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Title : A 24-week, Phase III, open-label, non-comparative, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese hemodialysis subjects with anemia associated with chronic kidney disease who are not taking erythropoiesis stimulating agents.

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| Clarification of inclusion criteri and clarification of study procedures. | | |
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| Clarification of the timing of eligibility assessment regarding exclusion criteria, addition of the prohibited medication, and correction of adverse events of special interest | | |
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INVESTIGATOR PROTOCOL AGREEMENT PAGE

[PHI204716 study]

- I confirm agreement to conduct the study in compliance with the protocol and protocol amendment.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

| | |
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1. PROTOCOL SYNOPSIS FOR STUDY PHI204716

Rationale

This Phase 3 clinical study (PHI204716) aims to evaluate the efficacy and safety of GSK1278863 in Japanese hemodialysis (HD) patients with renal anemia not using erythropoiesis-stimulating agents (ESAs). The primary objective is to evaluate the initial response to GSK1278863 measured by hemoglobin (Hgb) levels in HD patients not using ESAs enrolled in this study. The study is designed to evaluate the appropriateness of the starting dose of GSK1278863 and of the GSK1278863 dose adjustment regimen to achieve or maintain the target Hgb levels. This study is positioned as one of the pivotal studies to support for an approval application in Japan for GSK1278863 for the treatment of renal anemia.

Objective(s)/Endpoint(s)

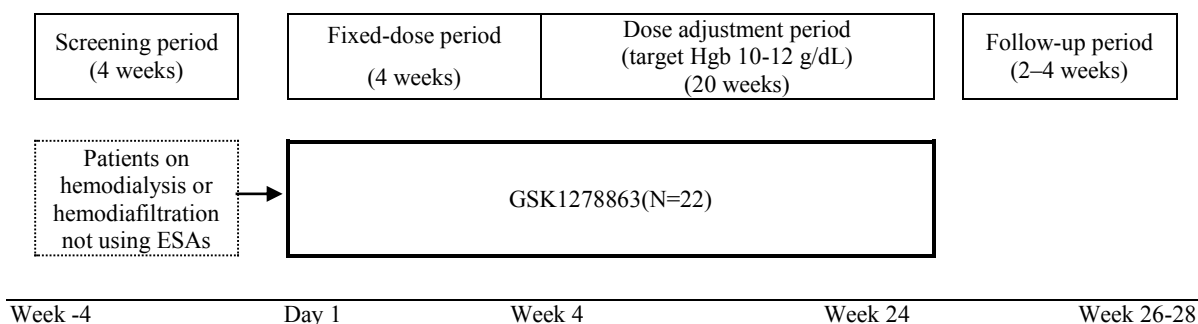
| Objectives | Endpoints |
|--|--|
| Primary | |
| <ul style="list-style-type: none"> To characterize the appropriateness of the starting dose of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> Change from baseline in Hgb at Week 4 Number (%) of subjects by Hgb change from baseline category at Week 4 |
| Secondary | |
| <ul style="list-style-type: none"> To characterize overall Hgb control of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> Hgb and changes from baseline Number (%) of subjects who have a Hgb level within the target range (10.0–12.0 g/dL) Time (in days) to reach the lower target Hgb level (10.0 g/dL) Number (%) of subjects who have a Hgb level of less than 7.5 g/dL Number (%) of subjects who have a Hgb increase of more than 2-g/dL over any 4 weeks Number (%) of subjects who have a Hgb level of more than 13.0 g/dL and number of episodes |
| <ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) of GSK1278863 | <ul style="list-style-type: none"> Area Under Curve (AUC) and Maximum Concentration (Cmax) of plasma GSK1278863 |
| <ul style="list-style-type: none"> To characterize the effect on iron use of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> Dose of intravenous iron Number (%) of subjects who used intravenous iron |
| <ul style="list-style-type: none"> To characterize the effect on iron metabolism of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> 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) |

| Objectives | Endpoints |
|---|--|
| <ul style="list-style-type: none"> To characterize dose adjustment of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> Distribution of dose level Duration of treatment interruption due to Hgb > 13 g/dL Frequency of dose adjustments |
| Safety | |
| <ul style="list-style-type: none"> To assess the safety and tolerability of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including adverse events of special interest (AESIs) Reasons for discontinuation of study medication Laboratory tests, Electrocardiogram (ECG), vital signs, and ophthalmology assessments |

Study Design

This is a 24-week, Phase 3, open-label, non-comparative, multicentre study to evaluate the efficacy and safety of GSK1278863 in Japanese HD patients with renal anemia not using ESAs. Subjects meeting the eligibility criteria will receive GSK1278863 orally once daily initially at 4 mg for 4 weeks from Day 1. Subsequently, subjects will receive GSK1278863 orally once a day according to a pre-defined study treatment dose adjustment algorithm to achieve or maintain Hgb within the target range (10.0–12.0 g/dL).

This study will consist of a 4-week screening period, a 24-week treatment period (4-week fixed-dose period and a 20-week dose adjustment period), and a 2- to 4-week follow-up period. The study design is illustrated as below. .



Study design

Treatment Groups and Study Periods

Screening period (4 weeks)

After informed consent, subjects meeting the eligibility criteria at screening (Week -4) (Sections 5.1. and 5.2.) will be provisionally enrolled. In subjects taking oral iron before participating in the study, the iron dose should not be changed during the screening period (intravenous iron should not be used).

Fixed-dose period (4 weeks)

Subjects meeting the eligibility criteria at the start of the treatment period (Day 1) will be formally enrolled, and will start administration of oral GSK1278863 once daily at the starting dose of 4 mg. In subjects taking oral iron before the study, their iron dose should not be changed during the fixed-dose period (intravenous iron should not be used).

Dose adjustment period (20 weeks)

After the starting fixed-dose period (4 weeks), GSK1278863 will be given orally once daily according to the dose adjustment schedule specified in Section 6.3. to achieve or maintain the target Hgb range (10.0–12.0 g/dL). Iron replacement therapy will be given according to the standard starting criteria as described in Section 6.11.

Follow-up period

Subjects will return to the study site for follow-up evaluation and observation at 2 to 4 weeks after completion or discontinuation of study treatment. During the follow-up period, treatment of renal anemia may be given as required at the discretion of the investigator.

Analysis

There will be no hypothesis testing performed in this study. Two-sided 95% confidence intervals will be used for efficacy estimation. Since HD patients not using ESAs in Japan are limited, the sample size of 22 as enrolled subjects was determined based on feasibility. For the change from baseline in Hgb at Week 4, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. The change in Hgb at Week 4 will be classified into different categories (i.e., ≤ -2 , > -2 to -1 , > -1 to 0 , > 0 to 1 , > 1 to 2 , and > 2 g/dL), and the number (%) of subjects in each category will be summarized.

2. INTRODUCTION

GSK1278863 is a member of an emerging new class of drugs called hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI), which act to promote erythropoiesis by a mechanism similar to intrinsic response to hypoxia, and is currently investigated for the treatment of renal anemia.

2.1. Study Rationale

This Phase 3 clinical study (PHI204716) aims to evaluate the efficacy and safety of GSK1278863 in Japanese HD patients with renal anemia not using ESAs. The primary objective is to evaluate the initial response to GSK1278863 measured by Hgb levels in HD patients not using ESAs enrolled in this study. The study is designed to evaluate the appropriateness of the starting dose of GSK1278863 and of the GSK1278863 dose adjustment regimen to achieve or maintain the target Hgb levels. This study is positioned as one of the pivotal studies to support for an approval application in Japan for GSK1278863 for the treatment of renal anemia.

2.2. Background

Renal anemia is diagnosed commonly in chronic kidney disease (CKD) patients, and advanced CKD is associated with a higher prevalence of renal anemia [Akizawa, 2011]. Causes of anemia in CKD patients include absolute or relative deficiency of erythropoietin (EPO), shortened red cell life-span, and decreased iron availability. Anemia can further worsen because of dialysis-related chronic exsanguination, infection, functional hemolysis, etc. [Tsubakihara, 2010].

GSK1278863 is an HIF-PHI being investigated for the treatment of renal anemia. GSK1278863 has been clinically evaluated as 4-week therapy in a Japanese Phase 2 study in Japanese HD patients (PHI116099; 97 Japanese), 24-week therapy in a global Phase 2 study in HD patients (PHI113633; including 24 Japanese), and 24-week therapy in a global Phase 2 study in non dialysis (ND) patients (PHI113747; including 42 Japanese). Clinical data from these studies demonstrate that GSK1278863 can increase endogenous EPO, reduce hepcidin, and increase Hgb in HD patients and ND patients including Japanese. Data suggest the increases in Hgb with GSK1278863 are achieved at blood EPO levels lower than those observed with ESAs.

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

3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|--|--|
| Primary | |
| <ul style="list-style-type: none"> To characterize the appropriateness of the starting dose of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> Change from baseline in Hgb at Week 4 Number (%) of subjects by Hgb change from baseline category at Week 4 |
| Secondary | |
| <ul style="list-style-type: none"> To characterize overall Hgb control of GSK1278863 in HD patients not using ESAs | <ul style="list-style-type: none"> Hgb and changes from baseline Number (%) of subjects who have a Hgb level within the target range (10.0–12.0 g/dL) Time (in days) to reach the lower target Hgb level (10.0 g/dL) Number (%) of subjects who have a Hgb level of less than 7.5 g/dL Number (%) of subjects who have a Hgb increase of more than 2 g/dL over any 4 weeks Number (%) of subjects who have a Hgb level of more than 13.0 g/dL and number of episodes |
| <ul style="list-style-type: none"> To characterize the PK of GSK1278863 | <ul style="list-style-type: none"> AUC and Cmax of plasma GSK1278863 |
| <ul style="list-style-type: none"> To characterize the effect on iron use of GSK1278863 | <ul style="list-style-type: none"> Dose of intravenous iron Number (%) of subjects who used intravenous iron |
| <ul style="list-style-type: none"> To characterize the effect on iron metabolism of GSK1278863 | <ul style="list-style-type: none"> Change from baseline in ferritin Change from baseline in TSAT Changes from baseline in hepcidin, serum iron, and TIBC |
| <ul style="list-style-type: none"> To characterize dose adjustment of GSK1278863 | <ul style="list-style-type: none"> Distribution of dose level Duration of treatment interruption due to Hgb > 13 g/dL Frequency of dose adjustments |
| Safety | |
| <ul style="list-style-type: none"> To assess the safety and tolerability of GSK1278863 | <ul style="list-style-type: none"> Incidence and severity of AEs and SAEs, including AESIs Reasons for discontinuation of study medication Laboratory tests, ECG, vital signs, and ophthalmology assessments |

4. STUDY DESIGN

4.1. Overall Design

This is a 24-week, Phase 3, open-label, non-comparative, multicentre study to evaluate the efficacy and safety of GSK1278863 in Japanese HD patients with renal anemia not using ESAs. Subjects meeting the eligibility criteria will receive GSK1278863 orally once daily initially at 4 mg for 4 weeks from Day 1. Subsequently, subjects will receive GSK1278863 orally once a day according to a pre-defined study treatment dose adjustment algorithm to achieve or maintain Hgb within the target range (10.0–12.0 g/dL).

This study will consist of a 4-week screening period, a 24-week treatment period (4-week fixed-dose period and a 20-week dose adjustment period), and a 2- to 4-week follow-up period. The study design is illustrated in Figure 1.

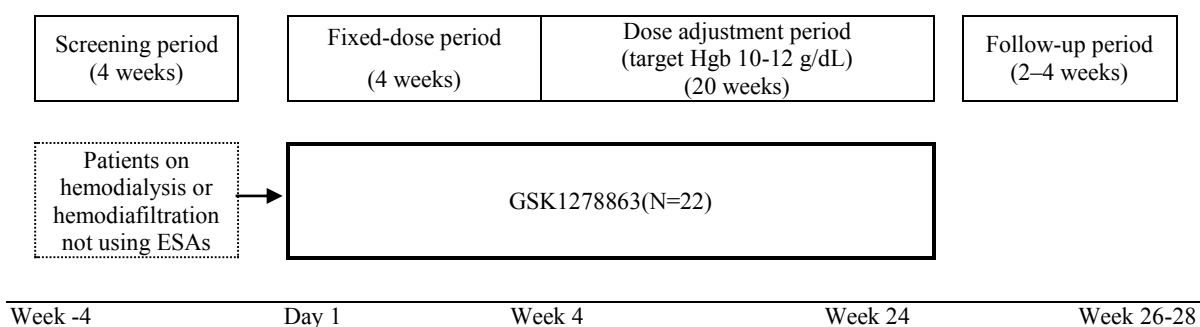


Figure 1 Study design

4.2. Treatment Groups and Study Periods

Individual study periods and study treatment are detailed below. A point-of-care Hgb measurement device (i.e., HemoCue®) will be uniformly used to measure Hgb for determination of subject eligibility, assessment against withdrawal criteria, and GSK1278863 dose adjustment in this study.

Screening period (4 weeks)

After informed consent, subjects meeting the eligibility criteria at screening (Week -4) (Sections 5.1. and 5.2.) will be provisionally enrolled. In subjects taking oral iron before participating in the study, the iron dose should not be changed during the screening period (intravenous iron should not be used).

Fixed-dose period (4 weeks)

Subjects meeting the eligibility criteria at the start of the treatment period (Day 1) will be formally enrolled, and will start administration of oral GSK1278863 once daily at the starting dose of 4 mg. In subjects taking oral iron before the study, their iron dose should not be changed during the fixed-dose period (intravenous iron should not be used).

Dose adjustment period (20 weeks)

After the starting fixed-dose period (4 weeks), GSK1278863 will be given orally once daily according to the dose adjustment schedule specified in Section 6.3. to achieve or maintain the target Hgb range

(10.0–12.0 g/dL). Iron replacement therapy will be given according to the standard starting criteria as described in Section 6.11.

Follow-up period

Subjects will return to the study site for follow-up evaluation and observation at 2 to 4 weeks after completion or discontinuation of study treatment. During the follow-up period, treatment of renal anemia may be given as required at the discretion of the investigator.

4.3. Target Population and Sample Size

This study will enrol at least 22 Japanese HD patients with renal anemia not using ESAs. Assuming a 25% drop-out rate during the screening period, approximately 30 patients should be screened.

Assuming a 20% drop-out rate after the start of study treatment, the number of subjects who complete the 24-week study treatment is estimated to be 17.

Table 1 Target Sample Size

| | |
|--|----|
| Screened | 30 |
| Enrolled | 22 |
| Completed fixed-dose period (Week 4) | 20 |
| Completed dose adjustment period (Week 24) | 17 |

4.4. Rationale for the Study Design

This is a Phase 3 study to evaluate the efficacy and safety of GSK1278863 in Japanese HD patients with renal anemia not using ESAs. The primary objective is to evaluate the initial response to GSK1278863 in HD patients not using ESAs. The target Hgb in this study range has been set with reference to the 2008 Japanese guideline for renal anemia in chronic kidney disease, issued by the Japanese Society for Dialysis Therapy [Tsubakihara, 2010]. The study has been designed to evaluate the appropriateness of the starting dose of GSK1278863 and of the GSK1278863 dose adjustment regimen to achieve or maintain the target Hgb levels.

4.5. Rationale for the Dosage

GSK1278863 starting dose and dose adjustment

The starting dose of GSK1278863 (4 mg) and the dose adjustment steps (maintenance dose range, 1–24 mg) are described in Section 6.3.

The GSK1278863 starting dose and the dose adjustment algorithm selected for this study in Japanese HD patients not using ESAs are based on the analysis results of longitudinal modelling of Hgb data and clinical data from a total of 6 Phase 2 studies conducted inside or outside Japan (PHI112844, PHI116581, PHI116582, PHI113633, PHI113747, and PHI116099). The data set used in the model analysis included GSK1278863 therapy data in a wide dose range (0–25 mg) from the studies, including the 4-week Japanese Phase 2 study (PHI116099) and 24-week global Phase 2b studies which Japanese subjects participated in (PHI113633 and PHI113747).

Starting dose

The longitudinal model simulation results and clinical study results from HD patients indicated that, in patients not using ESAs, 4 mg is the dose of GSK1278863 producing a modest increase in the Hgb

level (mean, 0.5 g/dL) without rapid increase by > 2 g/dL after 4 weeks of therapy. Covariate analyses elucidated that baseline Hgb, body weight, and prior ESA dose were the most relevant covariates of Hgb response to GSK1278863. However, the effect of these factors was smaller than the effect of inter-individual variability in the response to GSK1278863. Thus, the appropriate starting dose of GSK1278863 was considered to be 4 mg.

Maintenance dose range and dose adjustment algorithm

The longitudinal model simulation results indicated that the response to GSK1278863 greatly varies among different subjects, and the doses required to achieve and maintain the target Hgb levels range from 1 to 24 mg. Using 4 mg as the standard dose in patients with a standard therapeutic response, 8 different maintenance doses (1, 2, 4, 6, 8, 12, 18, 24 mg) were selected.

The dose adjustment algorithm was selected to maintain the target Hgb range (10.0–12.0 g/dL), which was set in line with the Japanese Guideline for Renal Anemia in Chronic Kidney Disease [Tsubakihara, 2010]. Since the guideline recommends that the Hgb increase per week should be limited to ≤ 0.5 g/dL for prevention of adverse reactions, if the Hgb level shows a > 2 g/dL increase over the past 4 weeks, the dose will be reduced to the next lower dose level. In subjects with Hgb levels warranting improvement of anemia (≥ 7.5 , < 10.0 g/dL), if the increase over the past 4 weeks is within 0.5–2 g/dL, the dose will be maintained, and if the increase over the past 4 weeks is < 0.5 g/dL, the dose will be increased to the next higher dose level.

4.6. Benefit: Risk Assessment

Summaries of findings from clinical and nonclinical studies of GSK1278863 can be found in the Investigator's Brochure (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.

4.6.2. Benefit Assessment

Study PHI204716 is a Phase 3 study in Japanese HD subjects with renal anemia not using ESAs. 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 PHI204716 will evaluate safety and efficacy data in Japanese HD subjects with renal anemia who are not using ESA, for a 24-week treatment period. Study participants who will receive GSK1278863 may benefit from the expected 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 (CV) risk [Szczzech, 2008], GSK1278863 may increase Hgb without increasing the CV 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 24 weeks in Japanese HD subjects with renal anemia who are not using ESA, and designed to administer GSK1278863 to all enrolled subjects; therefore, subjects enrolled are expected to benefit from the treatment.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (see Section 12.2.). 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 study treatment, which is possible to affect subject's eligibility, is provided in the Investigator's Brochure (IB)/IB supplement(s) and other pertinent documents.

Deviations from inclusion and exclusion criteria are not allowed because compliance with the protocol-specified inclusion and exclusion criteria is most important from the viewpoints of scientific integrity of the study, regulatory acceptability or subject safety.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply at provisional enrollment (Screening) and formal enrollment (Day 1) unless otherwise specified.

1. Age (at the time of informed consent): ≥ 20 years
2. Dialysis: Patients on HD or hemodiafiltration (HDF)
3. Use of any ESA:
 - Newly started dialysis (Dialysis newly started < 12 weeks before screening): Patients not using ESAs after the start of dialysis
 - Maintenance dialysis (Dialysis started ≥ 12 weeks before screening): Patients not using ESAs within 8 weeks before screening [including patients who are on treatment/interruption of ESA therapy and planned to interrupt ESA therapy for at least 8 weeks prior to Screening exam (at the time of informed consent)]
4. Hemoglobin (Hgb): ≥ 8.0 to < 10.0 g/dL [measured using a point-of-care Hgb measurement device (HemoCue) at the study site on Day 1]
5. Iron parameter: Ferritin > 100 ng/mL or TSAT $> 20\%$ (at screening only)
6. Gender (at screening only): Female or male

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

- 1) Females of non-reproductive potential defined as:
 - Pre-menopausal with one of the following and no plans to utilise assisted reproductive techniques (e.g., in vitro fertilisation or donor embryo transfer):
 - documented bilateral tubal ligation or salpingectomy
 - documented hysteroscopic tube occlusion procedure with follow-up confirmation of bilateral tubal occlusion
 - documented hysterectomy
 - documented bilateral oophorectomy
 - Post-menopausal 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 simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause is confirmatory (the reference values are provided separately)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue

their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

- 2) Females of reproductive potential who agree to follow one of the options listed in the “GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (Section 12.3.)” from 28 days before the first dose of study treatment until completion of the follow-up visit.
7. Informed consent: Subjects who can provide written informed consent to the study, involving compliance with the requirements and patient responsibilities stated in the consent form and the protocol, as described in Section 10.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply at provisional enrollment (Screening) or formal enrollment (Day 1) unless otherwise specified.

CKD related criteria

1. Kidney transplant: Planned living kidney transplant during the study period

Anemia-related criteria

2. Aplasia: History of bone marrow aplasia or pure red cell aplasia
3. Other causes of anemia: Pernicious anemia, thalassaemia, sickle cell disease, or myelodysplastic syndrome
4. Gastrointestinal bleeding: Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease or clinically significant gastrointestinal bleeding within 8 weeks before screening or during a period from screening to Day 1.

Cardiovascular disease-related criteria

5. History of myocardial infarction, acute coronary syndrome, stroke or transient ischemic attack: Diagnosed within 8 weeks before screening or during a period from screening to Day 1.
6. Heart failure: Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system
7. Q-T Interval Corrected for Heart Rate (QTc) (at screening only): $QTc > 500$ msec, or $QTc > 530$ msec in subject with bundle branch block
Note: Corrected QT interval using Bazett's formula (QTcB) (machine-read or manually) will be used.

Other disease-related criteria

8. Liver disease (if any of the following occurs):
 - (Screening verification only): Alanine Aminotransferase (ALT) > 2 x upper limit of normal (ULN)
 - (Screening verification only): Bilirubin > 1.5 x ULN (If bilirubin fractions are measured and direct bilirubin is $< 35\%$, isolated bilirubin > 1.5 x ULN will be acceptable.)

- 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.
9. Malignancy: History of malignancy within the two years prior to screening, known complex kidney cyst > 3 cm (II F, III or IV based on the Bosniak classification) or currently receiving treatment for cancer.
Note: The only exception is squamous cell or basal cell carcinoma of the skin that has been definitively treated \geq 8 weeks before screening.

Concomitant medications and other study treatment-related criteria

10. Iron medication: Planned use of any intravenous iron preparation during the screening period or from Day 1 to Week 4
Note:
- Patients on oral iron may be enrolled if the iron dose regimen is unchanged during the screening period and from Day 1 to Week 4.
 - Patients on anti-hyperphosphatemia medication containing iron (e.g., ferric citrate hydrate) for at least 12 weeks before screening may be enrolled if the medication is continued during the screening and from Day 1 to Week 4.
11. Severe allergic reactions: History of severe allergic or anaphylactic reactions or hypersensitivity to any excipients in the investigational product (see GSK1278863 Investigator's Brochure)
12. Drugs and dietary supplements: Current use of prohibited prescription drugs, non-prescription drugs, or dietary supplements or planned use of any of these drugs during the study period (prohibited drugs: strong Cytochrome P450 (CYP2C8) inducers and inhibitors; see Section 6.10.2.)
13. Exposure to any other investigational product: Use of an investigational product within the past 30 days or five half lives of that investigational product (whichever is longer).
14. Prior treatment with GSK1278863: Prior treatment with GSK1278863 for > 30 days

General health-related criteria

15. Other conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial, but are not subsequently officially enrolled in the study. A minimum set of information including Demography, Screen Failure details, Eligibility Criteria, and SAEs is required from screen failure subjects 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. In the rescreening case, the re-exams of the ophthalmology at the rescreening are not required if the investigator judges it appropriate to use the previous screening result (see Table 6).

5.4. Withdrawal Criteria

If subjects meet one of the following criteria, study treatment should be permanently discontinued and 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 (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.”

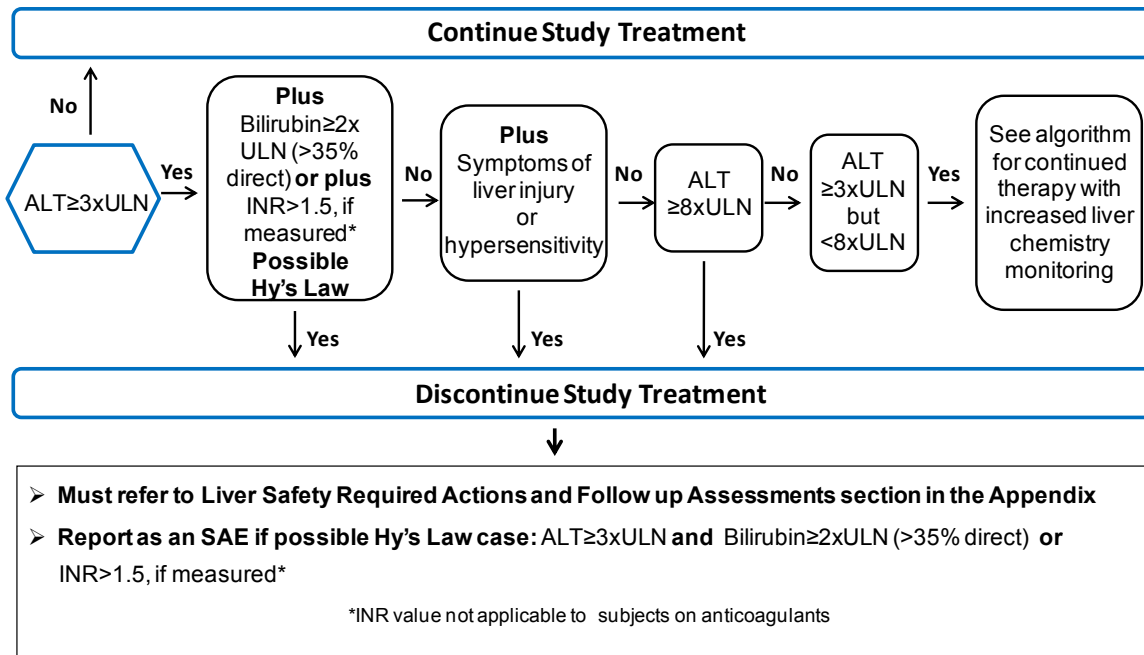
A subject may withdraw from the study at any time at his/her own request. The investigator (or subinvestigator) may withdraw a subject from the study at any time for safety or compliance reasons or study conduct considerations. If a subject withdraws from the study, he/she may request destruction

of any clinical samples taken, and the investigator (or subinvestigator) must document this in the site study records.

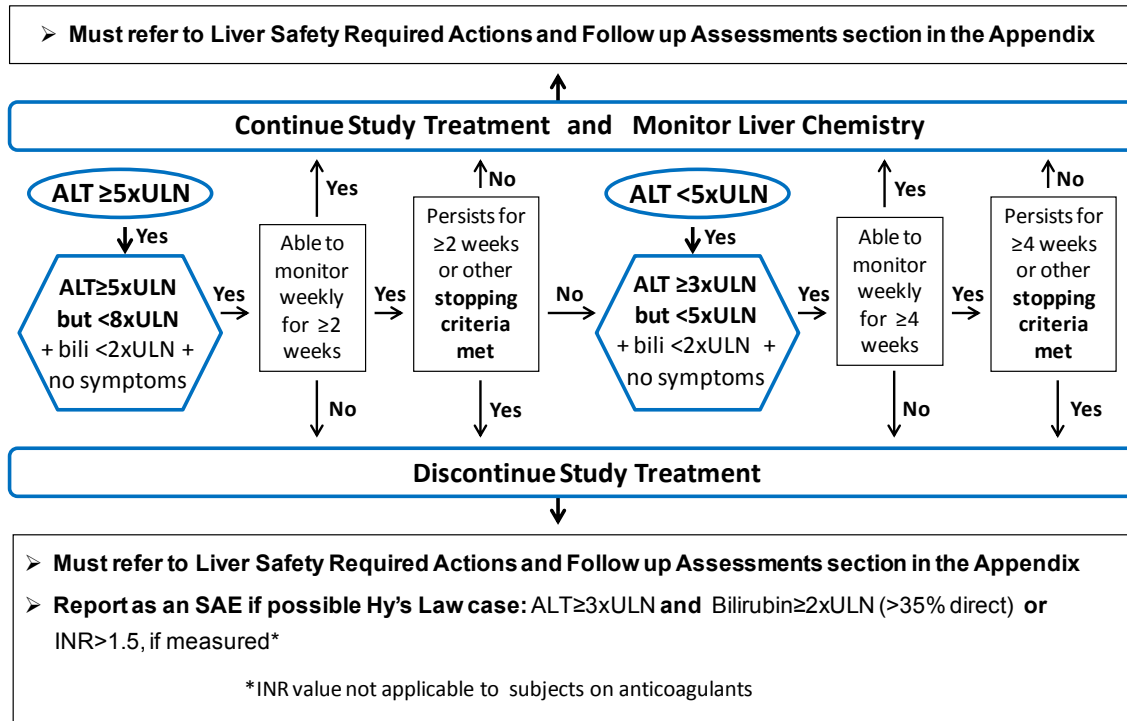
5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [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 can be found in Section 12.5.

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.

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 hemodialysis. The administration schedule (starting dose and dose adjustment) described in Section 6.3. 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.

6.2. Treatment Assignment

This is an open-label, non-comparative study. All eligible subjects will take GSK1278863. Refer to Study Reference Manual (SRM) regarding details such as allocation of randomization number.

6.3. Treatment Schedule

Starting dose (Day 1 to Week 4)

In the Japanese HD patients not using ESAs enrolled in the study, oral administration of GSK1278863 once daily at the starting dose of 4 mg will be started (Day 1), and continued until the day of Week 4.

Maintenance Dose (Week 4 to Week 24)

From Weeks 4 to 24, interruption of treatment or dose adjustments will be made within the maintenance dose range of 1-24 mg (Table 4) according to the dose adjustment algorithm (Table 5) to achieve and/or maintain Hgb within the target range (10.0-12.0 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 4 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 5 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 12.0 g/dL Resume treatment at the one lower dose level (resume treatment at 1 mg once the one-step dose increase criteria are met, if interrupted at 1 mg) |
| 12.0-13.0 | NA | One-step dose reduction |
| 10.0-<12.0 | >2.0 | One-step dose reduction |
| | ≤2.0 | Continue treatment at the current dose level |
| 7.5-<10.0 | >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 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 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 GSK1278863 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 an information related to 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

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).

6.8. Treatment of Study Treatment Overdose

In 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 this is not an effective method 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 CV events, increased heart rate and hematologic abnormalities.

6.9. Treatment after the End of the Study

Since the target disease studied is not life-threatening or severely debilitating and there are alternative treatments for the target disease, subjects will not receive any additional treatment from GSK after completion of the study. Regardless of whether the sponsor provides specific treatments after 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.

6.10. 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. 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). Refer to SRM for further details.

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 (Hemocue).

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 should 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)

Use of the following drug; from HD induction until the end of the treatment period for newly started dialysis, from 8 weeks prior to screening until the end of the treatment period for maintenance HD:

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

6.11. Supplemental Iron Therapy

Supplemental iron therapy will be administered if ferritin is ≤ 100 ng/mL and TSAT is $\leq 20\%$, according to the Guidelines for Renal Anemia [Tsubakihara, 2010]. The investigator (or subinvestigator) should 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

Time and Events Tables are provided in Table 6 and Table 7 for the overall study and for pharmacokinetic assessments. For subjects on dialysis twice or more per week, throughout the study period, including the screening, treatment and follow-up periods, the study visit days should occur on the first dialysis session day of the week (e.g., if Monday-Wednesday-Friday schedule, the study visit should be on Monday). Visit days are counted from the day of first dose of study treatment (Day 1). To allow for a flexible schedule, the allowable window for Screening Visit will be “4 weeks \pm 7 days prior to Day 1”, and that for the visits after Day 1 will be “ \pm 3 days”. In any case, the study visit should occur on the first dialysis session day of the week. Unless otherwise specified, all assessments should occur before dialysis on the day.

Table 6 Time and Events Table

| Period | Screening | | Treatment | | | | | | | | Follow-up |
|---|-----------|-----------------|-----------|--------|----------|---------|----------|----------|---------|--------------------------------|---|
| | | Week -4 | Day 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Early withdrawal ¹⁰ | 2-4 weeks after Week 24 or early withdrawal |
| Visits All assessments pre-dialysis, unless noted. | | | | | | | | | | | |
| Allowable window (days) | | ±7 | - | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | - | ±3 |
| Informed consent | X | | | | | | | | | | |
| Inclusion/exclusion | | X | X | | | | | | | | |
| Medical history, demography, height, body weight ¹ | | X | | | | | | | | | |
| Interactive Web Recognition System (IWRS) call | | X | X | X | X | X | X | X | X | X | X |
| Study medication dispensing ² | | | X | X | X | X | X | X | | | |
| Study medication compliance | | | | X | X | X | X | X | X | X | |
| Vital signs (before and after dialysis) ³ | | X | X | X | | X | | | X | X | X |
| Ophthalmology examination ⁴ | | X ¹¹ | | | | ↔ | | ↔ | ↔ | | |
| ECG | | X | | | | X | | | X | | |
| HemoCue Hgb | | | X | X | X | X | X | X | X | | |
| Hematology | | X ¹² | X | X | Hgb only | X | Hgb only | Hgb only | X | X | X |
| Clinical chemistry | | X | X | X | | X | | | X | X | X |
| Ferritin, TSAT | | X | X | X | | X | | | X | X | |
| Serum iron, TIBC, Unsaturated iron Binding Capacity (UIBC), serum transferrin, hepcidin | | | X | X | | X | | | X | X | |
| Serum pregnancy test ⁵ | | X | X | X | | X | | | X | X | X |
| Estradiol ⁵ , FSH ⁶ | | X | | | | | | | | | |
| Pharmacokinetics ⁷ | | | | | | X | | | X | | |
| Intact Parathyroid Hormone (iPTH) | | | X | X | | X | | | X | | |
| Genetics sample ⁸ | | | X | | | | | | | | |
| Adverse event assessment ⁹ | | | ↔ | | | | | | | | |
| Concomitant medication assessment | | ↔ | | | | | | | | | |

1. Body weight is measured after dialysis.
2. If a subject visit the study site only to receive study medication, only the IWRS call, study medication dispensing, and study medication compliance will be required.
3. At visits without dialysis, only one measurement of each parameter will be obtained.
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 20-24 (inclusive)
 - Early study medication discontinuation or study withdrawal: withdrawal eye exam as close to the last dose as possible. Re-conduct is not required if the exam is conducted within two weeks prior to withdrawal visit.
5. Only for females of reproductive potential.
6. Only at determination of menopausal status in female subjects (Section 5.1.).
7. See Table 7
8. For optional genetic research, informed consent should be obtained before the specimen collection.
9. See Section 7.4.1.
10. For examination at early withdrawal, the specified assessments should be performed as far as possible.
11. In the rescreening case, the previous result of ophthalmology exam at the screening may be used and the ophthalmology exam at the rescreening is not necessary, if the subject meets all of the following criteria and the investigator judges it appropriate.
 - There were no findings that would suggest a repeat ophthalmology exam performed within the next 3 months at the latest screening ophthalmology exam.
 - Subjects had no new eye-related symptoms or complaints since the latest screening ophthalmology exam until rescreening.
 - The latest screening ophthalmology exam was performed within 3 months prior to anticipated Day 1.
12. Exams should be conducted at least one week after ESA treatment.

Table 7 Blood Sampling Schedule for Pharmacokinetics

| 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 in consideration of 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

CV medical history/risk factors will be assessed (documented in the eCRF) at Screening. 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 (Sections 5.1. and 5.2.).

Full details of baseline assessments are provided in Table 6.

7.3. Efficacy

Efficacy will be assessed according to the Time and Event Table (Table 6).

Hgb concentrations measured by the central laboratory will be 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. Hgb concentrations measured by HemoCue will be used for eligibility (Sections 5.1 and 5.2.), withdrawal (Section 5.4.), and dose adjustment criteria (Section 6.3.).

In addition, assessments of iron metabolism parameters 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 6). 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.

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 7.4.1.3.), at the time points specified in the Time and Events Table (Table 6).
- 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.

- 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.

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.

7.4.1.4. Cardiovascular and Death Events

For any CV events detailed in Section 12.6. and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV 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 (MI), 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.

7.4.4. Vital Signs/Height/Weight

Systolic and diastolic blood pressure and heart rate will be measured before and after dialysis, in sitting or semi-supine position (chair for dialysis is acceptable) after at least 5 minutes rest at each visit. When measuring before dialysis, it should be conducted prior to blood sampling for lab tests. One reading of blood pressure and heart rate will be taken and recorded in the source document and the CRF. Height and weight will be measured at screening visit only. Weight should be measured after dialysis.

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. Measurement method and measurement timing (i.e., before or after dialysis) should be consistent as far as possible during the study period.

At Screening visit when an ECG is performed, two additional ECGs are required if initial ECG indicates prolonged QTcB. The average QTcB value calculated from 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 8, must be conducted in accordance with the Laboratory Manual and Protocol Time and Events Schedule (Table 6). Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and sample collection date. 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 8 Laboratory Assessments

| Laboratory assessment | Parameter | | |
|-----------------------|---------------------------------------|--|---|
| Hematology | Platelet count | RBC indices: | WBC Differential |
| | RBC count | Mean Corpuscular Volume (MCV) | Neutrophils |
| | Reticulocyte count | Mean Corpuscular Hemoglobin (MCH) | Lymphocytes |
| | Hemoglobin | Mean Corpuscular Hemoglobin Concentration (MCHC) | Monocytes |
| | Hematocrit | Red Blood Cell Distribution Width (RDW) | Eosinophils |
| | WBC count | | Basophils |
| Clinical chemistry | Sodium | Aspartate Aminotransferase (AST) | Bicarbonate |
| | Potassium | ALT | Inorganic phosphate |
| | Chloride | Creatinine | Glucose |
| | Calcium (total and albumin-corrected) | Total bilirubin | Direct/indirect bilirubin |
| | Albumin | Urea nitrogen | |
| | Total cholesterol | High Density Lipoprotein (HDL) cholesterol | Low Density Lipoprotein (LDL) cholesterol |
| Iron parameters | Serum Iron | Serum ferritin | Serum transferrin |
| | TIBC | UIBC | TSAT |
| | Hepcidin | | |
| Other laboratory | FSH ¹ | Estradiol ¹ | iPTH |

| | | | |
|-------|------------------------|--|--|
| tests | Serum hCG ² | | |
|-------|------------------------|--|--|

1. Measured in female subjects only to determine the menopausal status (See Section 5.1.)
2. Performed in females of childbearing potential (See Section5.1.)

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 SRM 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

The ophthalmologic examination 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 segment 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. Further details of the procedure are provided in the SRM.

7.5. Pharmacokinetics

Blood samples for PK analysis of GSK1278863 will be collected as outlined in Table 7, 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 SRM. 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 to genetics. 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.

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 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 Reporting and Analysis Plan (RAP). Any deviations from the analyses described in the protocol will be documented in the RAP or the final study report.

9.1. Hypotheses

This single arm study is a study with an aim of an estimation. The primary objective of this study is to evaluate the initial anemia correction of GSK1278863 in HD patients not using ESAs. There will be no hypothesis testing performed in this study. Two-sided 95% confidence intervals will be used for efficacy estimation.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Since the number of HD patients not using ESAs in Japan are limited, the sample size of 22 as enrolled was determined based on feasibility.

The precision of the mean change from baseline in Hgb at Week 4, which is the primary endpoint of this study, will be characterized by the half-width of the 95% confidence interval (distance from the mean to the confidence limit). If 20 subjects receive GSK1278863 up to Week 4 and the standard deviation is 1.5 g/dL, assuming t-distribution, the half-width of the 95% confidence interval for the mean change from baseline in Hgb at Week 4 would be 0.702 g/dL.

9.2.2. Sample Size Sensitivity

Table 9 shows the precision with different sample sizes and different standard deviations.

Table 9 Sample Size Sensitivity

| Sample size | Half-width of the 95% confidence interval (SD=1.0) | Half-width of the 95% confidence interval (SD=1.5) |
|-------------|--|--|
| 17 | 0.514 | 0.771 |
| 20 | 0.468 | 0.702 |
| 22 | 0.443 | 0.665 |

SD = Standard Deviation

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned in 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.

- All Treated Subjects Population

The All Treated Subjects Population will consist of all subjects who received at least one dose of GSK1278863. This population will be used for evaluation of the efficacy, safety and demographic data.

- PK Population

The PK Population will consist of all subjects who received GSK1278863 with the PK samples collected and analyzed.

Additional populations may be defined in the RAP.

9.3.2. Interim Analysis

No interim analysis is planned.

9.3.3. Final Analysis

Once all subjects complete protocol-defined visits, final analysis will be performed after database lock.

9.4. Key Elements of Analysis Plan**9.4.1. Efficacy Analysis****9.4.1.1. Primary Analysis**

The primary analysis is to assess modest increase in Hgb in initial response to GSK1278863 (i.e., Hgb increase by ≤ 2 g/dL after 4 weeks of treatment), on the basis of the mean change from baseline in Hgb at Week 4 as well as the number (%) of subjects by Hgb change from baseline category at Week 4 as the primary efficacy endpoints.

For the change from baseline in Hgb at Week 4, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. The change in Hgb at Week 4 will be classified into different categories (i.e., ≤ -2 , > -2 to -1 , > -1 to 0 , > 0 to 1 , > 1 to 2 , and > 2 g/dL), and the number (%) of subjects in each category will be summarized.

9.4.1.2. Secondary Analysis

The secondary analysis is to assess appropriate control of Hgb within the target range, on the basis of the Hgb mean at Week 24 and the number (%) of subjects with Hgb within the target range as secondary endpoints.

For the Hgb at Week 24, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. The percentage of subjects with Hgb within the target range will be calculated at Week 24, with calculation of exact two-sided 95% confidence interval based on binomial distribution. In addition, the time (in days) to reach the lower target Hgb level (10.0 g/dL) will be calculated in each subject, and summarized descriptively.

Also for other secondary efficacy endpoints, such as iron use and iron metabolism, the data will be summarized descriptively.

9.4.2. Safety Analysis

9.4.2.1. Exposure

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

9.4.2.2. Adverse Events

Adverse events will be classified by System Organ Class and Preferred Term of the MedDRA, and the number and percentage of subjects with each event will be summarized. All adverse events, serious adverse events, adverse events leading to discontinuation of study treatment, and adverse events of special interest will be summarized separately. Similar summary will be provided for adverse events related to GSK1278863.

9.4.2.3. Other Safety Measures

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 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.

9.4.3. Pharmacokinetic Analysis

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

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 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 enough 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 Publicly Available Clinical Trials Registers and Publication

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

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

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

10.8. 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 Julia K, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney International*. 2008;74:791-8.

Tsubakihara Yoshiharu, Nishi Shinichi, Akiba Takashi, et al. 2008 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in Chronic Kidney Disease. *Therapeutic Apheresis and Dialysis*. 2010;14(3):240-75.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

| | |
|---------|--|
| ALT | Alanine Aminotransferase |
| AMD | Age-Related Macular Degeneration |
| AST | Aspartate Aminotransferase |
| AUC | Area Under Curve |
| BCRP | Breast Cancer Resistance Protein |
| CKD | Chronic Kidney Disease |
| Cmax | Maximum Concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CPK | Creatine Phosphokinase |
| CT | Computed Tomography |
| CYP | Cytochrome P450 |
| CV | Cardiovascular |
| DNA | Deoxyribonucleic Acid |
| ECG | Electrocardiogram |
| EPO | Erythropoietin |
| ESA | Erythropoiesis Stimulating Agent |
| FDA | Food and Drug Administration |
| FRP | Females of Reproductive Potential |
| FSH | Follicle Stimulating Hormone |
| GSK | GlaxoSmithKline |
| hCG | Human Chorionic Gonadotrophin |
| HD | Hemodialysis |
| HDF | Hemodiafiltration |
| HDL | High Density Lipoprotein |
| HDPE | High Density Polyethylene |
| Hgb | Hemoglobin |
| HIF | Hypoxia-Inducible Factor |
| HRT | Hormone Replacement Therapy |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| IB | Investigator's Brochure |
| INR | International Normalized Ratio |
| iPTH | Intact Parathyroid Hormone |
| IWRS | Interactive Web Recognition System |
| LDH | Lactate Dehydrogenase |
| LDL | Low Density Lipoprotein |
| MAD | Maximum Acceptable Dose |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| ND | Non dialysis |
| NYHA | New York Heart Association |
| OATP | Organic Anion Transporting Polypeptide |
| PAH | Pulmonary Arterial Hypertension |

| | |
|-------|---------------------------------------|
| PHI | Prolyl Hydroxylase Inhibitor |
| PK | Pharmacokinetic |
| 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 |
| rhEPO | Recombinant Human Erythropoietin |
| RNA | Ribonucleic Acid |
| SD | Standard Deviation |
| SRM | Study Reference Manual |
| TIBC | Total Iron Binding Capacity |
| TSAT | Transferrin Saturation |
| UIBC | Unsaturated iron Binding Capacity |
| ULN | Upper Limit of Normal |
| VEGF | Vascular Endothelial Growth Factor |

Trademark Information

| |
|--|
| Trademarks of the GlaxoSmithKline group of companies |
| None |
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| 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. | <ul style="list-style-type: none"> • 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 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. |
| 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 recombinant human EPO (rhEPO)/ESAs have been associated with an increased risk for death and serious CV 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. | <ul style="list-style-type: none"> • Specific eligibility criteria related to CV risk are outlined in Section 7.4.1.1. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.4.1.4. • These risks have been identified as AEs |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|--|
| | | of special interest and will be monitored instreamly by the internal safety review team throughout the study period. |
| Esophageal and gastric erosions | <p>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.</p> <p>In rodents stomach erosions observed with intravenous and oral administration of GSK1278863.</p> <p>Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg).</p> <p>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.</p> <p>Following review of clinical data received to date, GI erosions have not been identified as a safety concern for GSK1278863.</p> | <ul style="list-style-type: none"> • 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 period. |
| Cancer-related mortality and tumor progression and recurrence | <p>In clinical trials, use of rhEPO in patients with cancer has been associated with increased risk of cancer related morbidity and mortality.</p> <p>Administration of 60 mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p> <p>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.</p> | <ul style="list-style-type: none"> • 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. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|--|--|
| | Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863. | |
| Pulmonary artery hypertension (PAH) | <p>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].</p> <p>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.</p> <p>Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with GSK1278863 5mg or 100 mg has no clinically significant effect on echocardiographically estimated pulmonary artery systolic pressure (PASP) under either normoxic or hypoxic conditions.</p> <p>ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in systolic pulmonary artery pressure (sPAP) in subjects not on dialysis. In hemodialysis subjects, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (GSK Total: 8 [7%]; Control 0) in subjects reaching the sPAP potential clinical importance (PCI) (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs</p> | <ul style="list-style-type: none"> • 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 |
|--|---|---|
| | <p>relative to dialysis day. Additionally, 2 of 3 subjects with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution of sPAP other than discontinuation of study treatment; and there was no dose relationship for subjects meeting the sPAP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863.</p> | |
| Cardiomyopathy | <p>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.</p> <p>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.</p> <p>Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization.</p> <p>ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in left ventricular ejection rate.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863.</p> | <ul style="list-style-type: none"> • 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 | <p>Increases in local (ocular) Vascular Endothelial Growth Factor (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].</p> <p>Administration of 60 mg/kg GSK1278863 to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p> | <ul style="list-style-type: none"> • Ophthalmology exams (defined in Section 7.4.7.) will be performed during screening, at approximately 12 weeks on-study, and at the end of treatment. • These risks have been identified as AEs |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | <p>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.</p> <p>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.</p> <p>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.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for GSK1278863.</p> | <p>of special interest and will be monitored instreamly by the internal safety review team throughout the study period.</p> <ul style="list-style-type: none"> • Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted. |
| Exacerbation of rheumatoid arthritis | <p>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].</p> <p>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.</p> | <ul style="list-style-type: none"> • 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 | <p>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.</p> | <p>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, 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.</p> |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|--|
| | <p>GSK1278863 is an inhibitor of CYP2C8 in vitro, with an IC50 value of 21 μM.</p> <p>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 Breast Cancer Resistance Protein (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).</p> <p>GSK1278863 is an inhibitor of Organic Anion Transporting Polypeptide (OATP)1B1/1B3 in vitro, with IC50 values of 6 μM and 11 μM, respectively. A clinical drug interaction study between 25 mg GSK1278863 with either a CYP2C8 substrate or an OATP1B1/1B3 substrate showed that there is no PK interaction at this dose of GSK1278863.</p> | <p>Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.10..</p> <ul style="list-style-type: none"> Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. <p>Specific guidance for dose adjustment, dose interruption, or discontinuation of GSK1278863 based on achieved Hgb concentrations/changes is provided in Section 6.3.</p> <p>Safety data will be monitored instreamly by the internal safety review team throughout the study period.</p> |

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 FRP

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

1. Contraceptive subdermal implant that meets the product label effectiveness criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 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 product label. 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. 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) |
| International Normalized Ratio (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 |
| Symptomatic³ | 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 |
| <ul style="list-style-type: none"> 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 SAE² 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 <p>MONITORING: <u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform | <ul style="list-style-type: none"> Viral hepatitis serology⁴ 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 dose⁵ 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 |

| | |
|--|--|
| <p>liver event follow up assessments within 24 hrs</p> <ul style="list-style-type: none"> • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended <p><u>For All other criteria:</u></p> <ul style="list-style-type: none"> • 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 | <p>alcohol intake case report form</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • 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 protein 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. |
|--|--|

13. 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.
14. 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
15. 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)
16. 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
17. 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 | <ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject |

| | |
|--|--|
| <p>be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks. OR ALT $\geq 3 \times \text{ULN}$ and $< 5 \times \text{ULN}$ and bilirubin $< 2 \times \text{ULN}$ without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p> | <p>safety.</p> <ul style="list-style-type: none"> • 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 within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT $\geq 5 \times \text{ULN}$ and $< 8 \times \text{ULN}$ to $\geq 3 \times \text{ULN}$ but $< 5 \times \text{ULN}$, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT $< 3 \times \text{ULN}$ and bilirubin $< 2 \times \text{ULN}$, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. |
|--|--|

Reference

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Protein Adducts 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 NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> ALT \geq 3xULN and total bilirubin* \geq 2xULN (>35% direct), or ALT \geq 3xULN and INR** > 1.5. <p>* Serum bilirubin fractionation should be performed if testing is available. If fractionation is</p> |

unavailable and ALT $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN, 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 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 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: Protocol Changes

12.8.1. Amendment 1 — Summary of Changes and Rationale

This is applicable to all study sites.

List of Protocol Changes with Rationale for Each

6.2. Treatment Assignment

Original Text:

This is an open-label, non-comparative study. All eligible subjects will take GSK1278863.

Revised Text:

This is an open-label, non-comparative study. All eligible subjects will take GSK1278863. Refer to Study Reference Manual (SRM) regarding details such as allocation of randomization number.

Reason:

To clarify procedure

7.1. Time and Events Table: Footnote 4

Original Text:

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 20-24 (inclusive)
 - Early study medication discontinuation or study withdrawal: withdrawal eye exam as close to the last dose as possible

Revised Text:

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 20-24 (inclusive)
 - Early study medication discontinuation or study withdrawal: withdrawal eye exam as close to the last dose as possible. Re-conduct is not required if the exam is conducted within two weeks prior to withdrawal visit.

Reason:

To clarify study procedure

7.1. Time and Events Table: Table 6 Time and Events Table, To add footnote 11**Revised Text:**

To add footnote 11 to 'Hematology' at Screening Visit

11. Exams should be conducted at least one week after ESA treatment.

Reason:

To clarify study procedure

7.4.5. Electrocardiogram (ECG)**Original Text:**

At the Day 1 visit when an ECG is performed, two additional ECGs are required if initial ECG indicates prolonged QTcB.

Revised Text:

At the Screening visit when an ECG is performed, two additional ECGs are required if initial ECG indicates prolonged QTcB.

Reason:

To correct an error

12.2. Appendix 2: Risk Assessment: 'Summary of Data/Rationale for Risk' with regards to one of Potential Risk: Pulmonary artery hypertension (PAH)**Original Text:**

- ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in systolic pulmonary artery pressure (sPAP) in subjects not on dialysis. Further interrogation of sPAP data in dialysis subjects is ongoing.

Revised Text:

- ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in systolic pulmonary artery pressure (sPAP) in subjects not on dialysis. In hemodialysis subjects, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (GSK Total: 8 [7%]; Control 0) in subjects reaching the sPAP potential clinical importance (PCI) (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 subjects with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution of sPAP other than discontinuation of study treatment; and there was no dose relationship for subjects meeting the sPAP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat.

Reason:

To update 'Summary of Data/Rationale for Risk' to the latest information

12.2. Appendix 2: Risk Assessment: 'Mitigation Strategy' with regards to one of Potential Risks: Proliferative retinopathy, macular edema, choroidal neovascularization**Original Text:**

- Ophthalmology exams (defined in Section 7.4.7.) will be performed during screening, at approximately 12 weeks 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.

Revised Text:

- Ophthalmology exams (defined in Section 7.4.7.) will be performed during screening, at approximately 12 weeks 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.
- Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted.

Reason:

To clarify procedure to investigate and treat any eye related AESIs

12.5. Appendix 5: Liver Safety Required Actions and Follow up Assessments: 'Follow Up Assessments' of 'Required Actions and Follow up Assessments following ANY Liver Stopping Event'**Original Text:**

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

Revised Text:

For bilirubin or INR criteria:

- 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 protein adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

Reference

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.

Reason:

To clarify procedure of follow-up Assessment

12.8.2. Amendment 2 — Summary of Changes and Rationale

This is applicable to all study sites.

List of Protocol Changes with Rationale for Each**5.1. Inclusion Criteria****Original Text:**

3. Use of any erythropoiesis stimulating agent (ESA):

- Newly started dialysis (Dialysis newly started < 12 weeks before screening): Patients not using ESAs after the start of dialysis
- Maintenance dialysis (Dialysis started \geq 12 weeks before screening): Patients not using ESAs within 8 weeks before screening (including interruption of ESA therapy)

Revised Text:

3. Use of any erythropoiesis stimulating agent (ESA):

- Newly started dialysis (Dialysis newly started < 12 weeks before screening): Patients not using ESAs after the start of dialysis
- Maintenance dialysis (Dialysis started \geq 12 weeks before screening): Patients not using ESAs within 8 weeks before screening [including patients who are on treatment/interruption of ESA therapy and planned to intrupt ESA therapy for at least 8 weeks prior to Screening exam (at the time of informed consent)]

Reason:

To clarify that patients who plan to interrupt ESA therapy for \geq 8 weeks will be included in the maintenance dialysis population

5.3. Screening Failures**Original Text:**

No text

Revised Text:

In the rescreening case, the re-exams of the ophthalmology at the rescreening are not required if the investigator judges it appropriate to use the previous screening result (see Table 6).

Reason:

To clarify the ophthalmology exam procedure at rescreening.

6.9. Treatment after the End of the Study**Original Text:**

Since the target disease studied is not life-threatening or severely debilitating and there are alternative treatments for the target disease, 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.

Revised Text:

Since the target disease studied is not life-threatening or severely debilitating and there are alternative treatments for the target disease, subjects will not receive any additional treatment from GSK after completion of the study. Regardless of whether the sponsor provides specific treatments after 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.

Reason:

To correct an error.

7.1. Time and Events Table: Table 6 Time and Events Table, To add additional row for screening and move 'informed consent' to the left low**Reason:**

To clarify the informed consent process.

7.1. Time and Events Table: Table 6 Time and Events Table, To add footnote 11**Revised Text:**

11. In the rescreening case, the previous result of ophthalmology exam at the screening may be used and the ophthalmology exam at the rescreening is not necessary, if the subject meets all of the following criteria and the investigator judges it appropriate.

- There were no findings that would suggest a repeat ophthalmology exam performed within the next 3 months at the latest screening ophthalmology exam.
- Subjects had no new eye-related symptoms or complaints since the latest screening ophthalmology exam until rescreening.
- The latest screening ophthalmology exam was performed within 3 months prior to anticipated Day 1.

Reason:

To clarify the ophthalmology exam procedure at rescreening.

7.4.6. Clinical Laboratory Assessments

Original Text:

| | |
|------------------------------------|---------------------------------|
| Laboratory assessment ⁺ | |
| Hematology ⁺ | Platelet count ⁺ |
| | RBC count ⁺ |
| | Reticulocyte count ⁺ |
| | Hemoglobin ⁺ |
| | Hematocrit ⁺ |
| | ⁺ |

Revised Text:

| | |
|------------------------------------|---------------------------------|
| Laboratory assessment ⁺ | |
| Hematology ⁺ | Platelet count ⁺ |
| | RBC count ⁺ |
| | Reticulocyte count ⁺ |
| | Hemoglobin ⁺ |
| | Hematocrit ⁺ |
| | WBC count ⁺ |

Reason:

To correct an error.

12.6.6. Reporting of SAEs to GSK

Original Text:

- 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,

Revised Text:

- 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,

Reason:

To reflect amendment of procedure.

12.8.3. Amendment 3 — Summary of Changes and Rationale

This is applicable to all study sites.

List of Protocol Changes with Rationale for Each**Sponsor Signatory:****Original Text:**

Hiromu Nakajima

Head,

Medicines Development,

Japan Development and Medical Affairs (JDMA),
GlaxoSmithKline K. K.

Revised Text:

Kihito Takahashi

Director

Japan Development and Medical Affairs (JDMA),
GlaxoSmithKline K. K.

Reason:

To reflect change of Sponsor Signatory.

Emergency Contact**Original Text:**

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.

Revised Text:

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.

Reason:

To reflect change of company name.

5.2. Exclusion Criteria

Original Text:

8. Liver disease (if any of the following occurs):
- ALT > 2 x upper limit of normal (ULN)
 - Bilirubin > 1.5 x ULN (If bilirubin fractions are measured and direct bilirubin is < 35%, isolated bilirubin > 1.5 x ULN will be acceptable.)

Revised Text:

8. Liver disease (if any of the following occurs):
- (Screening verification only): ALT > 2 x upper limit of normal (ULN)
 - (Screening verification only): Bilirubin > 1.5 x ULN (If bilirubin fractions are measured and direct bilirubin is < 35%, isolated bilirubin > 1.5 x ULN will be acceptable.)

Reason:

To clarify the timing of eligibility assessment regarding exclusion criteria.

6.10.2. Prohibited Medications and Non-Drug Therapies

Original Text:

None

Revised Text:

Use of the following drug; from HD induction until the end of the treatment period for newly started dialysis, from 8 weeks prior to screening until the end of the treatment period for maintenance HD:

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

Reason:

To clarify that there is a limitation to use erythropoietin.

7.1. Time and Events Table

Original Text:

Unless otherwise specified, all assessments should occur before dialysis on the day.

Revised Text:

In any case, the study visit should occur on the first dialysis session day of the week. Unless otherwise specified, all assessments should occur before dialysis on the day.

Reason:

To clarify study proceduer.

7.4.2. Adverse Events of Special Interest**Original Text:**

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Death, myocardial infarction (MI), stroke, venous thromboembolism, thrombosis of vascular access
- Cardiomyopathy
- Pulmonary artery hypertension
- Cancer-related mortality and tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of inflammatory joint disease (e.g., rheumatoid arthritis)

Revised Text:

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Death, myocardial infarction (MI), 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

Reason:

To edit to correct text.

12.2. Appendix 2: Risk Assessment: ‘Mitigation Strategy’ with regards to one of Potential Risks: Drug-drug interactions**Original Text:**

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.

Revised Text:

Safety data will be monitored instreamly by the internal safety review team throughout the study period.

Reason:

To edit to correct text.

12.8.4. Amendment 4 — Summary of Changes and Rationale

This is applicable to all study sites.

List of Protocol Changes with Rationale for Each**1. PROTOCOL SYNOPSIS FOR STUDY PHI204716****Original Text:**

For the change from baseline in Hgb at Week 4, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. The change in Hgb at Week 4 will be classified into different categories (i.e., <-2, -2 to -1, -1 to 0, 0 to 1, 1 to 2, and >2 g/dL), and the number (%) of subjects in each category will be summarized.

Revised Text:

For the change from baseline in Hgb at Week 4, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. The change in Hgb at Week 4 will be classified into different categories (i.e., ≤-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, and >2 g/dL), and the number (%) of subjects in each category will be summarized.

Reason:

To update of the category for Hgb change from baseline at Week 4.

5.3. Screening Failures**Original Text:**

Screen failures are defined as subjects who consent to participate in the clinical trial and are screened, but are not subsequently officially enrolled in the study.

Revised Text:

Screen failures are defined as subjects who consent to participate in the clinical trial, but are not subsequently officially enrolled in the study.

Reason:

To change for definition of screen failures.

5.4. Withdrawal Criteria**Original Text:**

- Need for chronic (more than 14 days) use of prohibited medication

Revised Text:

- Need for chronic (more than 14 days) use of prohibited medication (strong inhibitors/ inducers of CYP2C8 meet this criteria)

Reason:

To clarify the withdrawal criteria for prohibited medication.

6.8. Treatment of Study Treatment Overdose**Original Text:**

No text

Revised Text:

In this study, an overdose of GSK1278863 is defined as any dose greater than the highest daily dose included in the protocol.

Reason:

To clarify the definition of overdose of GSK1278863.

7.4.2. Adverse Events of Special Interest**Original Text:**

- Death, myocardial infarction (MI), stroke, congestive heart failure, venous thromboembolism, thrombosis of vascular access

Revised Text:

- Death, myocardial infarction (MI), stroke, heart failure, thromboembolic events, thrombosis of vascular access

Reason:

To update AESI.

9.3.2. Interim Analysis**Original Text:**

No interim analysis is planned with the statistical aspects. However, since this study will be considered as Primary Completion Achieved when 4-week dosing is completed in all subjects, an analysis is will be performed based on all collected data.

Revised Text:

No interim analysis is planned

Reason:

To cancel the interim analysis.

9.4.1.1. Primary Analysis**Original Text:**

For the change from baseline in Hgb at Week 4, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. The change in Hgb at Week 4 will be classified into different categories (i.e., <-2, -2 to -1, -1 to 0, 0 to 1, 1 to 2, and >2 g/dL), and the number (%) of subjects in each category will be summarized.

Revised Text:

For the change from baseline in Hgb at Week 4, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. The change in Hgb at Week 4 will be classified into different categories (i.e., ≤-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, and >2 g/dL), and the number (%) of subjects in each category will be summarized.

Reason:

To update of the category for Hgb change from baseline at Week 4.

12.2. Appendix 2: Risk Assessment: Potential Risk of Clinical Significance**Original Text:**

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)

Revised Text:

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)

Reason:

To update AESI.