criteria are specified according to the presence or absence of prior ESA: ESA non-users with an Hgb level of ≥8.0 to <11.0 g/dL and ESA users with an Hgb level of 9.0 to 13.0 g/dL will be included in the study.
In Cohort 1, 270 eligible ND subjects will be stratified by the current ESA therapy (ESA non-user or ESA user) and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group (135 subjects per group).
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown in Figure 1.

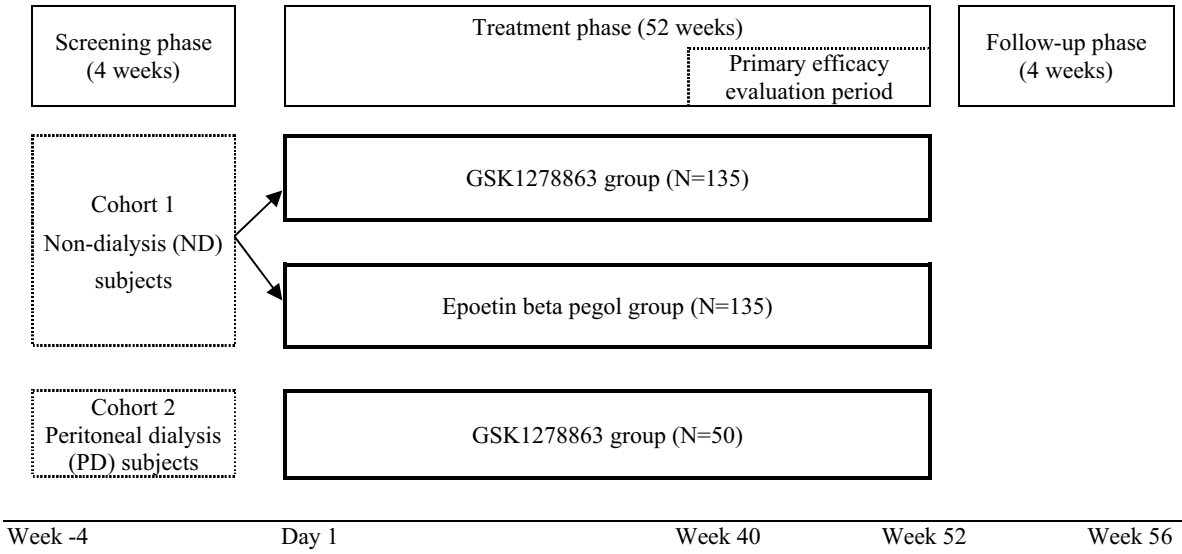


Figure 1 Study Design

4.2. Treatment Groups and Study Periods

Details for each study period and treatments are described below. In this study, a point-of-care Hgb analyzer (HemoCue®) will consistently be utilized for confirmation of subjects' eligibility, withdrawal criteria and dose adjustments of study medication.

Screening phase

Subjects who have provided informed consent and meet all of the eligibility criteria at screening (Week -4) (Sections 5.1 and 5.2) will be provisionally enrolled in the study. Subjects who have used ESA and/or oral iron since before the start of the study must remain on the same regimen throughout the screening phase (intravenous iron will not be allowed).

Treatment phase

Subjects who meet all of the eligibility criteria at the start of the treatment phase (Day 1) will be enrolled in the study. Study medication (either GSK1278863 or epoetin beta pegol group) will be administered for 52 weeks according to randomization in Cohort 1 and GSK1278863 will be administered in Cohort 2 for 52 weeks. For ESA users, prior ESA will be replaced with study medication on Day 1. GSK1278863 will be orally administered once daily, and epoetin beta pegol will be subcutaneously administered once every 2 or 4 weeks. In both groups, dose adjustments for study medication during the treatment phase will be made according to the administration schedule specified in Section 6.4. to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL). In addition, supplemental iron therapy will be administered according to the standard initiation criteria as described in Section 6.12.. It should be noted that intravenous iron or dose change for oral iron will not be allowed from Day 1 to Week 4.

Follow-up phase

Subjects will visit the site for follow-up assessments and observations 4 weeks after the completion/discontinuation of study treatment. During the follow-up phase, treatment of renal anemia will be allowed as necessary at the discretion of the investigator (or subinvestigator).

4.3. Study Subjects and Number of Subjects

In Cohort 1 involving ND subjects, a total of 270 subjects will be randomized (135 subjects in GSK1278863 group, 135 subjects in epoetin beta pegol group). The minimum target number of subjects is 50 ESA non-users and 50 ESA users to allow for evaluations by the current ESA therapy (ESA non-user or ESA user). Assuming a dropout rate of 35% during the screening phase, approximately 416 subjects need to be screened. Assuming a dropout rate of 25% after the start of study treatment, a total of 202 subjects are expected to complete the 52-week treatment.
In Cohort 2 involving PD subjects, 50 subjects will be enrolled (GSK1278863 group only). Since the number of PD patients is very limited in Japan, the target number of subjects is not set for either ESA non-users or users. Assuming a dropout rate of 35% during the screening phase, approximately 77 subjects need to be screened. Assuming a dropout rate of 25% after the start of study treatment, 38 subjects are expected to complete the 52-week treatment.

Table 1 Target Number of Subjects

	Cohort 1 (ND subjects)	Cohort 2 (PD subjects)
Screened	416	77
Randomized/enrolled	270 *	50
Completed 52-week treatment	202	38

*: At least 50 ESA non-users and at least 50 ESA users will be randomized.

4.4. Rationale for Study Design

Objectives and evaluations

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese ND and PD subjects with renal anemia. For Cohort 1, the study is designed as an active-controlled, parallel-group comparative study to meet the primary objective, that is, to demonstrate non-inferiority of GSK1278863 to the existing drug in ND subjects. For Cohort 2, the study is designed as an

uncontrolled study because there are not many PD patients. The target Hgb range was set for study treatment in line with the Guidelines for Renal Anemia in Chronic Kidney Disease issued by the Japanese Society for Dialysis Therapy in 2008 [The Japanese Society for Dialysis Therapy, 2008] to demonstrate that treatment with GSK1278863 can result in achievement and/or maintenance of target Hgb in ND and PD subjects, and evaluate the appropriateness of the starting dose of GSK1278863.

Control

For the ND patient population (Cohort 1), epoetin beta pegol, which has been widely used in Japanese patients with renal anemia, primarily ND patients, since its approval in Japan in 2011, was selected as control.

Open-label

If the study is conducted as a double-blind study, it is necessary to not only administer GSK1278863 orally (once daily) or epoetin beta pegol subcutaneously (once every 2 or 4 weeks), but also administer the matching placebo subcutaneously or orally. It will be more stressful for subjects and complicate treatment procedures to use both active drug and matching placebo for two drugs with different routes and intervals of administration for the purpose of maintaining the blind, and make dose adjustments for individual subjects according to the change in Hgb over time. Accordingly, this study is designed as an open-label study rather than a double-blind study, which seems infeasible. Since Hgb used for efficacy evaluation is an objective measure, and dose adjustments for study medication will be made according to the prespecified Hgb-based dose adjustment method in both GSK1278863 and epoetin beta pegol groups, it is unlikely that the open-label design will create any bias in the primary evaluation.

4.5. Rationale for Dose Levels

Starting dose and dose adjustments of GSK1278863

The starting dose (4 mg) and the dose adjustment method (maintenance dose range: 1-24 mg) for GSK1278863 are described in Section 6.4..

The starting dose and the dose adjustment algorithm selected for Japanese ND subjects in the present study are based on the results from a review of the longitudinal model constructed using Hgb data from six Japanese or overseas Phase II studies (PHI112844, PHI116581, PHI116582, PHI113633, PHI113747, and PHI116099) as well as the results from clinical studies. The data set used in the model analyses was based on the data of GSK1278863 administered in a wide dose range (0-25 mg) and included a Japanese Phase II 4-week treatment study (PHI116099) and international multi-center late Phase II 24-week treatment studies (PHI113633 and PHI113747) in which subjects in Japan participated. For PD subjects, the starting dose and the dose adjustment algorithm for ND subjects will be applied based on the PK/PD profiles in PD subjects determined from an interim analysis in an overseas 14-day treatment clinical pharmacology study (PHI200942).

Starting dose

Simulation results using the longitudinal model in ND subjects as well as the results from clinical studies indicated that GSK1278863 given at a dose of 4 mg may slowly increase Hgb (0.5-1.0 g/dL on average) without a rapid increase greater than 2 g/dL after 4 weeks of treatment in ESA non-users. 4 mg GSK1278863 may also maintain Hgb without a rapid increase greater than 2 g/dL for 4 weeks

after switching from prior ESA in ESA users. Covariate analyses identified baseline Hgb, body weight, and dose level of prior ESA as major factors affecting Hgb. However, Hgb was more greatly affected by inter-subject differences in drug response to GSK1278863 than these factors.
Taken together, 4 mg may be an appropriate starting dose of GSK1278863 for both ESA non-users and users.

Maintenance dose range and dose adjustment algorithm
Simulation results using the longitudinal model showed that drug response to GSK1278863 greatly varied among subjects, indicating that the dose range from 1 to 24 mg may be necessary to achieve and maintain target Hgb. Accordingly, a total of 8 dose levels (1, 2, 4, 6, 8, 12, 18, and 24 mg) were selected as the maintenance doses, with 4 mg intended for subjects with a standard drug response.
The dose adjustment algorithm was defined so that target Hgb (11.0-13.0 g/dL) set for the present study according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] can be maintained. Since the upper limit of the Hgb target (13.0 g/dL) is equivalent to the interruption criterion for ESA, the dose level of GSK1278863 will be reduced by one step when Hgb increases to more than 12.5 g/dL, and the dose level will be maintained while Hgb is in the range of 11.5-<12.5 g/dL. Since the guidelines state that an Hgb increase of 0.5 g/dL or less per week is appropriate to prevent adverse reactions, the dose level will be reduced by one step when Hgb increases by more than 2 g/dL over 4 weeks. For subjects whose anemia needs to be corrected (≥7.5 g/dL and <11.5 g/dL), the dose level will be maintained while the Hgb increase per 4 weeks is 0.5-2 g/dL, and the dose level will be increased by one step when the Hgb increase per 4 weeks is less than 0.5 g/dL.

Starting dose and dose adjustments of control (epoetin beta pegol)
The starting dose and the dose adjustment algorithm for epoetin beta pegol are described in Section 6.4..
The starting dose of epoetin beta pegol for subjects not using ESA or subjects on epoetin was selected based on the Prescribing Information in Japan. For subjects on darbepoetin alfa, darbepoetin alfa will be switched to epoetin beta pegol at a dose ratio of 6:5 according to overseas Prescribing Information, given no specification for dose conversion from darbepoetin currently approved in Japan to epoetin beta pegol.
The dose adjustment algorithm for epoetin beta pegol was determined based on the product information and previous Japanese clinical studies.

4.6. Benefit: Risk Assessment
Summaries of findings from clinical and nonclinical studies of GSK1278863 can be found in the IB and IB supplement. The risk assessment and risk minimization strategies for the present study are outlined in the following sections:

4.6.1. Risk Assessment
Based on the results of completed clinical and nonclinical studies of GSK1278863, the potential risks of clinical significance and the risk minimization strategies for the present study are outlined in Section 12.2. Appendix 2.

4.6.2. Benefit Assessment

Study PHI201753 is a Phase 3 study in Japanese ND and PD subjects with renal anemia. Previous clinical studies of GSK1278863 administered for up to 24 weeks in ND or HD subjects have demonstrated clinical efficacy (increase in and/or maintenance of Hgb) with serum EPO concentrations increased within the normal physiologic range in CKD subjects. Data obtained in Study PHI201753 will generate safety and efficacy data in Japanese ND and PD subjects with renal anemia for a 52-week treatment period. Study participants who will receive GSK1278863 may benefit from the expected clinical efficacy. Participants who will receive the control (epoetin beta pegol approved for the treatment of renal anemia in Japan) are also expected to benefit from the clinical efficacy.

GSK1278863 may have important advantages over existing ESAs. GSK1278863, which is orally administered and requires no cold chain management unlike ESAs, is more convenient to patients. GSK1278863 is shown to increase Hgb at lower EPO concentrations than ESAs. Since increased exposure to EPO following administration of ESAs may be associated with an increased cardiovascular risk [Szczech, 2008], GSK1278863 may increase Hgb without increasing the cardiovascular risk.

4.6.3. Overall Benefit: Risk Conclusion

GSK1278863 is shown to have a positive benefit-risk balance based on the following findings: in studies of GSK1278863 administered for up to 24 weeks, treatment with GSK1278863 resulted in achievement of target Hgb, and no adverse events have been identified as related to treatment with GSK1278863.

The present study is intended to evaluate the efficacy and safety of GSK1278863 administered for 52 weeks in Japanese ND and PD subjects with renal anemia, and designed to administer GSK1278863 or epoetin beta pegol as control to all enrolled subjects; therefore, subjects randomized in either treatment group are expected to benefit from the treatment.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (Section 12.2. Appendix 2). Given these precautions, as well as the potential benefit that GSK1278863 holds for the treatment of renal anemia compared with the current standard treatment, the overall benefit risk balance is considered to be positive.

5. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) and/or other pertinent documents.

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

5.1. Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the inclusion criteria.
Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

1. Age (at the time of informed consent): ≥20 years of age
2. Stage of chronic kidney disease (CKD) (ND patients only): CKD stages 3, 4, and 5 defined by eGFR using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Dialysis:
   - Not on dialysis for at least 12 weeks prior to screening (ND patients)
   - On peritoneal dialysis (PD patients)
4. Use of erythropoiesis-stimulating agent (ESA):
   - ESA non-users: Have not used ESAs for at least 8 weeks prior to screening
   - ESA users: Have used the same ESA for at least 8 weeks prior to screening. However, in the ND patients, the dose of darbepoetin alfa or epoetin beta pegol must be stable (administered once every 4 weeks and up to one-step dose change during at least 8 weeks prior to screening).
5. Hemoglobin (Hgb): Determined at the site using an Hgb analyzer (HemoCue)
   - ESA non-users: ≥8.0 g/dL and <11.0 g/dL
   - ESA users: ≥9.0 g/dL and ≤13.0 g/dL
6. Iron parameters: Ferritin >100 ng/mL or transferrin saturation (TSAT) >20% (screening verification only)
7. Gender (screening verification only): Female or male
   Females: Not pregnant [demonstrated to be negative for human chorionic gonadotropin (hCG) in urine or serum], not breast-feeding, and meet at least one of the following:
   1) Females of non-childbearing potential are defined as follows:
   - Pre-menopausal with at least one of the following and no plans to utilise assisted reproductive techniques (e.g., in vitro fertilisation or donor embryo transfer):
     - History of bilateral tubal ligation or salpingectomy
     - History of hysteroscopic tubal occlusion and postoperatively documented bilateral tubal obstruction
     - History of hysterectomy
     - History of bilateral oophorectomy
   - Postmenopausal defined as 1) females 60 years of age or older or 2) In females < 60 years of age, 12 months of spontaneous amenorrhea [in questionable cases a blood sample with postmenopausal follicle stimulating hormone (FSH) and estradiol concentrations is confirmatory (see separately specified reference ranges)]. Females on hormone replacement therapy (HRT) whose menopausal status is in doubt will be required to use one of the most 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.

2) Females of childbearing potential must agree to comply with one of the contraception methods listed as requirements in "GSK Listing of Most Effective Contraceptive Methods for Females of Childbearing Potential (Section 12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential)" from at least 28 days prior to the first dose of study medication until the completion of the follow-up visit (for subjects randomized to the GSK1278863 group) or 7 weeks after the last dose of study treatment (for subjects randomized to the Epoetin beta pegol group).

8. Informed consent: Written informed consent, including adherence to the requirements and conditions specified in the consent form and the protocol, must be obtained from each subject as specified in Section 10.2..

5.2. Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study.

Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

Chronic kidney disease (CKD)-related criteria

1. Dialysis
   - Cohort 1: Start or plan to initiate dialysis during the study
   - Cohort 2: Plan to stop peritoneal dialysis or start hemodialysis during the study
2. Kidney transplant: Planned living-related kidney transplant during the study

Anemia-related criteria

3. Aplasia: History of bone-marrow hypoplasia or pure red cell aplasia
4. Other causes of anemia: pernicious anemia, thalassemia, sickle cell anemia, or myelodysplastic syndromes
5. Gastrointestinal (GI) bleeding: Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding within 8 weeks prior to screening or during a period from screening to Day 1.

Cardiovascular disease-related criteria

6. Myocardial infarction, acute coronary syndrome, stroke, or transient ischemic attack: Diagnosed within 8 weeks prior to screening or during a period from screening to Day 1.
7. Heart failure: Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system
8. QTc (screening verification only): QTc >500 msec or QTc >530 msec in subjects with bundle branch block

   Note: QT interval corrected using the Bazett's formula (QTcB) will be used, and ECG can be mechanically or manually read.

Other disease-related criteria

9. Liver disease (if any of the following occurs):
   - Alanine transaminase (ALT) >2×upper limit of normal (ULN)

- Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- Current unstable active liver or biliary disease (generally defined by the onset of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal/gastric varices, persistent jaundice, or cirrhosis)
  Note: Stable liver disease (including asymptomatic gallstones, chronic hepatitis B/C, or Gilbert's syndrome) is acceptable if the subject otherwise meets entry criteria.

10. Malignancy: History of malignancy within 2 years prior to screening, or currently receiving treatment for cancer, (PD patients only) complex renal cystic >3 cm (II F, III or IV based on the Bosniak classification)
    Note (ND patients and PD patients): The only exception is squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥ 8 weeks before screening.
11. In the opinion of the investigator, Hgb increase to the target range (11.0-13.0 g/dL) is medically risky.

Concomitant medication and other study treatment-related criteria

12. Iron: Planned use of intravenous iron during the screening phase or during a period from Day 1 to Week 4
    Note: Oral iron is acceptable. However, the same dose regimen must be used throughout the screening phase and from Day 1 to Week 4. Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) are also acceptable only if used for at least 12 weeks prior to screening. However, they must be continued throughout the screening phase and from Day 1 to Week 4.
13. Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (see the GSK1278863 IB or epoetin beta pegol Prescribing Information)
14. Drugs and supplements: Use or planned use of any prescription or non-prescription drugs or dietary supplements that are prohibited during the study period (prohibited medications: strong inducers and inhibitor of CYP2C8, see Section 6.11.2.)
15. Prior investigational product exposure: Use of an investigational agent within 30 days or five half lives of the investigational agent (whichever is longer)
16. Prior treatment with GSK1278863: Any prior treatment with GSK1278863 for a treatment duration of >30 days

General health-related criteria

17. Other conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator (or subinvestigator) 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

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial and are screened, but are not subsequently randomized in the study. A minimum set of information is required from screen failure subjects including Demography, Screen Failure details, Eligibility Criteria, and SAEs in

order to report screen failures in a reliable manner, satisfy the requirements for publication defined by the Consolidated Standards of Reporting Trials (CONSORT), and respond to requests of the regulatory authorities.
Subjects that fail screening are eligible to be rescreened up to 3 times as soon as the investigator (or subinvestigator) assesses they may meet study entry criteria.

5.4. Withdrawal/Dropout Criteria

If subjects meet one of the following criteria, study treatment should be permanently discontinued and subjects will be withdrawn from the study. The withdrawal reason should be recorded.

- Hgb <7.5 g/dL
  Note: HemoCue Hgb values will be employed. If an initial Hgb value meets the Hgb stopping criteria, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be discontinued.
- Subject needs for maintenance dialysis or changes dialysis modality (PD subjects only) during the study period.
- Kidney transplant
- Subject becomes pregnant or intends to become pregnant during the study.
- Diagnosis of new or recurrent cancer
- Liver chemistry abnormalities exceeding the threshold criteria (see Section 5.4.1.)
- Need for chronic (more than 14 days) use of prohibited medication
- When the investigator (or subinvestigator) considers necessary to withdraw the subject from the study for other reasons

Subjects who meet any of the withdrawal criteria or are withdrawn for other reasons during the treatment phase should be assessed at withdrawal visit after study treatment is discontinued, and will then enter the follow-up phase.

Should a subject fail to attend a required study visit, the investigator (or subinvestigator) should take the following measures:

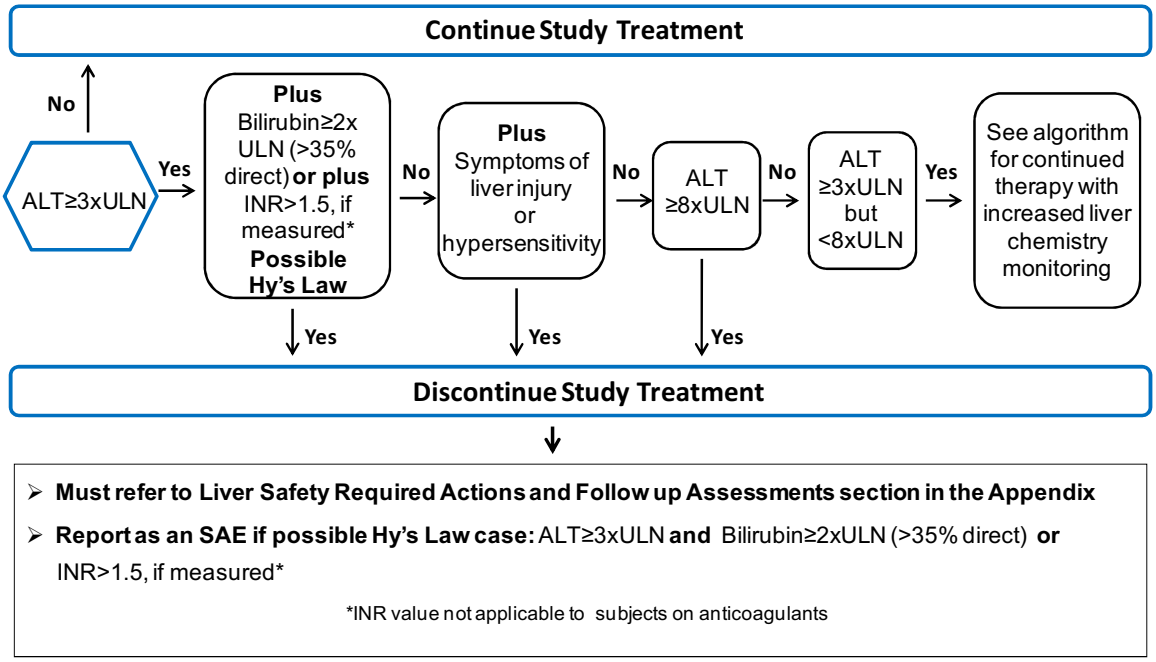
- The investigator (or subinvestigator) or designee should attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The investigator (or subinvestigator) should counsel the subject on the importance of maintaining the assigned visit schedule and determine whether the subject is willing to continue his/her participation in the study and/or whether the subject should remain in the study.
- The investigator (or subinvestigator) or designee should make every effort to regain contact with a subject who is deemed “Lost to Follow-up”. All efforts to contact the subject should be documented in the subject’s clinical charts.
- Should the subject continue to be unreachable, then and only then will he/she be considered “Lost to Follow-up.”

A subject may withdraw from the study at any time at his/her own request. The investigator (or subinvestigator) may withdraw a subject from the study at any time for safety or compliance reasons or study conduct considerations. If a subject withdraws from the study, he/she may request destruction of any clinical samples taken, and the investigator (or subinvestigator) must document this in the site study records.

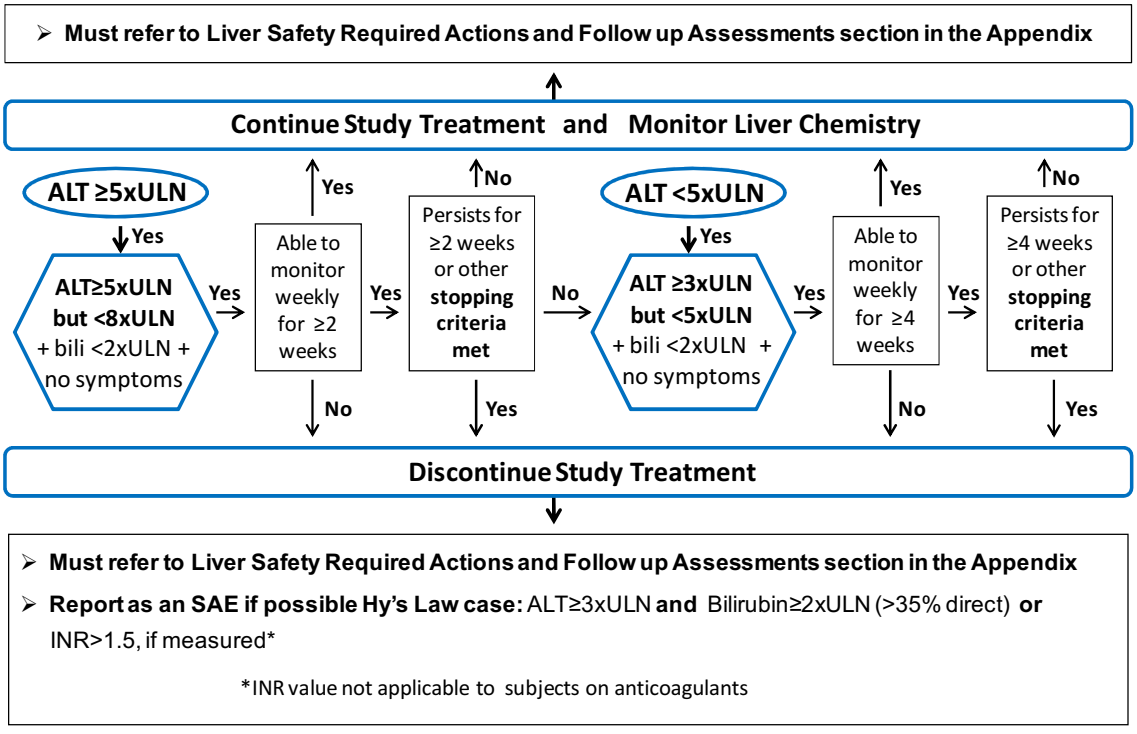
5.4.1. Liver Chemistry Stopping Criteria

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

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.5. Appendix 5

5.4.1.1. Study Treatment Restart or Rechallenge

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

5.5. Subject and Study Completion

A completed subject is one who has completed all periods of the study including the follow-up visit. The study will be completed with the last subject's last study visit.

6. STUDY TREATMENTS

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any products received by the subject as per the protocol design. Accordingly, 'study treatment' sometimes refers to each product and sometimes refers to multiple products.

GSK1278863 (study drug)

The study drug GSK1278863 will be supplied as fast-release film coated tablets for oral administration containing 1 mg, 2 mg, 4 mg, or 6 mg of GSK1278863 (Table 2). There are two sizes of GSK1278863 tablets.

Table 2 Description of GSK1278863 Tablets

GSK1278863 tablets of specific content	Description
1 mg tablets, 2 mg tablets, 4 mg tablets	7.0 mm round, standard biconvex, white film coated tablets containing 1 mg, 2 mg, or 4 mg of GSK1278863 as active ingredient
6 mg tablets	9.0 mm round, standard biconvex, white film coated tablets containing 6 mg of GSK1278863 as active ingredient

GSK1278863 tablets of specific content are packed in high density polyethylene (HDPE) bottles, with 35 tablets per bottle. Subjects are to take one to four tablets (Table 3) with water once daily according to the dose level indicated at each study visit. Subjects can take GSK1278863 tablets without regard to food or peritoneal dialysis. The administration schedule (starting dose and dose adjustment) described in Section 6.4.1. should be followed.

Table 3 Dose Levels of GSK1278863 and Number of Tablets Taken

Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Subjects should be instructed to bring GSK1278863 tablets with bottles at each study visit, and all unused GSK1278863 tablets will be collected from subjects at each study visit.

Epoetin beta pegol (control)

The control epoetin beta pegol (brand name: Mircera® Pre-filled Syringe) will be supplied by GSK. This product is an injectable formulation containing 25 µg, 50 µg, 75 µg, 100 µg, 150 µg, 200 µg, or 250 µg of epoetin beta pegol per syringe (0.3 mL) and is supplied as a glass syringe prefilled with epoetin beta pegol solution (clear colorless to pale yellow).
Subjects are to receive epoetin beta pegol subcutaneously once every 2 or 4 weeks at the site (Table 4). The administration schedule (starting dose and dose adjustment) described in Section 6.4.2. should be followed.

Table 4 Dose Levels of Epoetin Beta Pegol and Number of Subcutaneous Doses

Dose level of epoetin beta pegol (once every 2 or 4 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg
Number of subcutaneous doses of epoetin beta pegol	25 µg injection ×1	50 µg injection ×1	75 µg injection ×1	100 µg injection ×1	150 µg injection ×1	200 µg injection ×1	250 µg injection ×1

6.2. Medical Devices

The Epoetin beta pegol (Brand name :MIRCERA® Injection Syringe) marketed with the device (kit formulation which was filled liquid medication in glass syringe) provided for use in this study. Instructions for medical device are described in the Prescribing Infromation of MIRCERA® Injection Syringe.

The medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 7.4.4.

6.3. Treatment Assignment

The randomization schedule will be generated by GlaxoSmithKline (GSK) using the randomization system (Randall).

In Cohort 1 (ND subjects), subjects will be stratified by the current ESA therapy (ESA non-user or ESA user) and the Hgb level on Day 1 and randomized in a 1:1 ratio to one of the two treatment groups according to the randomization schedule. Randomization should precede the study treatment.

- GSK1278863 group
- Epoetin beta pegol group

In Cohort 2 (PD subjects), all eligible subjects will start treatment with GSK1278863 on Day 1.

Subjects will be assigned a randomization number by the Interactive Web Recognition System (IWRS). Once a randomization number has been assigned, it must not be re-assigned. Further details are provided in the Study Reference Manual (SRM).

6.4. Administration Schedule (Starting Dose, Dose Adjustment, and Dosing Frequency)

6.4.1. GSK1278863 (ND and PD Subjects)

6.4.1.1. Starting Dose

For ND (Cohort 1) and PD subjects (Cohort 2) randomized to the GSK1278863 group, both ESA non-users and users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.
ESA users should skip ESA on Day 1 when treatment with GSK1278863 is started.

6.4.1.2. Maintenance Dose

From Weeks 4 to 52, interruption of treatment or dose adjustments will be made within the maintenance dose range of 1-24 mg (Table 5) according to the dose adjustment algorithm (Table 6) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (1 mg), treatment should be interrupted; once the one-step dose increase criteria are met, treatment at 1 mg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (24 mg), treatment at 24 mg should be continued.

Table 5 Maintenance Dose of GSK1278863

Dose step	1	2	3	4	5	6	7	8
Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Table 6 Dose Adjustment Algorithm (GSK1278863)

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (If interrupted at 1 mg: resume treatment at 1 mg once the one-step dose increase criteria are met)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0	One-step dose reduction
	0.5-2.0	Continue treatment at the current dose level
	<0.5	One-step dose increase
<7.5	NA	Discontinue treatment permanently * and initiate another appropriate treatment

*: If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.4.2. Epoetin Beta Pegol (ND Subjects Only)

For ND subjects (Cohort 1) randomized to the epoetin beta pegol group, ESA non-users and users will receive epoetin beta pegol subcutaneously according to the treatment regimens described below.

6.4.2.1. Starting Dose for ESA Non-users

ESA non-users will start subcutaneous treatment with epoetin beta pegol at a dose of 25 µg once every 2 weeks (Day 1). Dose adjustments will be made within the initial dose range of 25-150 µg (Table 7) according to the dose adjustment criteria (Table 8) to increase Hgb to 11.0 g/dL (lower limit of the target) or more based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the dose reduction criteria shown in Table 8 is met during treatment with epoetin beta pegol at 25 µg, treatment should be interrupted; once the dose reduction criteria are not met any longer, treatment will be resumed at a dose of 25 µg.

Table 7 Initial Dose of Epoetin Beta Pegol (ESA Non-users)

Dose step	1	2	3	4	5
Dose level of epoetin beta pegol (once every 2 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg

Table 8 Initial Dose Adjustment Criteria for Epoetin Beta Pego (ESA Non-users)

Hgb	Treatment
Hgb increase <1.0 g/dL over past 4 weeks, OR Hgb <10.0 g/dL and Hgb increase ≤2.0 g/dL over past 4 weeks	One-step dose increase
Hgb increase >2.0 g/dL over past 4 weeks	One-step dose reduction
Otherwise	Continue treatment at the current dose level

Once Hgb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm (Table 12). The dosing interval should be changed from once every 2 weeks to once every 4 weeks with dose conversion for dosing interval change (Table 9) after it is confirmed that all of the following criteria are met:

- Hgb in the target range (11.0-13.0 g/dL)
- Hgb change ≤2.0 g/dL over past 4 weeks
- Equivalent dose will be given twice (at least 4 weeks)

Table 9 Dose Conversion of Epoetin Beta Pegol for Dosing Interval Change (ESA Non-users)

Initial dose of epoetin beta pegol (given once every 2 weeks)		Dose conversion of epoetin beta pegol (given once every 4 weeks)
25 µg	→	50 µg
50 µg	→	100 µg
75 µg	→	150 µg
100 µg	→	200 µg
150 µg	→	250 µg

6.4.2.2. Dose Conversion for ESA Users

For ESA users, prior ESA will be replaced with epoetin beta pegol at the equivalent dose once every 4 weeks (Day 1).

Table 10 Replacement with Epoetin Beta Pegol-Initial Dose (ESA Users)

Prior ESA		Epoetin beta pegol
Epoetin	<4500 IU per week	100 µg once every 4 weeks
	≥4500 IU per week	150 µg once every 4 weeks
Darbepoetin alfa	30 µg once every 4 weeks *	25 µg once every 4 weeks
	60 µg once every 4 weeks *	50 µg once every 4 weeks
	90 µg once every 4 weeks *	75 µg once every 4 weeks
	120 µg once every 4 weeks *	100 µg once every 4 weeks
	180 µg once every 4 weeks *	150 µg once every 4 weeks
Epoetin beta pegol	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks *	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks

*: Allowance of ±1 week
Maintenance treatment will be started at Week 4 as described in Section 6.4.2.3.

6.4.2.3. Maintenance Dose (ESA Non-users and Users)

Epoetin beta pegol will be administered once every 4 weeks from dosing interval change (once every 4 weeks) with Hgb ≥11.0 g/dL to Week 52 in ESA non-users and from Weeks 4 to 52 in ESA users. Interruption of treatment or dose adjustments will be made within the maintenance dose range of 25-250 µg (Table 11) according to the dose adjustment algorithm (Table 12) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (25 µg), treatment should be interrupted; once the one-step dose reduction criteria

are not met any longer, treatment at 25 μg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (250 μg), treatment at 250 μg should be continued.

Table 11 Maintenance Dose of Epoetin Beta Pegol

Dose step	1	2	3	4	5	6	7
Epoetin beta pegol (once every 4 weeks)	25 μg	50 μg	75 μg	100 μg	150 μg	200 μg	250 μg

Table 12 Dose Adjustment Algorithm (Epoetin Beta Pegol)

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (resume treatment at 25 μg if interrupted at 25 μg)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0	One-step dose reduction
	1.0-2.0	Continue treatment at the current dose level
	<1.0	One-step dose increase
<7.5	NA	Discontinue treatment permanently * and initiate another appropriate treatment

*: If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.5. Blinding

This is an open-label study.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

- No special preparation of study treatment is required.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study medications must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator (or subinvestigator) and authorized site staff.
- Subjects must bring all of supplied study medication bottles of GSK127886 at each study visit. Study staff will collect all of study medication bottles supplied at the previous study visit and supply new study medication bottles.

- The investigator (or subinvestigator), 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).
- Under normal conditions of handling and administration, study medication is not expected to pose significant safety risks to site staff. GSK will provide a document describing occupational hazards and recommended handling precautions either to the investigator (or subinvestigator) when necessary or upon request of the medical institution.
- Further details are provided in the SRM.

6.8. Compliance with Study Treatment Administration

GSK1278863

Since GSK1278863 is self-administered, compliance with GSK1278863 treatment will be assessed through an interview with subjects at each study visit and recorded in the source document and eCRF. A record of the number of GSK1278863 tablets dispensed to and taken by each subject will be maintained and reconciled with study treatment and compliance records. In addition, the number of GSK1278863 doses dispensed, used, and unused, as well as study treatment start and stop dates will be recorded in the eCRF (the number of doses returned and unreturned will also be recorded separately).

Epoetin beta pegol

Epoetin beta pegol will be subcutaneously administered to subjects at the site. Dosing details will be recorded in the source document and eCRF.

6.9. 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. GSK1278863 is highly protein bound; thus, clearance of GSK1278863 by hemodialysis or peritoneal dialysis is very low and these are not effective methods to enhance the elimination of GSK1278863. GSK1278863 metabolites are, in part, cleared via hemodialysis. 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, subjects should be monitored closely for cardiovascular events, increased heart rate and hematologic abnormalities.

Consult the respective approved Prescribing Information for information on overdose for epoetin beta pegol.

6.10. Treatment after the End of the Study

Since the target disease studied is not life-threatening or severely debilitating and there is the alternative therapy, subjects will not receive any additional treatment from GSK after completion of the study. The investigator (or subinvestigator) is responsible for ensuring that consideration has been given to post-study care of the subject's medical condition.

6.11. Concomitant Medications and Non-Drug Therapies

Concomitant medications, including over-the-counter medications and supplements, taken during the study will be recorded in the eCRF. Drug names and start/stop dates will be recorded for general concomitant medications, while additional details, including dose, route of administration, and dosing frequency, will be recorded for certain medications (e.g., ESAs, iron, anti-hypertensive medications). Further details are provided in the SRM.

6.11.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.11.2., all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned. Regular multivitamins (at recommended daily allowance) and other supplements such as calcium and vitamin D may be used if permitted by the investigator or his/her designee.

CYP2C8 is involved in the primary route of metabolism of GSK1278863. Accordingly, co-administration of GSK1278863 with moderate CYP2C8 inhibitors (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks using a point-of-care Hgb analyzer.

Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) may be started from Week 4 onwards unless any other antihyperphosphatemic agents are appropriate. Once started, iron-containing antihyperphosphatemic agents must be continued until the end of the study wherever possible.

6.11.2. Prohibited Medications and Non-Drug Therapies

Use of any of the following drugs from screening until 7 days after the last dose of study treatment is prohibited:

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

6.12. Supplemental Iron Therapy

Supplemental iron therapy will be administered according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] if ferritin is ≤100 ng/mL and TSAT is ≤20%. The investigator (or subinvestigator) can choose the route of administration and dose of prescription iron.

7. Study Assessments and Procedures

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

7.1. Time and Events Table

The time and events tables for the entire study and PK assessment are presented as Table 13 and Table 14, respectively. To allow scheduling flexibility, study visits may occur within a window of ±7 days on Day 1 scheduled 4 weeks after screening, within a window of ±3 days at Week 4, and within a

window of ±5 days for the rest of the study. However, subjects receiving the control epoetin beta pegol every 2 weeks should attend study visits, including those only for study treatment, within a window of ±3 days. Visit days are counted from Day 1.

Table 13 Time and Events Table

Phase	Screening	Treatment														Follow-up
Week	-4	Day 1	4	8	12	16	20	24	28	32	36	40	44	48	52	Early withdrawal[9]	4 weeks after 52 or withdrawal
Permissible range (days)	±7	-	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-	±7
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Medical history, demography, height, weight	X																
Registration with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication dispensing [1,2]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Study treatment compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X			X			X			X			X	X	X
Ophthalmology [3]	◄►				◄►									◄►		◄►	
ECG	X							X							X		
HemoCue Hgb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	X	X
Clinical chemistry	X	X	X			X			X			X			X	X	X
Urinalysis (ND subjects only)	X	X						X							X		X
Pregnancy test (urine or serum hCG) [4]	X	X	X			X			X			X			X	X	X
Estradiol, FSH [5]	X																
PK [6]					X			X									
Ferritin, TSAT	X	X	X			X			X			X			X	X	
Serum iron, TIBC, UIBC, serum transferrin, hepcidin		X	X			X			X			X			X	X	
iPTH		X							X						X		
HR-QoL		X			X				X						X	X	
Genetics sample [7]		X															
Adverse event assessment [8]		◄►															
Review Concomitant Medications	◄►																

1. In Cohort 1, ESA non-users randomized to the epoetin beta pegol group will start treatment with epoetin beta pegol at a dose of 25 µg once every 2 weeks. For these subjects, specified examinations will be performed every 4 weeks, and no study-related assessments will be necessary at study visits only for study treatment (e.g., Week 2, Week 6) (see Section 6.4.2). It should be noted that subjects receiving epoetin beta pegol once every 2 weeks should attend study visits within a window of ±3 days.
2. If a subject visit the study site only to receive study medication, only registration with the IWRS, study medication dispensing, and study medication compliance will be required.
3. Ophthalmology exams should be conducted at the following time points.

- Screening: anytime after consenting and prior to first dose of study medication (Day 1)
- Week 12: window from weeks 10-14 (inclusive)
- End of study: window from weeks 48-52 (inclusive)
- Early study medication discontinuation: withdrawal eye exam as close to the last dose as possible (the repeat exams are not required if one has been performed within the 2 prior weeks).

4. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.
5. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
6. See Table 14.
7. Informed consent for optional Genetic research should be obtained before collecting a sample (see Section 7.6.).
8. See Section 7.4.1.1..
9. For withdrawn subjects, specified assessments should be done wherever possible.

Table 14 Blood Sampling Schedule for Pharmacokinetics (Only Subjects in GSK1278863 Group)

PK sample	Week 12 [2]	Week 24 [2]
Blood sampling timing [1]	1, 2, 3, and 4 h after administration of GSK1278863	

Subjects must take the study medication with regard to blood sampling time. Subjects will record the date and time of the last two study medication doses taken prior to blood sampling in the medication diary. Preferably, there should be an interval of at least 12 h between these two doses.

1. Blood sampling should be completed within +/- 30 min of the planned collected time.
2. Blood sampling not performed at this visit may be postponed until the following visits.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed (documented in the eCRF) at baseline.
In addition, the following demographic information will be collected:

- Year of birth
- Gender
- Race and ethnic
- Medical history/treatment history/family history will be assessed in relation to the inclusion/exclusion criteria (Section 5.).

Full details of baseline assessments are provided in Table 13.

7.3. Efficacy

Efficacy will be assessed according to the Time and Event Table (Table 13).
Hgb concentrations measured by the central laboratory will be mainly used for efficacy assessment (see Section 7.4.7.).
GSK will supply a point-of-care Hgb analyzer (HemoCue) to each site for rapid and convenient measurement of Hgb and to ensure consistency of Hgb measurements across all sites participating in the study. Assessment for Hgb concentrations via HemoCue will be used for eligibility (Section 5.1.), withdrawal (Section 5.4.), and dose adjustment criteria (Section 6.4.).
In addition, assessments of iron metabolism parameters and measures of CKD progression (e.g., eGFR) used for efficacy assessment are outlined with specific procedures in Section 7.4.7..

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Table 13).
Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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

The definitions of an AE or SAE can be found in Section 12.6. Appendix 6.
The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3.), at the timepoints specified in the Time and Events Table (Table 13).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.6. Appendix 6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.6. Appendix 6.

7.4.1.2. Method of Detecting AEs and SAEs

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

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.2.) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.). Further information on follow-up procedures is given in Section 12.6. Appendix 6..

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.6. Appendix 6 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.

7.4.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.2. Adverse Events of Special Interest

The investigator (or subinvestigator) or designee will be responsible for detecting, documenting, and reporting any AEs of special interest listed below. These events have been identified based on the known safety profiles of ESAs, theoretical or potential risks based on the mechanism of action of GSK1278863, and findings from completed nonclinical studies of GSK1278863.

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Death, myocardial infarction, 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 inflammatory joint disease (e.g., rheumatoid arthritis)

Any relevant AE should be recorded in the relevant section of the subject's eCRF.

7.4.3. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the follow-up contact.

- 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 12.4.. Appendix 4.

Note: Subjects randomized in the epoetin beta pegol group should be advised to inform the investigator if they discover pregnancy in 7 weeks after the last dose of study treatment.

7.4.4. Medical Device Incidents (Including Malfunctions)

The medical devices are being provided for use in this study. The investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 8 (Section 12.8.)

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 7.4.1. and Appendix 6 (Section 12.6.) of the Protocol.

7.4.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a medical device provided for the study, the investigator will promptly notify GSK.

NOTE: The method of documenting Medical Device Incidents is provided in Appendix 8 (Section 12.8.).

7.4.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE, will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.). This applies to all subjects, including those withdrawn prematurely.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form ”Medical Device Incident Report Form” with all changes signed and dated by the investigator.

7.4.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the SAE contact information.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.4.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator, or responsible person will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.4.5. Vital Signs/Height/Weight

Systolic and diastolic blood pressure and pulse rate will be measured in sitting or semi-supine position after at least 5 minutes rest prior to clinical examination at each visit blood pressure and pulse rate. One reading of blood pressure and pulse rate will be taken and recorded in the source document and the CRF. Height and weight will be measured at screening visit only.

7.4.6. Electrocardiogram (ECG)

12-lead ECGs will be recorded in supine position. The heart rate, PR, QRS, and QT (pre-corrected) intervals will be measured. QTcB should be calculated by machine or manually by designated staff at each site. The investigator determines whether the ECG data is assessable or not.
At the Day 1 visit when an ECG is performed, two additional ECGs are required if initial ECG indicates prolonged QTc using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility.
QTc exclusion criteria can be found in Section 5.2. Refer to SRM for further details.

7.4.7. Clinical Laboratory Assessments

All study-required laboratory assessments will be performed by a central laboratory with the exception of HemoCue Hgb. The results of each HemoCue Hgb must be entered into the subject's eCRF. Details are provided in the SRM.
All laboratory assessments, as defined in Table 15, 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 labeled 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 central laboratory. Reference ranges for all parameters will be provided to the site by the central laboratory. Details of blood sampling (including the volume of blood to be collected) as well as procedures for processing, storage, and shipment of samples are provided in the SRM.
PK assessment of GSK1278863 is outlined in Section 7.5.

Table 15 Laboratory Assessments

Laboratory assessment	Parameter		
Hematology	Platelet count	RBC indices:	WBC count with Differential
	RBC count	MCV	Neutrophils
	Reticulocyte count	MCH	Lymphocytes
	Hemoglobin	MCHC	Monocytes
	Hematocrit	RDW	Eosinophils
			Basophils
Clinical chemistry	Sodium	AST	Bicarbonate
	Potassium	ALT	Inorganic phosphate
	Chloride	Creatinine	Glucose
	Calcium (total and albumin-corrected)	Total bilirubin	Direct/indirect bilirubin
	Albumin	Urea nitrogen	
	Total cholesterol	HDL cholesterol	LDL cholesterol
Iron parameters	Serum iron	Serum ferritin	Serum transferrin
	TIBC	UIBC	TSAT
	Hepcidin		
Urinalysis (ND subjects only)	Urine albumin	Urine creatinine	Urine albumin/creatinine ratio
Other laboratory tests	FSH [1]	Estradiol [1]	iPTH
	eGFR [2]	hCG (serum or urine) [3]	

1. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
2. Calculated from serum creatinine using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.

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 (or subinvestigator) (e.g., SAE or AE or dose modification), the results must be recorded in the eCRF.
Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study 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 (or subinvestigator), the etiology should be identified and the Sponsor notified.

7.4.8. Ophthalmology

Ophthalmology exams will be performed by a study-designated ophthalmology specialist. Each assessment will include a comprehensive eye exam with at least the following components: measurement of best corrected visual acuity, intraocular pressure, an anterior aqueous chamber exam, and a fundoscopic exam. These exams will be used for assessment of ocular adverse events. Assessment results will be captured on worksheets which will be transferred to the eCRF. Additional details on the process for completing these assessments are provided in the SRM.

7.5. Pharmacokinetics

Blood samples for PK analysis of GSK1278863 will be collected from only subjects in the GSK1278863 group as outlined in Table 14, and the date and time of the last two study medication doses taken prior to blood sampling as well as the date and time of sampling must be recorded in the eCRF.

Blood PK analysis will be performed under the control of GSK Platform Technologies and Science-Drug Metabolism and Pharmacokinetics (PTS-DMPK)/Scinovo and GSK-Japan Bioanalysis, the details of which will be included in the SPM. Concentrations of parent GSK1278863 will be determined in blood samples using the currently approved analytical methodology. Raw data will be archived at the bioanalytical site.

Procedures for processing, storage, and shipment of samples are provided in the SRM.

7.6. Genetics

A blood sample will be collected for genetic analysis from consenting subjects. This sample can be collected on Day 1 once written informed consent has been obtained. Information regarding genetic research is included in Section 12.7. Appendix 7.

7.7. Patient Reported Outcome (PRO)

The patient reported outcome (PRO) [e.g., symptoms, severity, health-related QOL (HR-QoL), health status] will be assessed using several rating scales.

All questionnaires used in this study have been translated into Japanese and validated.

Specific instructions on how the subject is to complete the scales and the process for data entry are provided in the SPM.

7.7.1. SF-36

The SF-36 acute version is a general health status questionnaire designed to elucidate the patient's perception of his/her health on several domains, including physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, and general health over the past seven days. The questionnaire contains 36 Likert type questions that ask the patient to recall how he/she felt during the past seven days.

7.7.2. EuroQol Health Utility Index (EQ-5D-5L)/EQ Visual Analogue Scale (EQ-VAS)

The EQ-5D-5L is intended to measure the general health status and health utility. The EQ-5D-5L consists of 2 concepts: self-reported health status consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses and self-rated health status on a visual analog scale (VAS), a thermometer-like line.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- 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

A detailed description of any planned analyses will be documented in a RAP..Any deviations from the analyses described in the protocol will be documented in the RAP or the final study report.

9.1. Hypotheses

The primary objective of the study is to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol based on mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52) in ND subjects (Cohort 1).

As a preliminary assessment, it will be confirmed whether the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-13.0 g/dL) at first. And then the following non-inferioritystatistical hypotheses are to be tested at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%):

- H_0: Treatment difference in mean Hgb during the primary efficacy evaluation period is -1.0 g/dL or less.
- H_1: Treatment difference in mean Hgb during the primary efficacy evaluation period is greater than -1.0 g/dL.

Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority according to the step-down procedure. More specifically, the superiority of GSK1278863 to epoetin beta pegol in terms of target Hgb control in ND subjects is to be demonstrated at a two-sided significance level of 5% by testing the following statistical hypotheses:

- H_0: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is equal between the treatment groups.
- H_1: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is different between the treatment groups.

No hypothesis will be tested in PD subjects (Cohort 2).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%) with a sample size of 100 subjects per group. Assuming a dropout rate of approximately 25%, 135 subjects will be randomized to each group. Given the results from previous non-inferiority studies of similar drugs (darbepoetin alfa, epoetin beta pegol, and peginesatide), the non-inferiority margin of -1.0 g/dL is set. Since an increase of 1.0 g/dL indicates improvement in anemia according to the guidelines for renal anemia in Japan, the non-inferiority margin of -1.0 g/dL may be the clinically acceptable largest difference in renal anemia.
While the present study is designed to ensure long-term safety data from 100 ND subjects, and the primary hypothesis test has at least 99% power to estimate the efficacy very precisely, non-inferiority can be statistically demonstrated with a minimum between-group difference of -0.582 g/dL.

For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half width of the 95% CI for mean Hgb during the primary efficacy evaluation period is 0.493 g/dL.

9.2.2. Sample Size Sensitivity

The power is shown according to treatment difference and standard deviation in Table 16.

Table 16 Power Sensitivity (100 Subjects Evaluated, Noninferiority Margin of -1.0, One-Sided Significance Level of 2.5%)

Treatment difference	Standard deviation		
	1.25	1.5	1.75
0	100.0%	**99.7%**	98.0%
-0.1	99.9%	98.8%	95.1%
-0.2	99.5%	96.4%	89.6%
-0.3	97.6%	90.7%	80.4%

9.2.3. 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

- All Screening Population

The All Screening Population consists of all subjects who are given subject number and whose data are collected, including demographics at screening.

- Intent-to-Treat (ITT) Population (All randomized population)

The Intention-To-Treat Population consists of all subjects who are given randomization number regardless of whether they actually receive study treatment. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of non-inferiority.

- modified ITT (mITT) Population

The mITT Population consists of all ITT subjects who have at least one Hgb measurement during the efficacy evaluation period. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of superiority.

- Per-Protocol (PP) Population

The PP Population consists of all mITT subjects who are not major protocol violators. Subjects will be analyzed according to the treatment received. Details will be defined in the RAP. This population will be used for efficacy sensitivity analyses.

- Safety Population

The Safety Population consists of all ITT subjects who receive at least one dose of study treatment. Subjects will be analyzed according to the treatment received. This population will be used for safety analyses.

- PK Population

The PK Population consists of all GSK1278863-treated subjects from whom PK samples are collected and analyzed.

Additional populations may be defined in the RAP.

9.3.2. Interim Analysis

No interim analysis is planned.

9.3.3. Adjustment for Multiplicity

Adjustment for multiplicity will be applied to maintain an overall type I error rate of 5%. After a preliminary assessment, the primary endpoint will be evaluated to demonstrate the non-inferiority at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%). Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority. Since the process will follow step-down manner, a multiplicity adjustment for significance level of 5% will not be needed according to a closed test procedure.
Other secondary endpoints, which will be evaluated on a complementary or exploratory basis, will be compared at a significance level of 5% without multiplicity adjustment.
Since Cohort 2 is a single-arm cohort, no testing will be performed to evaluate the efficacy in PD subjects.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Efficacy Analysis

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects. MMRM will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. This model includes treatment groups, baseline Hgb, assessment visits, interaction terms between treatment groups and assessment visits, as well as interaction terms between baseline Hgb and assessment visit. As a preliminary assessment, it will be confirmed if the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-13.0 g/dL) at first. This confirmation will be established if the lower and upper limit of 95% CI for the mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL). In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in the mean Hgb during the primary efficacy evaluation period will be estmated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e. lies fully within the range -0.75 to <0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimated in the GSK1278863 group is within the target range.

The primary efficacy population will be the ITT Population, and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted.Further details of sensitivity analyses will be provided in the RAP.

9.4.2. Principal Secondary Efficacy Analysis

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.

In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for odds ratio is greater than 1.0.

9.4.3. Other Secondary Efficacy Analyses

Among the secondary efficacy endpoints, the time (%) in Hgb target range during the primary efficacy evaluation period , proportion of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks, and changes in iron metabolism parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC), the point estimates and 95% CIs for the treatment difference (or odds ratio) in ND subjects will be calculated. Other secondary efficacy and exploratory endpoints will be summarized by each treatment group.

For PD subjects, the efficacy endpoints will be descriptively summarized.

9.4.4. Safety Analyses

In principle, safety data will be summarized by each cohort and each treatment group in the Safety Population.

9.4.4.1. Exposure

Exposure information will be listed for all subjects. The duration of treatment (number of days) and cumulative dose will be tabulated. In addition, distribution of the dose level at each assessment visit and final dosing visit will be tabulated. Frequency of dose adjustment and duration of treatment interruption due to Hgb >13 g/dL will be summarized.

9.4.4.2. Adverse Events

All AEs will be categorized by the MedDRA system organ class and preferred term to tabulate the number and incidence. All AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs of special interest will be summarized separately. Similar summary will be provided for study treatment-related AEs.

9.4.4.3. Other Safety Parameters

For laboratory tests, vital signs and ECG, parameters and/or changes from baseline will be summarized using summary statistics at each assessment visit. The number and percentage of subjects with values of the potential clinical importance values will be tabulated. The criteria for the potential clinical importance will be described in the RAP. For lipid parameters (total cholesterol, LDL cholesterol, and HDL cholesterol), percent changes will also be tabulated. The number (%) of subjects who have any change in anti-hypertensive medications (type and/or dose) due to increased blood pressure will be tabulated.

9.4.5. Pharmacokinetics Analyses

For plasma concentrations of GSK1278863 over time, individual data will be listed, and summary statistics at each time point will be calculated for each dose level. For PK parameters (AUC_{0-4} and Cmax), summary statistics will be calculated for each dose level, and scatter plots against the dose level will be generated.

9.4.6. PRO Data Analysis

Details of PRO data tabulation will be described in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and the Pharmaceutical Affairs Law.

GSK will submit the CTN to the regulatory authorities in accordance with with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- 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.

Informed Consent

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential subject and the subject's legally acceptable representative (as required) of the study including the written information. The investigator (or subinvestigator) should provide the subject and the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and the subject's legally acceptable representative should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home,

he/she may take the consent form home. The person who conducted the informed consent discussion and study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject and the subject's legally acceptable representative.

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

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

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

10.6. Records Retention

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

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

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

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

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

10.8. Study Period

See Exhibit 1

10.9. Study Administrative Structure

Sponsor information is included in Exhibit 2. List of Medical Institutions and Investigators is included in Exhibit 3.

11. REFERENCES

Akizawa Tadao, Makino Hirofumi, Matsuo Seiichi, et al. Management of anemia in chronic kidney disease patients: baseline findings from Chronic Kidney Disease Japan Cohort Study. Clin Exp Nephrol. 2011;15:248-57.

Szczech Lynda A, Barnhart Huiman X., Inrig Jula K., et al. Secondary analysis of the CHOIR trial epoetin-α dose and achieved hemoglobin outcomes. Kidney International. 2008;74:791-8.

Guidelines for Renal Anemia in Chronic Kidney Disease issued by the Japanese Society for Dialysis Therapy in 2008. Journal of Japanese Society for Dialysis Therapy. 2008;41(10):661-716

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Curve
CKD	Chronic Kidney Disease
Cmax	Maximum concentration
CPK	Creatine Phosphokinase
CYP	Cytochrome P450
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
EQ-5D-5L	EuroQol Health Utility Index
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotrophin
HD	Hemodialysis
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
Hgb	Hemoglobin
HIF	Hypoxia-Inducible Factor
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonization
INR	International Normalized Ratio
iPTH	Intact Parathyroid Hormone
ITT	Intent-to-Treat
IWRS	Interactive Web Recognition System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MCS	Mental Component Summary
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
ND	Non dialysis
NYHA	New York Heart Association
PCS	Physical Component Summary
PD	Peritoneal Dialysis
PHI	Prolyl Hydroxylase Inhibitor
PK	Pharmacokinetic
PP	Per-Protocol
PRO	Patient Reported Outcome
QT	Q-T Interval
QTc	Q-T Interval Corrected for Heart Rate
QTcB	Bazett's Correction of QT Interval

RAP	Reporting and Analysis Plan
RDW	Red Blood Cell Distribution Width
RNA	Ribonucleic Acid
rhEPO	Recombinant human erythropoietin
SAE	Serious Adverse Event
SRM	Study Reference Manual
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
UIBC	Unsaturated iron Binding Capacity
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Hemocue

12.2. Appendix 2: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK1278863		
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 5.1. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is provided in Section 6.4.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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)	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 5.2. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Suspected GI bleeding or significant symptoms consistent with erosion should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 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.	period.
Cancer-related mortality, 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 60 mg/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 been identified as a safety concern for GSK1278863.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 5.2.. ♣ Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.4. ♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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.	♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term therapy with GSK1278863 5 mg or 100 mg 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 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.	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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 (Campochiaro, 2006). Administration of 60 mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO increases were	• Ophthalmology exams will be performed during screening, at approximately Week 12 on-study, and at the end of treatment. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 25 mg, 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.	period. • Ophthalmology exams should be specified in Section 7.4.8. and monitored.
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.	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Co-administration of GSK1278863 with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.11.2. • Co-administration of GSK1278863 with moderate CYP2C8 inhibitors (i.e., clopidogrel,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 6.11.1. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.11. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is provided in Section 6.4.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
Other		
ESA risks (Control)	See risks outlined in table for GSK1278863 for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia; Risk of MI, stroke, venous thromboembolism, thrombosis of vascular access; and risk of cancer-related mortality and tumor progression. Hepatic function disorder with increase of AST, ALT and Gamma-glutamyltransferase, and jaundice have been reported as adverse drug reactions for other ESA according to the prescribing information of Epoetin beta pegol.	• The same mitigation strategies have been indentified in acoordance with the mitigation strategies for GSK1278863 • Liver function will be monitored throughout the dosing period as outlined in the Time and Events Table provided in Section 7.1.

References

Campochiaro et al., Ocular versus Extraocular Neovascularization: Mirror Images or Vague Resemblances; Invest Ophthalmol & Vis Sci 2006. 47:462-474.

Formenti et al., Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2alpha gain-of-function mutation. FASEB J. 2011, 25(6): 2001-2011.

Muz et al., The role of hypoxia and HIF-dependent signaling events in rheumatoid arthritis, Arthritis Research & Therapy 2009. 11:201-210.

Smith et al., Mutation of von Hippel–Lindau Tumour Suppressor and Human Cardiopulmonary Physiology PLOS 2006. 3:1176-1186.

Westra et al., Hypoxia-Inducible Factor-1 as Regulator of Angiogenesis in Rheumatoid Arthritis - Therapeutic Implications. Current Medicinal Chemistry 2010. 17:254-263.

12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential

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.

1. Contraceptive subdermal implant that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information
2. Intrauterine device or intrauterine system that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information [Hatcher, 2011]
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011].

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

References

Trussell J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, and Policar M (editors). Contraceptive Technology: Twentieth Revised Edition. New York: Ardent Media, 2011.

12.4. Appendix 4: 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 12.6. Appendix 6. 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 or be withdrawn from the study

12.5. Appendix 5: Liver Safety Required Actions and Follow up Assessments

Phase III-IV 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).

Phase III-IV liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
• If restart/rechallenge not allowed or not granted, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments

MONITORING:
<u>For bilirubin or INR criteria:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24</td><td>• Viral hepatitis serology[4]
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) and quantitative hepatitis B DNA
• Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours after last dose[5]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
<u>For bilirubin or INR criteria:</u></td></tr>
</table>

hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, (for ND patients only) if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase,

<2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

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

12.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.6.1. 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 meeting 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.

12.6.2. 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 and 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; (for ND patients only) if

unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. 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.

12.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

12.6.4. Recording of AEs and SAEs

AEs and SAE Recording:

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

12.6.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.6.6. 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 SAE contact.
- 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 or to the SAE contact by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.7. Appendix 7 - Genetic Research

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 objective of the genetic research is to understand the response to GSK1278863. To achieve this objective, the relationship between genetic variants and the followings may be investigated.

- Response to medicine, including GSK1278863, ESA, other study medicines or any concomitant medicines;
- Nephrogenic anemia and related conditions susceptibility, severity, and progression

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 which will be conducted for this study 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 related to GSK1278863 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 the 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, align with the purpose of the genetic research, 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

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

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

12.8. Appendix 8: Definition of and Procedures for Documenting Medical Device Incidents

12.8.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all medical devices provided for use in the study (see Section 6.2. for the list of the medical devices).

Medical Device Incident Definition:
• Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an incident associated with a device happened and
- the incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents
• a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse • a patient's treatment is interrupted or compromised by a medical device failure • misdiagnosis due to medical device failure leads to inappropriate treatment • a patient's health deteriorates due to medical device failure

12.8.1.1. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 12.6. (Appendix 6).). • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK.

- It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

TITLE PAGE

Division : Worldwide Development

Information Type : Clinical Protocol

Title : A 52-week, Phase III, open-label, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese non-dialysis and peritoneal dialysis subjects with anemia associated with chronic kidney disease.

Compound Number : GSK1278863

Development Phase III

Effective Date : 18-FEB-2016

Author(s) :

PPD

Sponsor Signatory:

Hiromu Nakajima Head, Medicines Development, Japan Development and Medical Affairs (JDMA), GlaxoSmithKline K. K.	**Date**

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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SAE contact information	Person in charge of GSK1278863 Clinical Operations dept.	PPD		GlaxoSmithKline K.K. 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN

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FAX: PPD

Emergency Contact at night and holiday (Mon to Fri 6pm to 10am, Sat, Sun, national holiday and year-end and New Year holidays)
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FAX: PPD (toll free)

Sponsor Legal Registered Address:

6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 JAPAN

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- 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 Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY PHI201753

Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

Objective(s)/Endpoint(s)

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	• Number (%) of subjects with mean Hgb in the target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change from baseline in Hgb at Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category at Week 4
• To evaluate dose adjustment scheme of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustment scheme of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control of GSK1278863 in PD subjects	• Hgb and change from baseline at each assessment visit • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment visit • Time (%) in Hgb target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52) • Time (in days) to reach the lower Hgb target

Objective	Endpoint
	(11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks • Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes
• To evaluate the effect on iron use of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate effect on iron use of GSK1278863 in PD subjects	• Dose of oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To evaluate the effect on iron metabolism of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on iron metabolism of GSK1278863 in PD subjects	• Change from baseline in ferritin • Change from baseline in transferrin saturation (TSAT) • Changes from baseline in hepcidin, serum iron, and total iron binding capacity (TIBC)
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To evaluate the effect on progression of Chronic Kidney Disease (CKD) of GSK1278863 in ND subjects using epoetin beta pegol as control	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To evaluate the effect on health-related QoL (HR-QoL) of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the effect on HR-QoL of GSK1278863 in PD subjects	SF-36 • Changes from baseline in SF-36 HR-QoL scores [Physical Component Summary (PCS), Mental Component Summary (MCS), and 8 subscales] EuroQol Health Utility Index (EQ-5D-5L) • Change from baseline in EQ-5D-5L score • Change from baseline in EQ-5D-5L Visual Analog Scale (VAS)
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest

Objective	Endpoint
	• Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

Study Design

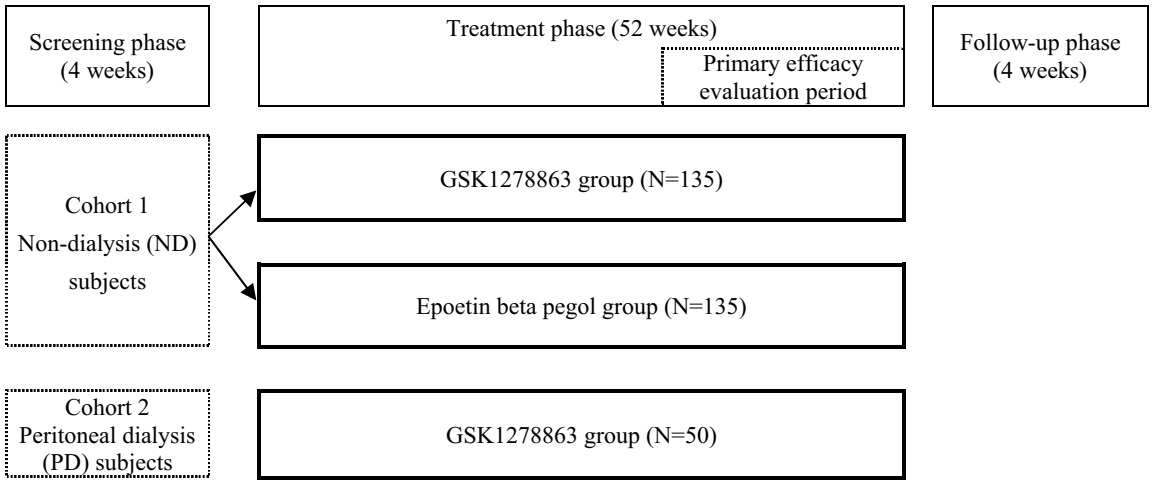
This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (demonstration of non-inferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 270 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. The study consists of the following 2 cohorts of different patient populations:

	Patient population	Presence or absence of ESA therapy (Hgb in subjects)	Treatment group	Target number of subjects (randomized/enrolled)
Cohort 1	ND patient	ESA non-user (Hgb 8.0-<11.0 g/dL) ESA user (Hgb 9.0-13.0 g/dL)	GSK1278863 group	135 subjects*
			Epoetin beta pegol group	135 subjects*
Cohort 2	PD patient	ESA non-user (Hgb 8.0-<11.0 g/dL) ESA user (Hgb 9.0-13.0 g/dL)	GSK1278863 group	50 subjects

*: At least 50 ESA users and at least 50 ESA non-users will be randomized to Cohort 1.
ESA: erythropoiesis-stimulating agent

In Cohort 1, 270 eligible ND subjects will be stratified by the current ESA therapy and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group (135 subjects per group).
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown below.



Week -4 Day 1 Week 40 Week 52 Week 56

Method of Administration of Study Medication in Each Treatment Group

In each treatment group, study medication will be administered as follows:

- GSK1278863 group (ND and PD subjects): Treatment with GSK1278863 will be started at a dose of 4 mg once daily on Day 1. From Week 4 onwards, dose adjustments will be made within the dose range of 1-24 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13 0 g/dL).
- Epoetin beta pegol group (ND subjects):
  - ESA non-users: Subcutaneous treatment with epoetin beta pegol will be started at a dose of 25 μg once every 2 weeks on Day 1. Subsequently, dose adjustments will be made within the dose range of 25-150 μg every 4 weeks according to the prespecified treatment criteria to achieve the lower limit of the Hgb target (11.0 g/dL). Once Hgb increases to 11.0 g/dL or more, dosing frequency will be changed to once every 4 weeks, and dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target Hgb range (11.0-13.0 g/dL).
  - ESA users: Prior ESA therapy will be replaced with subcutaneous treatment with epoetin beta pegol at the equivalent dose once every 4 weeks according to prespecified dose conversion. Subsequently, dose adjustments will be made within the dose range of 25-250 μg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL).

Analysis

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during in the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a two-sided significance level of 5% with a sample size of 100 subjects per group. Assuming a dropout rate of approximately 25%, 135 subjects will be randomized to each group. For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half the width of the 95% CI for mean Hgb during in the primary efficacy evaluation period is 0.493 g/dL.

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects. A mixed model for repeated measurements (MMRM) will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. As a preliminary assessment, it will be confirmed if the lower and upper limit of 95% CI for mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL) In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in mean Hgb during the primary efficacy evaluation period will be estimated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e. lies fully within the range -0.75 to <0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimate in the GSK1278863 group is within the target range.

The primary efficacy population will be the ITT Population, and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted. Further details of sensitivity analyses will be provided in the Reporting and Analysis Plan (RAP).

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.
In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and the current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for the odds ratio is greater than 1.0.

2. INTRODUCTION

GSK1278863 is a hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitor (PHI) that stimulates erythropoiesis in the same manner as innate response to hypoxia and is currently being developed as a new treatment for renal anemia.

2.1. Study Rationale

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese non-dialysis (ND) and peritoneal dialysis (PD) subjects with renal anemia. The primary objective is to demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in the ND patient population included in this study. Study results will be used as pivotal study data for an NDA submitted for GSK1278863 for the treatment of renal anemia in Japan.

2.2. Background

Renal anemia is diagnosed in many patients with CKD, and the prevalence of renal anemia increases with progression of CKD [Akizawa, 2011]. Causes of anemia in CKD patients include absolute or relative deficiency of erythropoietin (EPO), shortened erythrocyte survival, and reduced iron availability. Anemia is further exacerbated by chronic blood loss associated with hemodialysis procedure, infection, and functional hemolysis [Japanese Society for Dialysis Therapy, 2008].

GSK1278863 is a hypoxia-inducible factor-prolyl hydroxylase inhibitor that is currently being developed as a treatment for renal anemia. Data in Japanese patients have been collected from a Japanese Phase II 4-week treatment study in Japanese hemodialysis (HD) subjects (PHI116099: 97 Japanese subjects), an international multi-center Phase II 24-week treatment study in HD subjects (PHI113633: including 24 Japanese subjects), and an international multi-center Phase II 24-week treatment study in ND subjects (PHI113747: including 42 Japanese subjects). In these clinical studies, GSK1278863 increased endogenous EPO, reduced hepcidin, and increased Hgb in HD and ND subjects including Japanese subjects. In addition, GSK1278863 increased Hgb at lower blood EPO concentrations than existing erythropoiesis-stimulating agents (ESAs).

Data from completed clinical and clinical pharmacology studies and the preclinical data safety package are provided in the Development Core Safety Information found in the current GSK1278863 Investigator Brochure (IB). A benefit: risk assessment, including risk mitigation strategies, is outlined in Section 4.6.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary (efficacy)	
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal secondary (efficacy)	
• To demonstrate superiority of	• Number (%) of subjects with mean Hgb in the

Objective	Endpoint
GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other secondary (efficacy, PK)	
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change in Hgb from baseline to Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change from baseline category to Week 4
• To evaluate dose adjustments of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustments of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control by GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control by GSK1278863 in PD subjects	• Hgb at each assessment time point and change in Hgb from baseline to each assessment time point • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment time point • Proportion (%) of time with Hgb within the target range (11.0-13.0 g/dL) in the primary efficacy evaluation period (Weeks 40 to 52) • Time (number of days) to the lower Hgb target (11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks before Week 52 • Number (%) of subjects who achieve an Hgb level of more than 13.0 g/dL and number of episodes
• To compare the effect of GSK1278863 versus epoetin beta pegol on iron use in ND subjects • To evaluate the effect of GSK1278863 on iron use in PD subjects	• Dose of oral iron in the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)
• To compare the effect of GSK1278863	• Change in ferritin from baseline

Objective	Endpoint
versus epoetin beta pegol on iron metabolism in ND subjects • To evaluate the effect of GSK1278863 on iron metabolism in PD subjects	• Change in transferrin saturation (TSAT) from baseline • Changes in hepcidin, serum iron, and total iron binding capacity (TIBC) from baseline
• To evaluate the PK of GSK1278863	• AUC and Cmax of plasma GSK1278863
Exploratory (efficacy)	
• To compare the effect of GSK1278863 versus epoetin beta pegol on progression of CKD in ND subjects	• Estimated glomerular filtration rate (eGFR) and change from baseline • Serum creatinine and change from baseline • Urine creatinine and urine albumin, and changes from baseline • Urine albumin/creatinine ratio and change from baseline
Patient reported outcome	
• To compare the effect of GSK1278863 versus epoetin beta pegol on health-related QoL (HR-QoL) in ND subjects • To evaluate the effect of GSK1278863 on H-RQoL in PD subjects	SF-36 • Changes in SF-36 HR-QoL scores (PCS, MCS, and 8 subscales) from baseline EuroQol Health Utility Index (EQ-5D-5L) • Change in EQ-5D-5L score from baseline • Change in EQ-5D-5L Visual Analog Scale (VAS) from baseline
Safety	
• To evaluate the safety and tolerability of GSK1278863 in ND and PD subjects	• Incidence and severity of AEs and SAEs, including AEs of special interest • Reasons for discontinuation of study medication • Laboratory tests, ECG, vital signs, and ophthalmology assessments

4. STUDY DESIGN

4.1. Overall Design

This is a Phase III, open-label, active-controlled, parallel-group, multi-center study to compare the efficacy (verification of noninferiority) and safety of GSK1278863 administered for 52 weeks versus epoetin beta pegol in approximately 270 Japanese ND subjects with renal anemia. This study also includes an open-label, uncontrolled part to evaluate the efficacy and safety of GSK1278863 in approximately 50 Japanese PD subjects. The study consists of the following 2 cohorts of different patient populations. At least 50 ESA users and at least 50 ESA non-users will be randomized to evaluate by current ESA therapy(ESA user or ESA non-user).

- Cohort 1: ND subjects (GSK1278863 and epoetin beta pegol groups)
- Cohort 2: PD subjects (GSK1278863 group)

For both patient populations, the Hgb criteria are specified according to the presence or absence of prior ESA: ESA non-users with an Hgb level of ≥8.0 to <11.0 g/dL and ESA users with an Hgb level of 9.0 to 13.0 g/dL will be included in the study.
In Cohort 1, 270 eligible ND subjects will be stratified by the current ESA therapy (ESA non-user or ESA user) and baseline Hgb (ESA non-users: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) and then randomized in a 1:1 ratio to GSK1278863 or epoetin beta pegol group (135 subjects per group).
In Cohort 2, 50 eligible PD subjects will be included in the GSK1278863 group.

This study consists of a 4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 4-week follow-up phase following the treatment phase. The study design is shown in Figure 1.

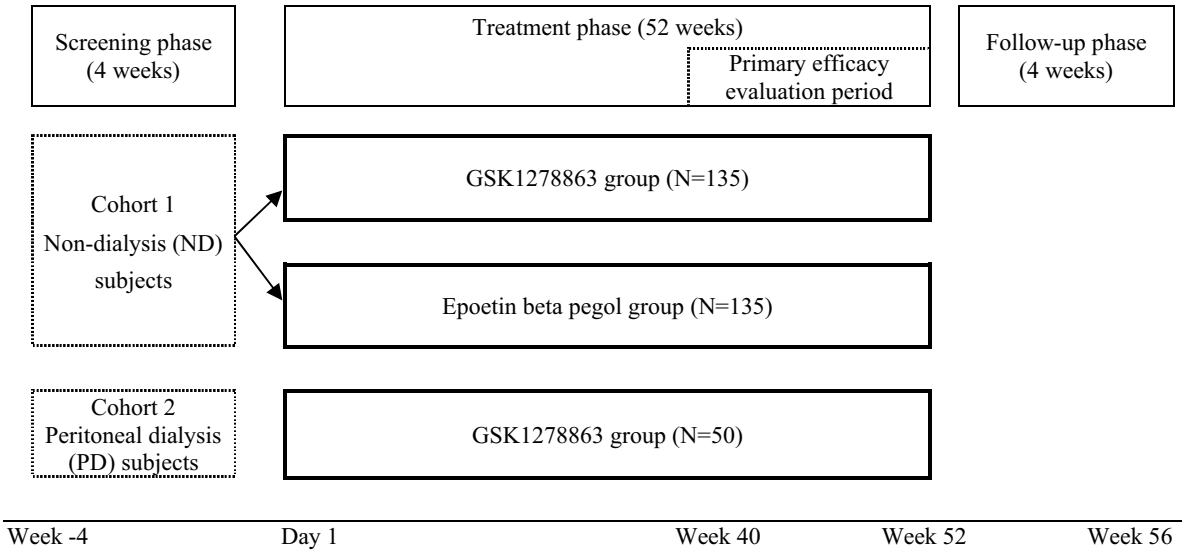


Figure 1 Study Design

4.2. Treatment Groups and Study Periods

Details for each study period and treatments are described below. In this study, a point-of-care Hgb analyzer (HemoCue®) will consistently be utilized for confirmation of subjects' eligibility, withdrawal criteria and dose adjustments of study medication.

Screening phase

Subjects who have provided informed consent and meet all of the eligibility criteria at screening (Week -4) (Sections 5.1 and 5.2) will be provisionally enrolled in the study. Subjects who have used ESA and/or oral iron since before the start of the study must remain on the same regimen throughout the screening phase (intravenous iron will not be allowed).

Treatment phase

Subjects who meet all of the eligibility criteria at the start of the treatment phase (Day 1) will be enrolled in the study. Study medication (either GSK1278863 or epoetin beta pegol group) will be administered for 52 weeks according to randomization in Cohort 1 and GSK1278863 will be administered in Cohort 2 for 52 weeks. For ESA users, prior ESA will be replaced with study medication on Day 1. GSK1278863 will be orally administered once daily, and epoetin beta pegol will be subcutaneously administered once every 2 or 4 weeks. In both groups, dose adjustments for study medication during the treatment phase will be made according to the administration schedule specified in Section 6.3. to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL). In addition, supplemental iron therapy will be administered according to the standard initiation criteria as described in Section 6.11.. It should be noted that intravenous iron or dose change for oral iron will not be allowed from Day 1 to Week 4.

Follow-up phase

Subjects will visit the site for follow-up assessments and observations 4 weeks after the completion/discontinuation of study treatment. During the follow-up phase, treatment of renal anemia will be allowed as necessary at the discretion of the investigator (or subinvestigator).

4.3. Study Subjects and Number of Subjects

In Cohort 1 involving ND subjects, a total of 270 subjects will be randomized (135 subjects in GSK1278863 group, 135 subjects in epoetin beta pegol group). The minimum target number of subjects is 50 ESA non-users and 50 ESA users to allow for evaluations by the current ESA therapy (ESA non-user or ESA user). Assuming a dropout rate of 35% during the screening phase, approximately 416 subjects need to be screened. Assuming a dropout rate of 25% after the start of study treatment, a total of 202 subjects are expected to complete the 52-week treatment.
In Cohort 2 involving PD subjects, 50 subjects will be enrolled (GSK1278863 group only). Since the number of PD patients is very limited in Japan, the target number of subjects is not set for either ESA non-users or users. Assuming a dropout rate of 35% during the screening phase, approximately 77 subjects need to be screened. Assuming a dropout rate of 25% after the start of study treatment, 38 subjects are expected to complete the 52-week treatment.

Table 1 Target Number of Subjects

	Cohort 1 (ND subjects)	Cohort 2 (PD subjects)
Screened	416	77
Randomized/enrolled	270 *	50
Completed 52-week treatment	202	38

*: At least 50 ESA non-users and at least 50 ESA users will be randomized.

4.4. Rationale for Study Design

Objectives and evaluations

This is a Phase III study to evaluate the efficacy and safety of GSK1278863 in Japanese ND and PD subjects with renal anemia. For Cohort 1, the study is designed as an active-controlled, parallel-group comparative study to meet the primary objective, that is, to demonstrate non-inferiority of GSK1278863 to the existing drug in ND subjects. For Cohort 2, the study is designed as an

uncontrolled study because there are not many PD patients. The target Hgb range was set for study treatment in line with the Guidelines for Renal Anemia in Chronic Kidney Disease issued by the Japanese Society for Dialysis Therapy in 2008 [The Japanese Society for Dialysis Therapy, 2008] to demonstrate that treatment with GSK1278863 can result in achievement and/or maintenance of target Hgb in ND and PD subjects, and evaluate the appropriateness of the starting dose of GSK1278863.

Control

For the ND patient population (Cohort 1), epoetin beta pegol, which has been widely used in Japanese patients with renal anemia, primarily ND patients, since its approval in Japan in 2011, was selected as control.

Open-label

If the study is conducted as a double-blind study, it is necessary to not only administer GSK1278863 orally (once daily) or epoetin beta pegol subcutaneously (once every 2 or 4 weeks), but also administer the matching placebo subcutaneously or orally. It will be more stressful for subjects and complicate treatment procedures to use both active drug and matching placebo for two drugs with different routes and intervals of administration for the purpose of maintaining the blind, and make dose adjustments for individual subjects according to the change in Hgb over time. Accordingly, this study is designed as an open-label study rather than a double-blind study, which seems infeasible. Since Hgb used for efficacy evaluation is an objective measure, and dose adjustments for study medication will be made according to the prespecified Hgb-based dose adjustment method in both GSK1278863 and epoetin beta pegol groups, it is unlikely that the open-label design will create any bias in the primary evaluation.

4.5. Rationale for Dose Levels

Starting dose and dose adjustments of GSK1278863

The starting dose (4 mg) and the dose adjustment method (maintenance dose range: 1-24 mg) for GSK1278863 are described in Section 6.3..

The starting dose and the dose adjustment algorithm selected for Japanese ND subjects in the present study are based on the results from a review of the longitudinal model constructed using Hgb data from six Japanese or overseas Phase II studies (PHI112844, PHI116581, PHI116582, PHI113633, PHI113747, and PHI116099) as well as the results from clinical studies. The data set used in the model analyses was based on the data of GSK1278863 administered in a wide dose range (0-25 mg) and included a Japanese Phase II 4-week treatment study (PHI116099) and international multi-center late Phase II 24-week treatment studies (PHI113633 and PHI113747) in which subjects in Japan participated. For PD subjects, the starting dose and the dose adjustment algorithm for ND subjects will be applied based on the PK/PD profiles in PD subjects determined from an interim analysis in an overseas 14-day treatment clinical pharmacology study (PHI200942).

Starting dose

Simulation results using the longitudinal model in ND subjects as well as the results from clinical studies indicated that GSK1278863 given at a dose of 4 mg may slowly increase Hgb (0.5-1.0 g/dL on average) without a rapid increase greater than 2 g/dL after 4 weeks of treatment in ESA non-users. 4 mg GSK1278863 may also maintain Hgb without a rapid increase greater than 2 g/dL for 4 weeks

after switching from prior ESA in ESA users. Covariate analyses identified baseline Hgb, body weight, and dose level of prior ESA as major factors affecting Hgb. However, Hgb was more greatly affected by inter-subject differences in drug response to GSK1278863 than these factors.
Taken together, 4 mg may be an appropriate starting dose of GSK1278863 for both ESA non-users and users.

Maintenance dose range and dose adjustment algorithm
Simulation results using the longitudinal model showed that drug response to GSK1278863 greatly varied among subjects, indicating that the dose range from 1 to 24 mg may be necessary to achieve and maintain target Hgb. Accordingly, a total of 8 dose levels (1, 2, 4, 6, 8, 12, 18, and 24 mg) were selected as the maintenance doses, with 4 mg intended for subjects with a standard drug response.
The dose adjustment algorithm was defined so that target Hgb (11.0-13.0 g/dL) set for the present study according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] can be maintained. Since the upper limit of the Hgb target (13.0 g/dL) is equivalent to the interruption criterion for ESA, the dose level of GSK1278863 will be reduced by one step when Hgb increases to more than 12.5 g/dL, and the dose level will be maintained while Hgb is in the range of 11.5-<12.5 g/dL. Since the guidelines state that an Hgb increase of 0.5 g/dL or less per week is appropriate to prevent adverse reactions, the dose level will be reduced by one step when Hgb increases by more than 2 g/dL over 4 weeks. For subjects whose anemia needs to be corrected (≥7.5 g/dL and <11.5 g/dL), the dose level will be maintained while the Hgb increase per 4 weeks is 0.5-2 g/dL, and the dose level will be increased by one step when the Hgb increase per 4 weeks is less than 0.5 g/dL.

Starting dose and dose adjustments of control (epoetin beta pegol)
The starting dose and the dose adjustment algorithm for epoetin beta pegol are described in Section 6.3..
The starting dose of epoetin beta pegol for subjects not using ESA or subjects on epoetin was selected based on the Prescribing Information in Japan. For subjects on darbepoetin alfa, darbepoetin alfa will be switched to epoetin beta pegol at a dose ratio of 6:5 according to overseas Prescribing Information, given no specification for dose conversion from darbepoetin currently approved in Japan to epoetin beta pegol.
The dose adjustment algorithm for epoetin beta pegol was determined based on the product information and previous Japanese clinical studies.

4.6. Benefit: Risk Assessment
Summaries of findings from clinical and nonclinical studies of GSK1278863 can be found in the IB and IB supplement. The risk assessment and risk minimization strategies for the present study are outlined in the following sections:

4.6.1. Risk Assessment
Based on the results of completed clinical and nonclinical studies of GSK1278863, the potential risks of clinical significance and the risk minimization strategies for the present study are outlined in Section 12.2. Appendix 2.

4.6.2. Benefit Assessment

Study PHI201753 is a Phase 3 study in Japanese ND and PD subjects with renal anemia. Previous clinical studies of GSK1278863 administered for up to 24 weeks in ND or HD subjects have demonstrated clinical efficacy (increase in and/or maintenance of Hgb) with serum EPO concentrations increased within the normal physiologic range in CKD subjects. Data obtained in Study PHI201753 will generate safety and efficacy data in Japanese ND and PD subjects with renal anemia for a 52-week treatment period. Study participants who will receive GSK1278863 may benefit from the expected clinical efficacy. Participants who will receive the control (epoetin beta pegol approved for the treatment of renal anemia in Japan) are also expected to benefit from the clinical efficacy.

GSK1278863 may have important advantages over existing ESAs. GSK1278863, which is orally administered and requires no cold chain management unlike ESAs, is more convenient to patients. GSK1278863 is shown to increase Hgb at lower EPO concentrations than ESAs. Since increased exposure to EPO following administration of ESAs may be associated with an increased cardiovascular risk [Szczech, 2008], GSK1278863 may increase Hgb without increasing the cardiovascular risk.

4.6.3. Overall Benefit: Risk Conclusion

GSK1278863 is shown to have a positive benefit-risk balance based on the following findings: in studies of GSK1278863 administered for up to 24 weeks, treatment with GSK1278863 resulted in achievement of target Hgb, and no adverse events have been identified as related to treatment with GSK1278863.

The present study is intended to evaluate the efficacy and safety of GSK1278863 administered for 52 weeks in Japanese ND and PD subjects with renal anemia, and designed to administer GSK1278863 or epoetin beta pegol as control to all enrolled subjects; therefore, subjects randomized in either treatment group are expected to benefit from the treatment.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (Section 12.2. Appendix 2). Given these precautions, as well as the potential benefit that GSK1278863 holds for the treatment of renal anemia compared with the current standard treatment, the overall benefit risk balance is considered to be positive.

5. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) and/or other pertinent documents.

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

5.1. Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the inclusion criteria.
Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

1. Age (at the time of informed consent): ≥20 years of age
2. Stage of chronic kidney disease (CKD) (ND patients only): CKD stages 3, 4, and 5 defined by eGFR using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Dialysis:
   - Not on dialysis for at least 12 weeks prior to screening (ND patients)
   - On peritoneal dialysis (PD patients)
4. Use of erythropoiesis-stimulating agent (ESA):
   - ESA non-users: Have not used ESAs for at least 8 weeks prior to screening
   - ESA users: Have used the same ESA for at least 8 weeks prior to screening. However, in the ND patients, the dose of darbepoetin alfa or epoetin beta pegol must be stable (administered once every 4 weeks and up to one-step dose change during at least 8 weeks prior to screening).
5. Hemoglobin (Hgb): Determined at the site using an Hgb analyzer (HemoCue)
   - ESA non-users: ≥8.0 g/dL and <11.0 g/dL
   - ESA users: ≥9.0 g/dL and ≤13.0 g/dL
6. Iron parameters: Ferritin >100 ng/mL or transferrin saturation (TSAT) >20% (screening verification only)
7. Gender (screening verification only): Female or male
   Females: Not pregnant [demonstrated to be negative for human chorionic gonadotropin (hCG) in urine or serum], not breast-feeding, and meet at least one of the following:
   1) Females of non-childbearing potential are defined as follows:
   - Pre-menopausal with at least one of the following and no plans to utilise assisted reproductive techniques (e.g., in vitro fertilisation or donor embryo transfer):
     - History of bilateral tubal ligation or salpingectomy
     - History of hysteroscopic tubal occlusion and postoperatively documented bilateral tubal obstruction
     - History of hysterectomy
     - History of bilateral oophorectomy
   - Postmenopausal defined as 1) females 60 years of age or older or 2) In females < 60 years of age, 12 months of spontaneous amenorrhea [in questionable cases a blood sample with postmenopausal follicle stimulating hormone (FSH) and estradiol concentrations is confirmatory (see separately specified reference ranges)]. Females on hormone replacement therapy (HRT) whose menopausal status is in doubt will be required to use one of the most 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.

2) Females of childbearing potential must agree to comply with one of the contraception methods listed as requirements in "GSK Listing of Most Effective Contraceptive Methods for Females of Childbearing Potential (Section 12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential)" from at least 28 days prior to the first dose of study medication until the completion of the follow-up visit (for subjects randomized to the GSK1278863 group) or 7 weeks after the last dose of study treatment (for subjects randomized to the Epoetin beta pegol group).

8. Informed consent: Written informed consent, including adherence to the requirements and conditions specified in the consent form and the protocol, must be obtained from each subject as specified in Section 10.2..

5.2. Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study.

Note: Verification at both provisional enrolment (screening) and official enrolment (Day 1) is required, unless otherwise specified.

Chronic kidney disease (CKD)-related criteria

1. Dialysis
   - Cohort 1: Start or plan to initiate dialysis during the study
   - Cohort 2: Plan to stop peritoneal dialysis or start hemodialysis during the study
2. Kidney transplant: Planned living-related kidney transplant during the study

Anemia-related criteria

3. Aplasia: History of bone-marrow hypoplasia or pure red cell aplasia
4. Other causes of anemia: pernicious anemia, thalassemia, sickle cell anemia, or myelodysplastic syndromes
5. Gastrointestinal (GI) bleeding: Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding within 8 weeks prior to screening or during a period from screening to Day 1.

Cardiovascular disease-related criteria

6. Myocardial infarction, acute coronary syndrome, stroke, or transient ischemic attack: Diagnosed within 8 weeks prior to screening or during a period from screening to Day 1.
7. Heart failure: Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system
8. QTc (screening verification only): QTc >500 msec or QTc >530 msec in subjects with bundle branch block

   Note: QT interval corrected using the Bazett's formula (QTcB) will be used, and ECG can be mechanically or manually read.

Other disease-related criteria

9. Liver disease (if any of the following occurs):
   - Alanine transaminase (ALT) >2×upper limit of normal (ULN)

- Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- Current unstable active liver or biliary disease (generally defined by the onset of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal/gastric varices, persistent jaundice, or cirrhosis)
  Note: Stable liver disease (including asymptomatic gallstones, chronic hepatitis B/C, or Gilbert's syndrome) is acceptable if the subject otherwise meets entry criteria.

10. Malignancy: History of malignancy within 2 years prior to screening, or currently receiving treatment for cancer, (PD patients only) complex renal cystic >3 cm (II F, III or IV based on the Bosniak classification)
    Note (ND patients and PD patients): The only exception is squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥ 8 weeks before screening.
11. In the opinion of the investigator, Hgb increase to the target range (11.0-13.0 g/dL) is medically risky.

Concomitant medication and other study treatment-related criteria

12. Iron: Planned use of intravenous iron during the screening phase or during a period from Day 1 to Week 4
    Note: Oral iron is acceptable. However, the same dose regimen must be used throughout the screening phase and from Day 1 to Week 4. Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) are also acceptable only if used for at least 12 weeks prior to screening. However, they must be continued throughout the screening phase and from Day 1 to Week 4.
13. Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (see the GSK1278863 IB or epoetin beta pegol Prescribing Information)
14. Drugs and supplements: Use or planned use of any prescription or non-prescription drugs or dietary supplements that are prohibited during the study period (prohibited medications: strong inducers and inhibitor of CYP2C8, see Section 6.10.2.)
15. Prior investigational product exposure: Use of an investigational agent within 30 days or five half lives of the investigational agent (whichever is longer)
16. Prior treatment with GSK1278863: Any prior treatment with GSK1278863 for a treatment duration of >30 days

General health-related criteria

17. Other conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator (or subinvestigator) 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

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial and are screened, but are not subsequently randomized in the study. A minimum set of information is required from screen failure subjects including Demography, Screen Failure details, Eligibility Criteria, and SAEs in

order to report screen failures in a reliable manner, satisfy the requirements for publication defined by the Consolidated Standards of Reporting Trials (CONSORT), and respond to requests of the regulatory authorities.
Subjects that fail screening are eligible to be rescreened up to 3 times as soon as the investigator (or subinvestigator) assesses they may meet study entry criteria.

5.4. Withdrawal/Dropout Criteria

If subjects meet one of the following criteria, study treatment should be permanently discontinued and subjects will be withdrawn from the study. The withdrawal reason should be recorded.

- Hgb <7.5 g/dL
  Note: HemoCue Hgb values will be employed. If an initial Hgb value meets the Hgb stopping criteria, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be discontinued.
- Kidney transplant
- Subject becomes pregnant or intends to become pregnant during the study.
- Diagnosis of new or recurrent cancer
- Liver chemistry abnormalities exceeding the threshold criteria (see Section 5.4.1.)
- Need for chronic (more than 14 days) use of prohibited medication
- When the investigator (or subinvestigator) considers necessary to withdraw the subject from the study for other reasons

Subjects who meet any of the withdrawal criteria or are withdrawn for other reasons during the treatment phase should be assessed at withdrawal visit after study treatment is discontinued, and will then enter the follow-up phase. Subjects who start dialysis or change dialysis modality (from PD to hemodialysis) during the study period will remain in the study if they are willing to continue their participation in the study.
Should a subject fail to attend a required study visit, the investigator (or subinvestigator) should take the following measures:

- The investigator (or subinvestigator) or designee should attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The investigator (or subinvestigator) should counsel the subject on the importance of maintaining the assigned visit schedule and determine whether the subject is willing to continue his/her participation in the study and/or whether the subject should remain in the study.
- The investigator (or subinvestigator) or designee should make every effort to regain contact with a subject who is deemed “Lost to Follow-up”. All efforts to contact the subject should be documented in the subject’s clinical charts.
- Should the subject continue to be unreachable, then and only then will he/she be considered “Lost to Follow-up.”

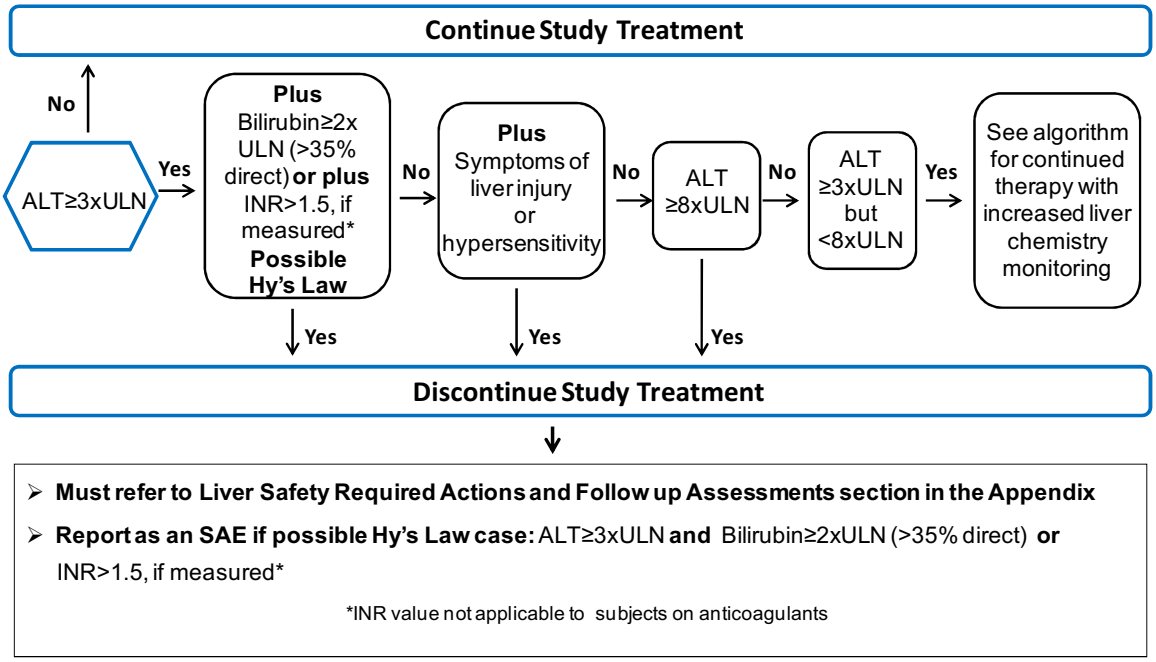
A subject may withdraw from the study at any time at his/her own request. The investigator (or subinvestigator) may withdraw a subject from the study at any time for safety or compliance reasons

or study conduct considerations. If a subject withdraws from the study, he/she may request destruction of any clinical samples taken, and the investigator (or subinvestigator) must document this in the site study records.

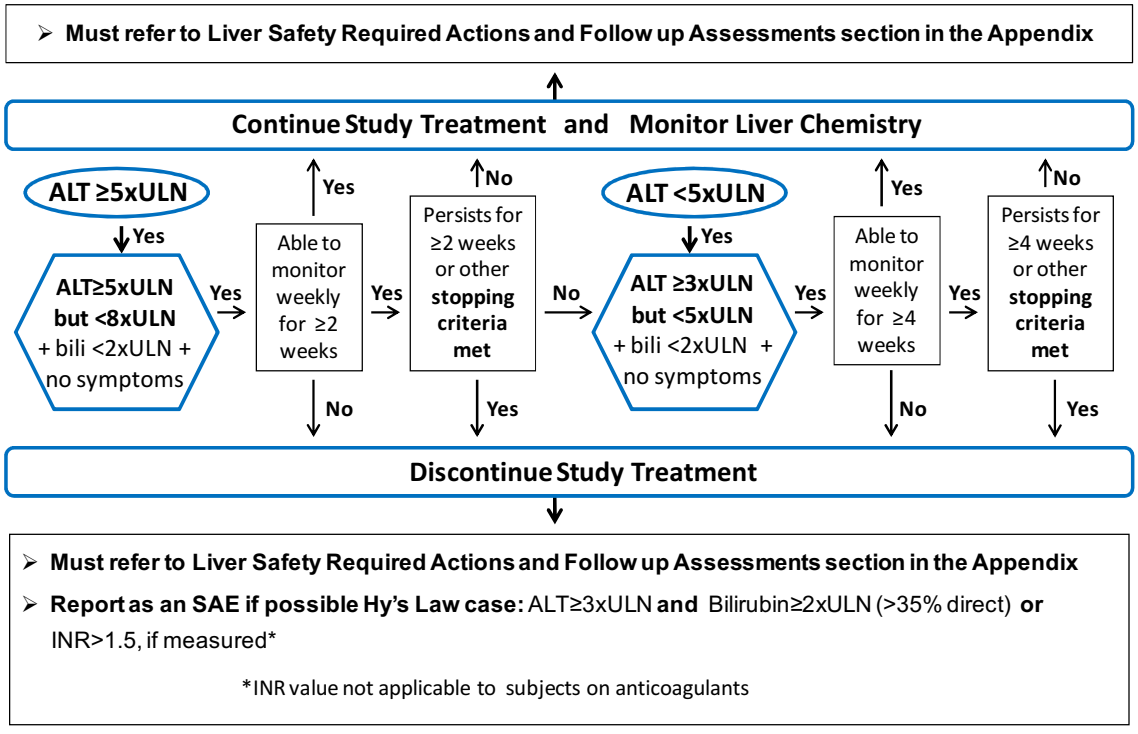
5.4.1. Liver Chemistry Stopping Criteria

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

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.5. Appendix 5

5.4.1.1. Study Treatment Restart or Rechallenge

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

5.5. Subject and Study Completion

A completed subject is one who has completed all periods of the study including the follow-up visit. The study will be completed with the last subject's last study visit.

6. STUDY TREATMENTS

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any products received by the subject as per the protocol design. Accordingly, 'study treatment' sometimes refers to each product and sometimes refers to multiple products.

GSK1278863 (study drug)

The study drug GSK1278863 will be supplied as fast-release film coated tablets for oral administration containing 1 mg, 2 mg, 4 mg, or 6 mg of GSK1278863 (Table 2). There are two sizes of GSK1278863 tablets.

Table 2 Description of GSK1278863 Tablets

GSK1278863 tablets of specific content	Description
1 mg tablets, 2 mg tablets, 4 mg tablets	7.0 mm round, standard biconvex, white film coated tablets containing 1 mg, 2 mg, or 4 mg of GSK1278863 as active ingredient
6 mg tablets	9.0 mm round, standard biconvex, white film coated tablets containing 6 mg of GSK1278863 as active ingredient

GSK1278863 tablets of specific content are packed in high density polyethylene (HDPE) bottles, with 35 tablets per bottle. Subjects are to take one to four tablets (Table 3) with water once daily according to the dose level indicated at each study visit. Subjects can take GSK1278863 tablets without regard to food or peritoneal dialysis. The administration schedule (starting dose and dose adjustment) described in Section 6.3.1. should be followed.

Table 3 Dose Levels of GSK1278863 and Number of Tablets Taken

Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Subjects should be instructed to bring GSK1278863 tablets with bottles at each study visit, and all unused GSK1278863 tablets will be collected from subjects at each study visit.

Epoetin beta pegol (control)

The control epoetin beta pegol (brand name: Mircera® Pre-filled Syringe) will be supplied by GSK. This product is an injectable formulation containing 25 µg, 50 µg, 75 µg, 100 µg, 150 µg, 200 µg, or 250 µg of epoetin beta pegol per syringe (0.3 mL) and is supplied as a glass syringe prefilled with epoetin beta pegol solution (clear colorless to pale yellow).
Subjects are to receive epoetin beta pegol subcutaneously once every 2 or 4 weeks at the site (Table 4). The administration schedule (starting dose and dose adjustment) described in Section 6.3.2. should be followed.

Table 4 Dose Levels of Epoetin Beta Pegol and Number of Subcutaneous Doses

Dose level of epoetin beta pegol (once every 2 or 4 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg
Number of subcutaneous doses of epoetin beta pegol	25 µg injection ×1	50 µg injection ×1	75 µg injection ×1	100 µg injection ×1	150 µg injection ×1	200 µg injection ×1	250 µg injection ×1

6.2. Treatment Assignment

The randomization schedule will be generated by GlaxoSmithKline (GSK) using the randomization system (Randall).

In Cohort 1 (ND subjects), subjects will be stratified by the current ESA therapy (ESA non-user or ESA user) and the Hgb level on Day 1 and randomized in a 1:1 ratio to one of the two treatment groups according to the randomization schedule. Randomization should precede the study treatment.

- GSK1278863 group
- Epoetin beta pegol group

In Cohort 2 (PD subjects), all eligible subjects will start treatment with GSK1278863 on Day 1.

Subjects will be assigned a randomization number by the Interactive Web Recognition System (IWRS). Once a randomization number has been assigned, it must not be re-assigned. Further details are provided in the Study Reference Manual (SRM).

6.3. Administration Schedule (Starting Dose, Dose Adjustment, and Dosing Frequency)

6.3.1. GSK1278863 (ND and PD Subjects)

6.3.1.1. Starting Dose

For ND (Cohort 1) and PD subjects (Cohort 2) randomized to the GSK1278863 group, both ESA non-users and users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4.
ESA users should skip ESA on Day 1 when treatment with GSK1278863 is started.

6.3.1.2. Maintenance Dose

From Weeks 4 to 52, interruption of treatment or dose adjustments will be made within the maintenance dose range of 1-24 mg (Table 5) according to the dose adjustment algorithm (Table 6) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (1 mg), treatment should be interrupted; once the one-step dose increase criteria are met, treatment at 1 mg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (24 mg), treatment at 24 mg should be continued.

Table 5 Maintenance Dose of GSK1278863

Dose step	1	2	3	4	5	6	7	8
Dose level of GSK1278863 (once daily)	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	18 mg	24 mg
Number of GSK1278863 tablets taken	1 mg tablet ×1	2 mg tablet ×1	4 mg tablet ×1	6 mg tablet ×1	4 mg tablet ×2	6 mg tablet ×2	6 mg tablet ×3	6 mg tablet ×4

Table 6 Dose Adjustment Algorithm (GSK1278863)

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (If interrupted at 1 mg: resume treatment at 1 mg once the one-step dose increase criteria are met)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0	One-step dose reduction
	0.5-2.0	Continue treatment at the current dose level
	<0.5	One-step dose increase
<7.5	NA	Discontinue treatment permanently * and initiate another appropriate treatment

*: If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.3.2. Epoetin Beta Pegol (ND Subjects Only)

For ND subjects (Cohort 1) randomized to the epoetin beta pegol group, ESA non-users and users will receive epoetin beta pegol subcutaneously according to the treatment regimens described below.

6.3.2.1. Starting Dose for ESA Non-users

ESA non-users will start subcutaneous treatment with epoetin beta pegol at a dose of 25 µg once every 2 weeks (Day 1). Dose adjustments will be made within the initial dose range of 25-150 µg (Table 7)

according to the dose adjustment criteria (Table 8) to increase Hgb to 11.0 g/dL (lower limit of the target) or more based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. If any of the dose reduction criteria shown in Table 8 is met during treatment with epoetin beta pegol at 25 µg, treatment should be interrupted; once the dose reduction criteria are not met any longer, treatment will be resumed at a dose of 25 µg.

Table 7 Initial Dose of Epoetin Beta Pegol (ESA Non-users)

Dose step	1	2	3	4	5
Dose level of epoetin beta pegol (once every 2 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg

Table 8 Initial Dose Adjustment Criteria for Epoetin Beta Pego (ESA Non-users)

Hgb	Treatment
Hgb increase <1.0 g/dL over past 4 weeks, OR Hgb <10.0 g/dL and Hgb increase ≤2.0 g/dL over past 4 weeks	One-step dose increase
Hgb increase >2.0 g/dL over past 4 weeks	One-step dose reduction
Otherwise	Continue treatment at the current dose level

Once Hgb increases to 11.0 g/dL or more, the dosing interval should be changed from once every 2 weeks to once every 4 weeks with dose conversion for dosing interval change (Table 9) after it is confirmed that all of the following criteria are met:

- Hgb in the target range (11.0-13.0 g/dL)
- Hgb change ≤2.0 g/dL over past 4 weeks
- Equivalent dose will be given twice (at least 4 weeks)

Table 9 Dose Conversion of Epoetin Beta Pegol for Dosing Interval Change (ESA Non-users)

Initial dose of epoetin beta pegol (given once every 2 weeks)		Dose conversion of epoetin beta pegol (given once every 4 weeks)
25 µg	→	50 µg
50 µg	→	100 µg
75 µg	→	150 µg
100 µg	→	200 µg
150 µg	→	250 µg

After the dosing interval is changed to once every 4 weeks according to the criteria described above, maintenance treatment will be started as described in Section 6.3.2.3.

6.3.2.2. Dose Conversion for ESA Users

For ESA users, prior ESA will be replaced with epoetin beta pegol at the equivalent dose once every 4 weeks (Day 1).

Table 10 Replacement with Epoetin Beta Pegol-Initial Dose (ESA Users)

Prior ESA		Epoetin beta pegol
Epoetin	<4500 IU per week	100 µg once every 4 weeks
	≥4500 IU per week	150 µg once every 4 weeks
Darbepoetin alfa	30 µg once every 4 weeks *	25 µg once every 4 weeks
	60 µg once every 4 weeks *	50 µg once every 4 weeks
	90 µg once every 4 weeks *	75 µg once every 4 weeks
	120 µg once every 4 weeks *	100 µg once every 4 weeks
	180 µg once every 4 weeks *	150 µg once every 4 weeks
Epoetin beta pegol	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks *	25, 50, 75, 100, 150, 200, 250 µg once every 4 weeks

*: Allowance of ±1 week
Maintenance treatment will be started at Week 4 as described in Section 6.3.2.3.

6.3.2.3. Maintenance Dose (ESA Non-users and Users)

Epoetin beta pegol will be administered once every 4 weeks from dosing interval change (once every 4 weeks) with Hgb ≥11.0 g/dL to Week 52 in ESA non-users and from Weeks 4 to 52 in ESA users. Interruption of treatment or dose adjustments will be made within the maintenance dose range of 25-250 µg (Table 11) according to the dose adjustment algorithm (Table 12) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. If any of the one-step dose reduction criteria is met during treatment at the minimum maintenance dose (25 µg), treatment should be interrupted; once the one-step dose reduction criteria are not met any longer, treatment at 25 µg will be resumed. If the one-step dose increase criterion is met during treatment at the maximum maintenance dose (250 µg), treatment at 250 µg should be continued.

Table 11 Maintenance Dose of Epoetin Beta Pegol

Dose step	1	2	3	4	5	6	7
Epoetin beta pegol (once every 4 weeks)	25 µg	50 µg	75 µg	100 µg	150 µg	200 µg	250 µg

Table 12 Dose Adjustment Algorithm (Epoetin Beta Pegol)

Hgb (g/dL)	Hgb increase over 4 weeks (g/dL)	Treatment
>13.0	NA	Interrupt treatment until Hgb decreases to less than 12.5 g/dL Resume treatment at the one lower dose level (resume treatment at 25 µg if interrupted at 25 µg)
12.5-13.0	NA	One-step dose reduction
11.5-<12.5	>2.0	One-step dose reduction
	≤2.0	Continue treatment at the current dose level
7.5-<11.5	>2.0	One-step dose reduction
	1.0-2.0	Continue treatment at the current dose level
	<1.0	One-step dose increase
<7.5	NA	Discontinue treatment permanently * and initiate

		another appropriate treatment

*: If an initial Hgb value is less than 7.5 g/dL, measurement will be repeated at the same study visit (using the same sample) to calculate the average. If the average meets the Hgb stopping criteria, study treatment will be permanently discontinued.

6.4. Blinding

This is an open-label study.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

- No special preparation of study treatment is required.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study medications must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator (or subinvestigator) and authorized site staff.
- Subjects must bring all of supplied study medication bottles of GSK127886 at each study visit. Study staff will collect all of study medication bottles supplied at the previous study visit and supply new study medication bottles.
- The investigator (or subinvestigator), 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).
- Under normal conditions of handling and administration, study medication is not expected to pose significant safety risks to site staff. GSK will provide a document describing occupational hazards and recommended handling precautions either to the investigator (or subinvestigator) when necessary or upon request of the medical institution.
- Further details are provided in the SRM.

6.7. Compliance with Study Treatment Administration

GSK1278863

Since GSK1278863 is self-administered, compliance with GSK1278863 treatment will be assessed through an interview with subjects at each study visit and recorded in the source document and eCRF. A record of the number of GSK1278863 tablets dispensed to and taken by each subject will be maintained and reconciled with study treatment and compliance records. In addition, the number of GSK1278863 doses dispensed, used, and unused, as well as study treatment start and stop dates will be recorded in the eCRF (the number of doses returned and unreturned will also be recorded separately).

Epoetin beta pegol

Epoetin beta pegol will be subcutaneously administered to subjects at the site. Dosing details will be recorded in the source document and eCRF.

6.8. 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. GSK1278863 is highly protein bound; thus, clearance of GSK1278863 by hemodialysis or peritoneal dialysis is very low and these are not effective methods to enhance the elimination of GSK1278863. GSK1278863 metabolites are, in part, cleared via hemodialysis. 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, subjects should be monitored closely for cardiovascular events, increased heart rate and hematologic abnormalities.

Consult the respective approved Prescribing Information for information on overdose for epoetin beta pegol.

6.9. Treatment after the End of the Study

Since the target disease studied is not life-threatening or severely debilitating and there is the alternative therapy, subjects will not receive any additional treatment from GSK after completion of the study. The investigator (or subinvestigator) is responsible for ensuring that consideration has been given to post-study care of the subject's medical condition.

6.10. Concomitant Medications and Non-Drug Therapies

Concomitant medications, including over-the-counter medications and supplements, taken during the study will be recorded in the eCRF. Drug names and start/stop dates will be recorded for general concomitant medications, while additional details, including dose, route of administration, and dosing frequency, will be recorded for certain medications (e.g., ESAs, iron, anti-hypertensive medications). Further details are provided in the SRM.

6.10.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.10.2., all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned. Regular multivitamins (at recommended daily allowance) and other supplements such as calcium and vitamin D may be used if permitted by the investigator or his/her designee.

CYP2C8 is involved in the primary route of metabolism of GSK1278863. Accordingly, co-administration of GSK1278863 with moderate CYP2C8 inhibitors (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks using a point-of-care Hgb analyzer.

Antihyperphosphatemic agents containing iron (e.g., ferric citrate hydrate) may be started from Week 4 onwards unless any other antihyperphosphatemic agents are appropriate. Once started, iron-containing antihyperphosphatemic agents must be continued until the end of the study wherever possible.

6.10.2. Prohibited Medications and Non-Drug Therapies

Use of any of the following drugs from screening until 7 days after the last dose of study treatment is prohibited:

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

6.11. Supplemental Iron Therapy

Supplemental iron therapy will be administered according to the Guidelines for Renal Anemia [The Japanese Society for Dialysis Therapy, 2008] if ferritin is ≤100 ng/mL and TSAT is ≤20%. The investigator (or subinvestigator) can choose the route of administration and dose of prescription iron.

7. Study Assessments and Procedures

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

7.1. Time and Events Table

The time and events tables for the entire study and PK assessment are presented as Table 13 and Table 14, respectively. To allow scheduling flexibility, study visits may occur within a window of ±7 days on Day 1 scheduled 4 weeks after screening, within a window of ±3 days at Week 4, and within a window of ±5 days for the rest of the study. However, subjects receiving the control epoetin beta pegol every 2 weeks should attend study visits, including those only for study treatment, within a window of ±3 days. Visit days are counted from Day 1.

Table 13 Time and Events Table

Phase	Screening	Treatment														Follow-up
Week	-4	Day 1	4	8	12	16	20	24	28	32	36	40	44	48	52	Early withdrawal[10]	4 weeks after 52 or withdrawal
Permissible range (days)	±7	-	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-	±7
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Medical history, demography, height, weight	X																
Registration with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication dispensing [1,2]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Study treatment compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs [3]	X	X	X			X			X			X			X	X	X
Ophthalmology [4]	◄►				◄►									◄►			
ECG	X							X							X		
HemoCue Hgb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	X	X
Clinical chemistry	X	X	X			X			X			X			X	X	X
Urinalysis (ND subjects only)	X	X						X							X		X
Pregnancy test (urine or serum hCG) [5]	X	X	X			X			X			X			X	X	X
Estradiol, FSH [6]	X																
PK [7]					X			X									
Ferritin, TSAT	X	X	X			X			X			X			X	X	
Serum iron, TIBC, UIBC, serum transferrin, hepcidin		X	X			X			X			X			X	X	
iPTH		X							X						X		
HR-QoL		X			X				X						X	X	
Genetics sample [8]		X															
Adverse event assessment [9]		◄►															
Review Concomitant Medications	◄►																

1. In Cohort 1, ESA non-users randomized to the epoetin beta pegol group will start treatment with epoetin beta pegol at a dose of 25 µg once every 2 weeks. For these subjects, specified examinations will be performed every 4 weeks, and no study-related assessments will be necessary at study visits only for study treatment (e.g., Week 2, Week 6) (see Section 6.3.2). It should be noted that subjects receiving epoetin beta pegol once every 2 weeks should attend study visits within a window of ±3 days.
2. If a subject visit the study site only to receive study medication, only registration with the IWRS, study medication dispensing, and study medication compliance will be required.
3. Vital signs will be measured before and after dialysis if applicable.

4. Ophthalmology exams should be conducted at the following time points.
   - Screening: anytime after consenting and prior to first dose of study medication (Day 1)
   - Week 12: window from weeks 10-14 (inclusive)
   - End of study: window from weeks 48-52 (inclusive)
   - Early study medication discontinuation: withdrawal eye exam as close to the last dose as possible
5. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.
6. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
7. See Table 14.
8. Informed consent for optional Genetic research should be obtained before collecting a sample (see Section 7.6.).
9. See Section 7.4.1.1..
10. For withdrawn subjects, specified assessments should be done wherever possible.

Table 14 Blood Sampling Schedule for Pharmacokinetics (Only Subjects in GSK1278863 Group)

PK sample	Week 12 [2]	Week 24 [2]
Blood sampling timing [1]	1, 2, 3, and 4 h after administration of GSK1278863	

Subjects must take the study medication with regard to blood sampling time. Subjects will record the date and time of the last two study medication doses taken prior to blood sampling in the medication diary. Preferably, there should be an interval of at least 12 h between these two doses.

1. Blood sampling should be completed within +/- 30 min of the planned collected time.
2. Blood sampling not performed at this visit may be postponed until the following visits.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed (documented in the eCRF) at baseline.
In addition, the following demographic information will be collected:

- Year of birth
- Gender
- Race and ethnic
- Medical history/treatment history/family history will be assessed in relation to the inclusion/exclusion criteria (Section 5.).

Full details of baseline assessments are provided in Table 13.

7.3. Efficacy

Efficacy will be assessed according to the Time and Event Table (Table 13).
Hgb concentrations measured by the central laboratory will be mainly used for efficacy assessment (see Section 7.4.6.).
GSK will supply a point-of-care Hgb analyzer (HemoCue) to each site for rapid and convenient measurement of Hgb and to ensure consistency of Hgb measurements across all sites participating in the study. Assessment for Hgb concentrations via HemoCue will be used for eligibility (Section 5.1.), withdrawal (Section 5.4.), and dose adjustment criteria (Section 6.3.).
In addition, assessments of iron metabolism parameters and measures of CKD progression (e.g., eGFR) used for efficacy assessment are outlined with specific procedures in Section 7.4.6..

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Table 13).
Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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

The definitions of an AE or SAE can be found in Section 12.6. Appendix 6.
The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3.), at the timepoints specified in the Time and Events Table (Table 13).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.6. Appendix 6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.6. Appendix 6.

7.4.1.2. Method of Detecting AEs and SAEs

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

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.2.) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.). Further information on follow-up procedures is given in Section 12.6. Appendix 6..

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.6. Appendix 6 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.

7.4.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.2. Adverse Events of Special Interest

The investigator (or subinvestigator) or designee will be responsible for detecting, documenting, and reporting any AEs of special interest listed below. These events have been identified based on the known safety profiles of ESAs, theoretical or potential risks based on the mechanism of action of GSK1278863, and findings from completed nonclinical studies of GSK1278863.

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Death, myocardial infarction, 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 inflammatory joint disease (e.g., rheumatoid arthritis)

Any relevant AE should be recorded in the relevant section of the subject's eCRF.

7.4.3. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the follow-up contact.

- 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 12.4.. Appendix 4.

Note: Subjects randomized in the epoetin beta pegol group should be advised to inform the investigator if they discover pregnancy in 7 weeks after the last dose of study treatment.

7.4.4. Vital Signs/Height/Weight

Systolic and diastolic blood pressure and pulse rate will be measured in sitting or semi-supine position after at least 5 minutes rest prior to clinical examination at each visit blood pressure and pulse rate. One reading of blood pressure and pulse rate will be taken and recorded in the source document and the CRF. Height and weight will be measured at screening visit only.

7.4.5. Electrocardiogram (ECG)

12-lead ECGs will be recorded in supine position. The heart rate, PR, QRS, and QT (pre-corrected) intervals will be measured. QTcB should be calculated by machine or manually by designated staff at each site. The investigator determines whether the ECG data is assessable or not.

At the Day 1 visit when an ECG is performed, two additional ECGs are required if initial ECG indicates prolonged QTc using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility.

QTc exclusion criteria can be found in Section 5.2. Refer to SRM for further details.

7.4.6. Clinical Laboratory Assessments

All study-required laboratory assessments will be performed by a central laboratory with the exception of HemoCue Hgb. The results of each HemoCue Hgb must be entered into the subject's eCRF. Details are provided in the SRM.

All laboratory assessments, as defined in Table 15, 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 labeled 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 central laboratory. Reference ranges for all parameters will be provided to the site by the central laboratory. Details of blood sampling (including the volume of blood to be collected) as well as procedures for processing, storage, and shipment of samples are provided in the SRM.

PK assessment of GSK1278863 is outlined in Section 7.5.

Table 15 Laboratory Assessments

Laboratory assessment	Parameter		
Hematology	Platelet count	RBC indices:	WBC count with Differential
	RBC count	MCV	Neutrophils
	Reticulocyte count	MCH	Lymphocytes
	Hemoglobin	MCHC	Monocytes
	Hematocrit	RDW	Eosinophils
			Basophils
Clinical chemistry	Sodium	AST	Bicarbonate
	Potassium	ALT	Inorganic phosphate
	Chloride	Creatinine	Glucose
	Calcium (total and albumin-corrected)	Total bilirubin	Direct/indirect bilirubin
	Albumin	Urea nitrogen	
	Total cholesterol	HDL cholesterol	LDL cholesterol
Iron parameters	Serum iron	Serum ferritin	Serum transferrin
	TIBC	UIBC	TSAT
	Hepcidin		
Urinalysis (ND subjects only)	Urine albumin	Urine creatinine	Urine albumin/creatinine ratio
Other laboratory tests	FSH [1]	Estradiol [1]	iPTH
	eGFR [2]	hCG (serum or urine) [3]	

1. Measured in female subjects only to determine the menopausal status (see Section 5.1.)
2. Calculated from serum creatinine using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) formula
3. Performed in females of childbearing potential: serum pregnancy test will be performed if urine pregnancy test is not feasible.

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 (or subinvestigator) (e.g., SAE or AE or dose modification), the results must be recorded in the eCRF.
Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study 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 (or subinvestigator), the etiology should be identified and the Sponsor notified.

7.4.7. Ophthalmology

Ophthalmology exams will be performed by a study-designated ophthalmology specialist. Each assessment will include a comprehensive eye exam with at least the following components: measurement of best corrected visual acuity, intraocular pressure, an anterior aqueous chamber exam, and a fundoscopic exam. These exams will be used for assessment of ocular adverse events. Assessment results will be captured on worksheets which will be transferred to the eCRF. Additional details on the process for completing these assessments are provided in the SRM.

7.5. Pharmacokinetics

Blood samples for PK analysis of GSK1278863 will be collected from only subjects in the GSK1278863 group as outlined in Table 14, and the date and time of the last two study medication doses taken prior to blood sampling as well as the date and time of sampling must be recorded in the eCRF.

Blood PK analysis will be performed under the control of GSK Platform Technologies and Science-Drug Metabolism and Pharmacokinetics (PTS-DMPK)/Scinovo and GSK-Japan Bioanalysis, the details of which will be included in the SPM. Concentrations of parent GSK1278863 will be determined in blood samples using the currently approved analytical methodology. Raw data will be archived at the bioanalytical site.

Procedures for processing, storage, and shipment of samples are provided in the SRM.

7.6. Genetics

A blood sample will be collected for genetic analysis from consenting subjects. This sample can be collected on Day 1 once written informed consent has been obtained. Information regarding genetic research is included in Section 12.7. Appendix 7.

7.7. Patient Reported Outcome (PRO)

The patient reported outcome (PRO) [e.g., symptoms, severity, health-related QOL (HR-QoL), health status] will be assessed using several rating scales.

All questionnaires used in this study have been translated into Japanese and validated.

Specific instructions on how the subject is to complete the scales and the process for data entry are provided in the SPM.

7.7.1. SF-36

The SF-36 acute version is a general health status questionnaire designed to elucidate the patient's perception of his/her health on several domains, including physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, and general health over the past seven days. The questionnaire contains 36 Likert type questions that ask the patient to recall how he/she felt during the past seven days.

7.7.2. EuroQol Health Utility Index (EQ-5D-5L)/EQ Visual Analogue Scale (EQ-VAS)

The EQ-5D-5L is intended to measure the general health status and health utility. The EQ-5D-5L consists of 2 concepts: self-reported health status consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses and self-rated health status on a visual analog scale (VAS), a thermometer-like line.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- 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

A detailed description of any planned analyses will be documented in a RAP..Any deviations from the analyses described in the protocol will be documented in the RAP or the final study report.

9.1. Hypotheses

The primary objective of the study is to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol based on mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52) in ND subjects (Cohort 1).

As a preliminary assessment, it will be confirmed whether the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-13.0 g/dL) at first. And then the following non-inferioritystatistical hypotheses are to be tested at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%):

- H_0: Treatment difference in mean Hgb during the primary efficacy evaluation period is -1.0 g/dL or less.
- H_1: Treatment difference in mean Hgb during the primary efficacy evaluation period is greater than -1.0 g/dL.

Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority according to the step-down procedure. More specifically, the superiority of GSK1278863 to epoetin beta pegol in terms of target Hgb control in ND subjects is to be demonstrated at a two-sided significance level of 5% by testing the following statistical hypotheses:

- H_0: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is equal between the treatment groups.
- H_1: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is different between the treatment groups.

No hypothesis will be tested in PD subjects (Cohort 2).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Assuming a non-inferiority margin of -1.0 g/dL, a treatment difference of 0.0 g/dL, and a standard deviation of 1.5 g/dL for mean Hgb during the primary efficacy evaluation period in ND subjects, two-sample t-test has at least 99% power at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%) with a sample size of 100 subjects per group. Assuming a dropout rate of approximately 25%, 135 subjects will be randomized to each group. Given the results from previous non-inferiority studies of similar drugs (darbepoetin alfa, epoetin beta pegol, and peginesatide), the non-inferiority margin of -1.0 g/dL is set. Since an increase of 1.0 g/dL indicates improvement in anemia according to the guidelines for renal anemia in Japan, the non-inferiority margin of -1.0 g/dL may be the clinically acceptable largest difference in renal anemia.
While the present study is designed to ensure long-term safety data from 100 ND subjects, and the primary hypothesis test has at least 99% power to estimate the efficacy very precisely, non-inferiority can be statistically demonstrated with a minimum between-group difference of -0.582 g/dL.

For PD subjects, the sample size is based on the feasibility. Assuming a sample size of 38 subjects and a standard deviation of 1.5 g/dL, the half width of the 95% CI for mean Hgb during the primary efficacy evaluation period is 0.493 g/dL.

9.2.2. Sample Size Sensitivity

The power is shown according to treatment difference and standard deviation in Table 16.

Table 16 Power Sensitivity (100 Subjects Evaluated, Noninferiority Margin of -1.0, One-Sided Significance Level of 2.5%)

Treatment difference	Standard deviation		
	1.25	1.5	1.75
0	100.0%	**99.7%**	98.0%
-0.1	99.9%	98.8%	95.1%
-0.2	99.5%	96.4%	89.6%
-0.3	97.6%	90.7%	80.4%

9.2.3. 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

- All Screening Population

The All Screening Population consists of all subjects who are given subject number and whose data are collected, including demographics at screening.

- Intent-to-Treat (ITT) Population (All randomized population)

The Intention-To-Treat Population consists of all subjects who are given randomization number regardless of whether they actually receive study treatment. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of non-inferiority.

- modified ITT (mITT) Population

The mITT Population consists of all ITT subjects who have at least one Hgb measurement during the efficacy evaluation period. Subjects will be analyzed according to randomized treatment. This population will be the primary population for an assessment of superiority.

- Per-Protocol (PP) Population

The PP Population consists of all mITT subjects who are not major protocol violators. Subjects will be analyzed according to the treatment received. Details will be defined in the RAP. This population will be used for efficacy sensitivity analyses.

- Safety Population

The Safety Population consists of all ITT subjects who receive at least one dose of study treatment. Subjects will be analyzed according to the treatment received. This population will be used for safety analyses.

- PK Population

The PK Population consists of all GSK1278863-treated subjects from whom PK samples are collected and analyzed.

Additional populations may be defined in the RAP.

9.3.2. Interim Analysis

No interim analysis is planned.

9.3.3. Adjustment for Multiplicity

Adjustment for multiplicity will be applied to maintain an overall type I error rate of 5%. After a preliminary assessment, the primary endpoint will be evaluated to demonstrate the non-inferiority at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%). Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority. Since the process will follow step-down manner, a multiplicity adjustment for significance level of 5% will not be needed according to a closed test procedure.
Other secondary endpoints, which will be evaluated on a complementary or exploratory basis, will be compared at a significance level of 5% without multiplicity adjustment.
Since Cohort 2 is a single-arm cohort, no testing will be performed to evaluate the efficacy in PD subjects.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Efficacy Analysis

The primary endpoint, which is the mean Hgb during the primary efficacy evaluation period, will be analyzed to demonstrate the non-inferiority of GSK1278863 to epoetin beta pegol in ND subjects. MMRM will be used to estimate the mean Hgb during the primary efficacy evaluation period and its 95% CI by treatment groups. This model includes treatment groups, baseline Hgb, assessment visits, interaction terms between treatment groups and assessment visits, as well as interaction terms between baseline Hgb and assessment visit. As a preliminary assessment, it will be confirmed if the mean Hgb during the primary efficacy evaluation period in GSK1278863 group would be in target range (11.0-13.0 g/dL) at first. This confirmation will be established if the lower and upper limit of 95% CI for the mean Hgb in GSK1278863 group would lie fully within target range (11.0-13.0 g/dL). In addition, the point estimate and 95% CI for the treatment difference (GSK1278863-epoetin beta pegol) in the mean Hgb during the primary efficacy evaluation period will be estmated. Non-inferiority will be established if the lower limit of the 95% CI is greater than -1.0 g/dL. Even if the 95% CI for the difference is completely negative (i.e. lies fully within the range -0.75 to <0 g/dL) non-inferiority would still be concluded on condition that the mean Hgb estimated in the GSK1278863 group is within the target range.

The primary efficacy population will be the ITT Population, and the analysis will be repeated in the mITT and PP Population to evaluate the robustness of the conclusion. The subgroup analysis by the current ESA therapy (presence or absence) will also be conducted.Further details of sensitivity analyses will be provided in the RAP.

9.4.2. Principal Secondary Efficacy Analysis

The principal secondary endpoint, which is the proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range will be analyzed to demonstrate the superiority of GSK1278863 to epoetin beta pegol in ND subjects.

In the mITT Population, a logistic regression model including treatment group, baseline Hgb, and current ESA therapy (presence or absence) as covariates will be used to estimate the point estimate and 95% CI for the odds ratio (GSK1278863/epoetin beta pegol). This analysis will be performed to demonstrate the superiority at a two-sided significance level of 5%, conditional on the primary endpoint achieving noninferiority. Superiority will be established if the lower limit of the 95% CI for odds ratio is greater than 1.0.

9.4.3. Other Secondary Efficacy Analyses

Among the secondary efficacy endpoints, the time (%) in Hgb target range during the primary efficacy evaluation period , proportion of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks, and changes in iron metabolism parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC), the point estimates and 95% CIs for the treatment difference (or odds ratio) in ND subjects will be calculated. Other secondary efficacy and exploratory endpoints will be summarized by each treatment group.

For PD subjects, the efficacy endpoints will be descriptively summarized.

9.4.4. Safety Analyses

In principle, safety data will be summarized by each cohort and each treatment group in the Safety Population.

9.4.4.1. Exposure

Exposure information will be listed for all subjects. The duration of treatment (number of days) and cumulative dose will be tabulated. In addition, distribution of the dose level at each assessment visit and final dosing visit will be tabulated. Frequency of dose adjustment and duration of treatment interruption due to Hgb >13 g/dL will be summarized.

9.4.4.2. Adverse Events

All AEs will be categorized by the MedDRA system organ class and preferred term to tabulate the number and incidence. All AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs of special interest will be summarized separately. Similar summary will be provided for study treatment-related AEs.

9.4.4.3. Other Safety Parameters

For laboratory tests, vital signs and ECG, parameters and/or changes from baseline will be summarized using summary statistics at each assessment visit. The number and percentage of subjects with values of the potential clinical importance values will be tabulated. The criteria for the potential clinical importance will be described in the RAP. For lipid parameters (total cholesterol, LDL cholesterol, and HDL cholesterol), percent changes will also be tabulated. The number (%) of subjects who have any change in anti-hypertensive medications (type and/or dose) due to increased blood pressure will be tabulated.

9.4.5. Pharmacokinetics Analyses

For plasma concentrations of GSK1278863 over time, individual data will be listed, and summary statistics at each time point will be calculated for each dose level. For PK parameters (AUC_{0-4} and Cmax), summary statistics will be calculated for each dose level, and scatter plots against the dose level will be generated.

9.4.6. PRO Data Analysis

Details of PRO data tabulation will be described in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and the Pharmaceutical Affairs Law.

GSK will submit the CTN to the regulatory authorities in accordance with with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- 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.

Informed Consent

Prior to participation in the study, the investigator (or subinvestigator) should fully inform the potential subject and the subject's legally acceptable representative (as required) of the study including the written information. The investigator (or subinvestigator) should provide the subject and the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and the subject's legally acceptable representative should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home,

he/she may take the consent form home. The person who conducted the informed consent discussion and study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator (or subinvestigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject and the subject's legally acceptable representative.

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

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

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

10.6. Records Retention

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

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

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

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

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

10.8. Study Period

See Exhibit 1

10.9. Study Administrative Structure

Sponsor information is included in Exhibit 2. List of Medical Institutions and Investigators is included in Exhibit 3.

11. REFERENCES

Akizawa Tadao, Makino Hirofumi, Matsuo Seiichi, et al. Management of anemia in chronic kidney disease patients: baseline findings from Chronic Kidney Disease Japan Cohort Study. Clin Exp Nephrol. 2011;15:248-57.

Szczech Lynda A, Barnhart Huiman X., Inrig Jula K., et al. Secondary analysis of the CHOIR trial epoetin-α dose and achieved hemoglobin outcomes. Kidney International. 2008;74:791-8.

Guidelines for Renal Anemia in Chronic Kidney Disease issued by the Japanese Society for Dialysis Therapy in 2008. Journal of Japanese Society for Dialysis Therapy. 2008;41(10):661-716

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Curve
CKD	Chronic Kidney Disease
Cmax	Maximum concentration
CPK	Creatine Phosphokinase
CYP	Cytochrome P450
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
EQ-5D-5L	EuroQol Health Utility Index
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotrophin
HD	Hemodialysis
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
Hgb	Hemoglobin
HIF	Hypoxia-Inducible Factor
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonization
INR	International Normalized Ratio
iPTH	Intact Parathyroid Hormone
ITT	Intent-to-Treat
IWRS	Interactive Web Recognition System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MCS	Mental Component Summary
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
ND	Non dialysis
NYHA	New York Heart Association
PCS	Physical Component Summary
PD	Peritoneal Dialysis
PHI	Prolyl Hydroxylase Inhibitor
PK	Pharmacokinetic
PP	Per-Protocol
PRO	Patient Reported Outcome
QT	Q-T Interval
QTc	Q-T Interval Corrected for Heart Rate
QTcB	Bazett's Correction of QT Interval

RAP	Reporting and Analysis Plan
RDW	Red Blood Cell Distribution Width
RNA	Ribonucleic Acid
rhEPO	Recombinant human erythropoietin
SAE	Serious Adverse Event
SRM	Study Reference Manual
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
UIBC	Unsaturated iron Binding Capacity
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Hemocue

12.2. Appendix 2: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK1278863		
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 5.1. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is provided in Section 6.3.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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)	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 5.2. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Suspected GI bleeding or significant symptoms consistent with erosion should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 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.	period.
Cancer-related mortality, 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 60 mg/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 been identified as a safety concern for GSK1278863.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 5.2.. ♣ Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.4. ♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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.	♣ These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term therapy with GSK1278863 5 mg or 100 mg 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 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.	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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 (Campochiaro, 2006). Administration of 60 mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO increases were	• Ophthalmology exams will be performed during screening, at approximately Week 12 on-study, and at the end of treatment. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 25 mg, 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.	period. • Ophthalmology exams should be specified in Section 7.4.7. and monitored.
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.	• These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
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	• Co-administration of GSK1278863 with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.10.2. • Co-administration of GSK1278863 with moderate CYP2C8 inhibitors (i.e., clopidogrel,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 6.10.1. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.10. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb is provided in Section 6.3.1. • These risks have been identified as AEs of special interest and will be monitored instreamly by the internal safety review team throughout the study period.
Other		
ESA risks (Control)	See risks outlined in table for GSK1278863 for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia; Risk of MI, stroke, venous thromboembolism, thrombosis of vascular access; and risk of cancer-related mortality and tumor progression. Hepatic function disorder with increase of AST, ALT and Gamma-glutamyltransferase, and jaundice have been reported as adverse drug reactions for other ESA according to the prescribing information of Epoetin beta pegol.	• The same mitigation strategies have been indentified in acoordance with the mitigation strategies for GSK1278863. • Liver function will be monitored throughout the dosing period as outlined in the Time and Events Table provided in Section 7.1.

References

Campochiaro et al., Ocular versus Extraocular Neovascularization: Mirror Images or Vague Resemblances; Invest Ophthalmol & Vis Sci 2006. 47:462-474.

Formenti et al., Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2alpha gain-of-function mutation. FASEB J. 2011, 25(6): 2001-2011.

Muz et al., The role of hypoxia and HIF-dependent signaling events in rheumatoid arthritis, Arthritis Research & Therapy 2009. 11:201-210.

Smith et al., Mutation of von Hippel–Lindau Tumour Suppressor and Human Cardiopulmonary Physiology PLOS 2006. 3:1176-1186.

Westra et al., Hypoxia-Inducible Factor-1 as Regulator of Angiogenesis in Rheumatoid Arthritis - Therapeutic Implications. Current Medicinal Chemistry 2010. 17:254-263.

12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of reproductive potential

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.

1. Contraceptive subdermal implant that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information
2. Intrauterine device or intrauterine system that meets the Prescribing Information effectiveness criteria including a <1% rate of failure per year, as stated in the Prescribing Information [Hatcher, 2011]
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011].

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

References

Trussell J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, and Policar M (editors). Contraceptive Technology: Twentieth Revised Edition. New York: Ardent Media, 2011.

12.4. Appendix 4: 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 12.6. Appendix 6. 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 or be withdrawn from the study

12.5. Appendix 5: Liver Safety Required Actions and Follow up Assessments

Phase III-IV 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).

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24**	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) and quantitative hepatitis B DNA • Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>**

hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, (for ND patients only) if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to

be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

12.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.6.1. 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 meeting 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.

12.6.2. 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 and 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; (for ND patients only) if

unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. 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.

12.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

12.6.4. Recording of AEs and SAEs

AEs and SAE Recording:

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

12.6.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.6.6. 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 SAE contact.
- 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 or to the SAE contact by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.7. Appendix 7 - Genetic Research

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 objective of the genetic research is to understand the response to GSK1278863. To achieve this objective, the relationship between genetic variants and the followings may be investigated.

- Response to medicine, including GSK1278863, ESA, other study medicines or any concomitant medicines;
- Nephrogenic anemia and related conditions susceptibility, severity, and progression

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 which will be conducted for this study 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 related to GSK1278863 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 the 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, align with the purpose of the genetic research, 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

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