

## TITLE PAGE

**Division:** Worldwide Development  
**Information Type:** Protocol Amendment

<b>Title:</b>	A repeat-dose, open-label, parallel-group study to assess the pharmacokinetics of GSK1278863 and metabolites in subjects with End Stage Renal Disease undergoing peritoneal dialysis
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**Compound Number:** GSK1278863

**Development Phase:** I

**Effective Date:** 20-JUN-2016

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**Author (s):**

PPD

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## Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2013N179529_00	2014-APR-11	Original
2013N179529_01	2014-JUN-06	Amendment No. 1
<p>Section 4.2.1. Inclusion Criteria, Inclusion#8; hemoglobin levels are updated based on the feedback received from FDA. It was <math>\leq 11</math> g/dL for ESA naïve subjects, it is updated as <math>&lt; 10.0</math> g/dL; it was <math>\leq 12.0</math> g/dL for subjects receiving ongoing ESA treatment, it is updated as <math>\leq 11.0</math> g/dL.</p> <p>Section 4.2.2. Exclusion Criteria, the numbering of exclusion criteria was inadvertently incremented from previous section. The numbering now starts from “1”.</p> <p>Section 5.3.3. Stopping Criteria; the stopping criteria related to the hemoglobin level is updated per the FDA’s feedback received. A previous criterion required subjects to have their absolute hemoglobin level <math>\geq 13.0</math> g/dL to stop the dosing. The hemoglobin level for stopping the dosing is now updated as <math>&gt; 11.0</math> g/L.</p> <p>Section 6.1. Time and Events Table, Protocol Activity “Urine Drug and Alcohol Screen” is updated as “Drug and Alcohol Screen” with a new footnote “m”. Majority of subjects with ESRD undergoing peritoneal dialysis will not be able to produce urine samples. For these subjects this screening test will be serum-based.</p> <p>Section 6.3.2. Vital Signs; body temperature measurement was not included under vital signs assessment. It is now included as a part of vital signs assessment since it is a measurement performed as a standard practice at the site. Section 6.3.3. Electrocardiogram (ECG), instruction for Day -1 ECG measurement is updated as it indicated that ECG measurement should be done 2 h prior to dosing. The first dosing day is Day 1, and there will be no ECG measurement on the dosing day. This is now corrected.</p>		
2013N179529_02	2014-JUN-24	Amendment No. 2
<p>Section 6.1. Time and Events Table, Footnote m is revised to make the Drug and Alcohol test type flexible. At screening and on Day -1, this test would have been performed urine based or alternatively serum based. However, it was recognized that each site has their standard tests for this assessment. At the discretion of the investigator, sites will be able to use their standard test in order to ensure that the test results will be ready for an evaluation prior the dosing. Test will also be performed on Day 13.</p> <p>Section 6.1. Time and Events Table, a new footnote, footnote n, is included to clarify how hemoglobin can be assessed on Day 3, Day 7, and Day 11 visits.</p>		
2013N179529_03	2014-JUL-01	Amendment No. 3
<p>Section 4.2.2., Inclusion and Exclusion Criteria, the numbering of each criterion was inadvertently changed starting from subtitles “Efficacy” and “Other”. After subtitle</p>		

“Safety”, the numbering was not consecutively increasing for the remaining inclusion and exclusion criteria. The inclusion and exclusion criteria numbers were changed to be consecutive. Inclusion criteria numbers now starts from 1 and goes up to 12, exclusion criteria numbers start from 1 and goes up to 28.

Section 4.3.3. Caffeine, Alcohol, and Tobacco, the word “sample” was missing after the word “the final pharmacokinetic” in the last part of the first sentence, this is now included.

2013N179529\_04

2014-DEC-12

Amendment No. 4

List of Abbreviations, the abbreviation for kilocalorie, kcal, is listed as it is now included in the text.

Regulatory Agency Identifying Number(s), the EudraCT number was inadvertently provided as 2013-002681-39 which belongs to phase II program of this compound. The EudraCT number is now updated as “2014-001197-34” with this amendment which is the correct number for this specific protocol.

Section 4.2.1 Inclusion Criteria, Efficacy, inclusion criteria#5; the urine output and Kt/V values were revised for subject’s eligibility after study investigators provided further information gathered about these conditions for the subjects who are on peritoneal dialysis.

Section 4.2.1. Inclusion Criteria, Efficacy, inclusion#8; hemoglobin levels are updated to meet with country specific requirements. **For UK only site(s)**, hemoglobin value is updated as  $\leq 11$  g/dL for ESA naïve subjects and as  $\leq 12.0$  g/dL for subjects receiving ongoing ESA treatment.

Section 5.3.3. Stopping Criteria; the stopping criteria related to the hemoglobin level is updated to meet with country specific requirements. **For UK only site(s)**, stopping criteria for absolute hemoglobin level now is  $\geq 12.0$  g/dL to stop the dosing.

Section 4.2.2. Exclusion Criteria, Safety, exclusion criteria#15; it was revised to be flexible for those subjects who have not received their ophthalmology exam within 12 months prior to Screening, so they may take their exam with a referral from the study investigators during Screening period.

Section 4.3.2 Meals and Dietary Restrictions; it was stated that subjects would not consume any food and drinks (except water) during 4 h fasting period after dosing on Day 1 and Day 14. Based on the initial feedback from one of study sites, some subjects on peritoneal dialysis are very hungry after they finish night portion therapy on peritoneal dialysis cyler. This is most likely due to the relatively high insulin dose required to mitigate high dextrose content in the peritoneal dialysis fluid needed to achieve adequate ultrafiltration. Thus this section was revised to allow subjects to have a light snack and a beverage which would not exceed 500 kcal during this 4 h fasting period after dosing.

Section 6.4.2. Dialysate Sample Collection, on Day 1 and Day 14, the volume of dialysate solution to be collected for analysis was specified as 10 mL aliquot. This is revised to 1.5 mL as 10 mL aliquot would have exceeded the required amount for the pharmacokinetic analysis.

Section 6.1, Time and Events Table, there was a typo error on the Day of Follow-up visit.

It was entered as Day 23. This is now corrected as Day 22.		
2013N179529_05	2014-DEC-15	Amendment No. 4 (Republishing)
The abbreviation “PD” included in Revision Chronology in 2013N179529_04 was required to change to “peritoneal dialysis” as “PD” in this protocol refers to “Pharmacodynamic”. The abbreviation “PD” in this section could have been misinterpreted if it was left as is. Thus, Amendment No. 4 was republished with this update in order to prevent any confusions.		
2013N179529_06	2015-SEP-10	Amendment No. 5
<p>This protocol amendment is to clarify several sections of protocol text and to confirm that there will be informal reviews of the available PK data to assist Phase III development of the compound. Additionally, if during the informal review of the available PK data it is determined that there are no clinically-significant differences in PK between the CAPD and APD populations, the planned number of subjects may be reduced. All changes are detailed in Appendix 5.</p> <p>In order to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Section 4.4 has subsequently been updated to document that screen failure information is being collected. The analysis populations (Section 9.3.1) have also been expanded to clarify the screen failure population.</p> <p>Wording in Section 4.3.2 has been amended to clarify the duration for which subjects need to avoid consumption of red wine, grapefruit (juice), blood orange (juice), star fruit, onions, kale, broccoli, green beans, or apples, specifically are all prohibited from <b>7 days prior to the first dose</b> of GSK1278863 until the Follow-Up visit, unless in the opinion of the investigator and GSK Medical Monitor this will not interfere with the study procedures and compromise subject safety</p> <p>Wording in Section 5.10 has been amended to ensure the text is current regarding use of concomitant medications.</p> <p>The following protocol sections were updated accordingly:  Section 4.1, Section 4.3.2, Section 5.10, Section 9.3.1, Section 9.3.2. Section 11, Appendix 5</p>		
2013N179529_07	2016-JUN-20	Amendment No. 6
This protocol amendment is to reduce the number of subjects in the study (either cohort) to a total of 8 completed subjects. This study has been active for 2 years and only 6 (1 CAPD and 5 APD) subjects have completed the study. Given the recruitment challenges in general, and the CAPD population in particular, the protocol was amended to enroll ESRD subjects undergoing peritoneal dialysis from either the CAPD or APD population.		

**SPONSOR SIGNATORY**

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20 June 2016

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IND Number: 101, 291

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**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number 200942:

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

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

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

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

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## LIST OF ABBREVIATIONS

$\beta$ -HCG	Beta-Human Chorionic Gonadotropin
$\mu$ g	Microgram
$\mu$ L	Microliter
AB	Antibody
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AMD	Age-related macular degeneration
APD	Automated peritoneal dialysis
AST	Aspartate aminotransferase (SGOT)
AUC(0- $\infty$ )	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0- $\tau$ )	Area under the concentration-time curve over the dosing interval
BCRP	Breast Cancer Resistance Protein
BP	Blood pressure
BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal dialysis
CI	Confidence Interval
CKD	Chronic kidney disease
CLCR	Creatinine clearance
CL <sub>r</sub>	Renal clearance
C <sub>max</sub>	Maximum observed concentration
CO <sub>2</sub>	Carbondioxide
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Coefficient of variance
CYP	Cytochrome P450 enzyme
C <sub><math>\tau</math></sub>	Pre-dose (trough) concentration at the end of the dosing interval
DILI	Drug Induced Liver Injury
dL	decilitre
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
EGLN	Egg-laying deficiency protein nine-like protein
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
ESRD	End stage renal disease
FDA	Food and Drug Administration
Fe	Iron
FSH	Follicle Stimulating Hormone
g	Gram
GCP	Good Clinical Practice

GGT	Gamma glutamyl transferase
GI	Gastro intestine
GSK	GlaxoSmithKline
h	Hour(s)
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HDD	Hemodialysis-dependent
HIF	Hypoxia-inducible factor
HIV	Human Immunodeficiency Virus
HR	Heart rate
HRT	Hormone replacement therapy
HWE	Hardy-Weinberg Equilibrium
IB	Investigator's Brochure
IC <sub>50</sub>	Half maximal inhibitory concentration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
IUS	Intrauterine system
K	Dialyzer clearance of urea
kcal	kilocalorie
KDOQI	Kidney Disease Outcomes Quality Initiative
Kg	Kilogram
L	Liter
LFTs	Liver function tests
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
Mg	Milligrams
mL	Milliliter
mmHg	Millimeters of mercury
MSDS	Material Safety Data Sheet
msec	Milliseconds
NDD	Non-dialysis dependent
NKF	National Kidney Foundation
nM	nanomolar
NOAEL	No observed adverse effect level
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association

OATP	Organic anion transporting polypeptide
°C	Celsius
°F	Fahrenheit
PD	Pharmacodynamic
pg	picogram
PGx	Pharmacogenetics
PHD	prolyl -4- hydroxylases
PK	Pharmacokinetic
pmol	picomoles
QTc	Corrected QT interval
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
R&D	Research and Development
RBC	Red blood cells
rhEPO	Recombinant erythropoietin
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPM	Study Procedures Manual
t	time
t <sub>1/2</sub>	Terminal phase half-life
TIBC	Total iron binding capacity
t <sub>max</sub>	Time of occurrence of C <sub>max</sub>
UK	United Kingdom
ULN	Upper limit of normal
US	United States
V	volume
WBC	White blood cells
μM	micromolar
τ	Dosing interval

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## 1. INTRODUCTION

### 1.1. Rationale

#### 1.1.1. Study Rationale

The purpose of this study is to characterize the pharmacokinetics (PK) of GSK1278863 and its metabolites in subjects with End Stage Renal Disease (ESRD) undergoing peritoneal dialysis, one of the target populations for Phase 3 studies.

Peritoneal dialysis represents a treatment modality for subjects with ESRD as an alternative to hemodialysis for removal of waste from the blood normally eliminated by the kidneys. Although peritoneal dialysis may allow greater freedom for subjects with ESRD to carry out normal activities of life, it is potentially less efficient at removing these wastes. In particular, subjects undergoing peritoneal dialysis have different clearances of waste products that can affect the disposition of drugs. As GSK1278863 is to be administered to anemic subjects with ESRD undergoing peritoneal dialysis, it is important to characterize the PK in this target patient population.

One modality of peritoneal dialysis is known as Continuous Ambulatory Peritoneal Dialysis (CAPD) and involves 3-5 manual exchanges per day of dialysis solution into the peritoneal cavity with a 4 to 8 hour dwell time. Automated Peritoneal Dialysis (APD) employs an automated peritoneal dialysis device, called cyclor to perform between 4 and 6 exchanges during the night time. Patients may drain completely or have additional dialysis solution fill in the morning after last drain on cyclor. Additional automated or manual exchange may be added during the day.

For the majority of patients, both peritoneal dialysis modalities are considered essentially equivalent, therefore, selection of modality typically is based on patient life style and preference, with APD allowing more free time during the day. As the proportion of peritoneal dialysis patients using either modality is approximately equal globally, it is considered important to enroll ESRD subjects on both CAPD and APD.

*In vitro* pharmacology has shown that all major metabolites of GSK1278863 are pharmacologically active and show  $pIC_{50s} > 8$  (<10 nM), comparable to the parent compound GSK1278863 for human prolyl -4- hydroxylases (PHDs). Therefore, there is the potential that the metabolites also may contribute to the clinical pharmacodynamics (PD) and therapeutic activity of GSK1278863. While a previous clinical study of GSK1278863 in subjects with impaired renal function had demonstrated that parent GSK1278863 has similar pharmacokinetic characteristics to subjects with normal renal function (Study PHI112843). Preliminary PK data suggests that the major metabolites of GSK1278863 have prolonged half-lives compared to parent GSK1278863, with some metabolites accumulating upon repeat-dose administration in subjects with chronic kidney disease (CKD; Study PHI115573). Full PK profiles of GSK1278863 and metabolites have not been collected following repeat-dose administration to the ESRD population undergoing peritoneal dialysis; therefore, the purpose of this study is to fully characterize the PK of GSK1278863 and metabolites following repeat-dose administration to this population. This open-label study will evaluate the PK of parent

GSK1278863 and metabolites in two cohorts of ESRD subjects undergoing peritoneal dialysis.

The effective date of the original protocol is 11-APR-2014. In the 2 years that the study has been active, only 6 subjects have completed the study. This includes 1 CAPD and 5 APD subjects. Considering the difficulties with recruitment in general, and the CAPD population in particular, this protocol will be amended to enroll ESRD subjects undergoing peritoneal dialysis of either modality (i.e., CAPD or APD). In addition, in a previous study (PHI115573), the pharmacokinetic properties of daprodustat and the predominant metabolites were able to be adequately characterized in an ESRD population undergoing hemodialysis with 8 subjects. Finally, preliminary results from this study has shown that a subject using CAPD had similar PK to the 3 subjects using APD suggesting that, if there are differences in the PK of daprodustat depending upon the peritoneal dialysis modality, they are likely to be not considered clinically significant.

## 1.2. Brief Background

Anemia is frequently present in patients with CKD, patients receiving chemotherapy, and patients with various chronic diseases. Anemia may result from several causes, including factors which shorten red blood cell life span, vitamin deficiency, uremia, iron deficiency, inflammation, and insufficient production of erythropoietin (EPO). Erythropoiesis-stimulating agents (ESAs), such as recombinant human erythropoietin (rhEPO), are commonly used in the treatment of patients with anemia, particularly anemia associated with chronic kidney disease.

Under hypoxic conditions, the hypoxia-inducible factor (HIF)-prolyl hydroxylases (PHDs) are inhibited, resulting in the accumulation of unhydroxylated HIF $\alpha$  subunits. These HIF $\alpha$  subunits dimerize with HIF $\beta$  subunits to effect the transcription of HIF-responsive genes, including the gene responsible for the production of EPO and others involved in increasing oxygen utilization (e.g., transferrin, heme oxygenase 1). Other functions regulated by HIFs include iron metabolism and utilization, angiogenesis, extracellular matrix metabolism, apoptosis, energy and glucose metabolism, vascular tone, cell adhesion, and motility ([Haase, 2013](#)).

GSK1278863 is a novel, orally-available, small molecule agent which stimulates erythropoiesis through inhibition of PHDs, mimicking the hypoxic state. This activity leads to increased transcription of HIF-responsive genes including the gene responsible for the production of EPO. This pharmacodynamic activity simulates components of the natural response to exposure to hypoxia.

## 1.3. Clinical Experience to Date

As of 28 August 2015, GSK1278863 has been administered as single oral doses ranging from 2 to 500 mg to 235 healthy, adult male and female subjects in nine completed Clinical Pharmacology and Biopharmaceutical studies (PHX111427, PHI112842, PHI112843, PHI116008, PHI115573, PHI113635, PHI113634, PHI114703, PHI115385)

and administered once daily (15 to 100 mg) or 25 mg twice daily for up to 14 days duration to 20 healthy subjects in completed study PHI112842.

Additionally, oral GSK1278863 has been administered to 234 subjects with CKD. Twelve CKD subjects received two doses of up to 150 mg GSK1278863 (PHI112843). Fourteen CKD subjects received 5 mg GSK1278863 for up to 15 days (PHI115573). Sixty-one non-dialysis dependent (NDD; Stage 3 to 5) and 31 hemodialysis-dependent (HDD; Stage 5) anemic CKD subjects received 10 mg to 100 mg GSK1278863 for up to 28 days in Study PHI112844. Fifty-four subjects with anemia associated with CKD (Stage 3/4/5) who were not taking rhEPO and who were not undergoing dialysis received 0.5, 2 or 5 mg GSK1278863 for up to 28 days (Study PHI116581). Sixty-two Stage 5 HDD subjects with anemia associated with CKD switching from stable rhEPO to GSK1278863 received 0.5, 2 or 5 mg GSK1278863 for up to 28 days (Study PHI116582).

Details of the completed studies, as well as available safety, pharmacokinetic and pharmacodynamic (PD) data, may be found in the Investigator's Brochure (IB) for GSK1278863 [GlaxoSmithKline Document Number [RM2008/00267/07](#)] and associated IB Supplements [GlaxoSmithKline Document Number [2015N266524\\_00](#), 17-Dec-2015; GlaxoSmithKline Document Number [2015N266524\\_01](#), 08-Apr-2016].

## 2. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
<b>Primary</b>	
Characterize the steady-state PK of GSK1278863 and metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13) in ESRD subjects undergoing peritoneal dialysis	<ul style="list-style-type: none"> <li>AUC(0-<math>\tau</math>), AUC(0-<math>\infty</math>) (Day 1 only), and Cmax of GSK1278863 and metabolites on Day 1 and Day 14</li> </ul>
<b>Secondary</b>	
Evaluate the safety and tolerability of GSK1278863 in ESRD subjects undergoing peritoneal dialysis	<ul style="list-style-type: none"> <li>Subject incidence of treatment-emergent adverse events, including clinically-significant changes in physical exams, laboratory safety tests, ECG and vital signs</li> </ul>
Characterize the peritoneal dialysis clearance of GSK1278863 and metabolites in ESRD subjects undergoing peritoneal dialysis	<ul style="list-style-type: none"> <li>Peritoneal dialysis clearance, tmax and t<math>\frac{1}{2}</math> of GSK1278863 and metabolites on Day 1 and Day 14</li> <li>Accumulation ratio and time invariance ratio (as data permit) of GSK1278863 and metabolites</li> </ul>

Objectives	Endpoints
Characterize the plasma profile of erythropoietin and hepcidin after repeat-dose administration of GSK1278863 in ESRD subjects undergoing peritoneal dialysis	<ul style="list-style-type: none"> <li>Erythropoietin and hepcidin plasma concentrations</li> </ul>
<b>Exploratory</b>	
Characterize the plasma protein binding of steady-state GSK1278863 and select metabolites in ESRD subjects undergoing peritoneal dialysis	<ul style="list-style-type: none"> <li>Steady-state GSK1278863 and metabolite unbound concentration and free fraction</li> </ul>
<b>Exploratory</b>	
Characterize the effect of different peritoneal dialysis solutions on GSK1278863 and metabolites in ESRD subjects undergoing peritoneal dialysis	<ul style="list-style-type: none"> <li>Descriptive summary of GSK1278863 and metabolite PK by different peritoneal dialysis solutions utilized</li> </ul>

### 3. STUDY DESIGN

#### 3.1. Study Design Detail

This is a repeat-dose, open label, 2 cohort study to assess the pharmacokinetics of GSK1278863 and metabolites in ESRD subjects undergoing peritoneal dialysis.

GSK1278863 (5 mg) will be orally administered once daily for 14 days to approximately 12 ESRD subjects;

- **Cohort 1** will enrol subjects on continuous ambulatory peritoneal dialysis (CAPD) to complete all dosing and critical assessments
- **Cohort 2** will enrol subjects on automated peritoneal dialysis (APD) to complete all dosing and critical assessments.

Once a total of 8 subjects across both cohorts collectively have completed the trial, enrolment will be stopped and the study will be concluded.

A sufficient number of ESRD subjects undergoing peritoneal dialysis will be enrolled in this study in order to ensure that at least 8 subjects total complete dosing and all critical assessments. However, if during an informal review of available PK data it is determined that the PK appears to be adequately characterized, the planned number of subjects may be reduced.

Blood samples for primary PK assessment will be collected on **Day 1** and **Day 14**.

To determine subject eligibility for enrolment in the study, a screening visit will be performed within 30 days of the start of dosing (prior to Day 1).

Subjects who are deemed eligible and sign the informed consent may remain in residence at the site from the afternoon of Day -1 through the last assessment on Day 17, at the discretion of the investigator or by request of the subject. Subjects will be offered to stay in residence at the study site (inpatient) or they are allowed to remain at home (outpatient) throughout the study. For subjects that choose to participate in the study as an outpatient, they will be released from the clinic and must return to the clinic for scheduled assessments.

At a minimum, study staff must ensure that subjects are in residence at the site on full PK Days (**Day 1** and **Day 14**), as well as on Days 15, and 16 for 48 and 72 h PK sampling.

All subjects are required to return to the unit 8 (+2) days from the last dose of GSK1278863 for a follow-up visit.

### **3.2. Discussion of Study Design**

The purpose of this study is to characterize the pharmacokinetics of GSK1278863 and metabolites in ESRD patients undergoing peritoneal dialysis. To date, GSK1278863 has not been administered to this patient population, and there have been differences in the PK of the metabolites in subjects with CKD (Stage 3/4), both in subjects not on dialysis as well as in subjects undergoing hemodialysis, as compared to subjects with normal renal function.

In this study, subjects will receive GSK1278863 for 14 days. Steady-state parent and metabolite PK have been evaluated after repeat-dose administration of 5 mg GSK1278863 in healthy subjects and subjects with renal impairment (Stage 3/4 NDD and Stage 5 HDD) in Study PHI115573. PK of parent GSK1278863 was generally similar across healthy, NDD, and HDD subjects; slightly (16%) higher AUC was observed in HDD subjects on a dialysis day (GSK1278863 dosed ~2 h prior to dialysis) compared to a non dialysis day.

Compared to healthy subjects, steady-state metabolite exposures were 2.3 to 3.6-fold higher in NDD subjects, 1.8 to 3.3-fold higher in HDD subjects on a dialysis day, and 3.0 to 6.9-fold higher in HDD subjects on a non-dialysis day.

In HDD subjects, metabolites demonstrated 1.7 to 2.3-fold higher exposure on a non-dialysis day compared to a dialysis day. Metabolite PK reached steady-state by 14 days.

Since no placebo treatment group is required in this PK study, an open-label study design will be used.

Plasma biomarker concentrations of on-target effects (erythropoietin and hepcidin) will be obtained to examine the time course of changes in erythropoietin and hepcidin after a 5 mg dose.

Samples for assessment of steady-state plasma protein binding will be collected (3 samples to obtain approximate peak and trough concentrations of GSK1278863 and metabolites, M4 (GSK2487818) and M5 (GSK2506102). Samples (aliquots) from the

peritoneal dialysis fluid (dialysate) will be collected for determination of clearance of GSK1278863 and metabolites at steady-state on Day 14.

### 3.2.1. Dose Rationale

A 5 mg 14-day repeat dose schedule was selected for this study to allow direct comparison to a recent study with a similar study design in subjects with normal, Stage 3/4, and Stage 5 (HDD) renal function (PHI115573).

In previous studies, single oral doses of 50 mg and 150 mg, and repeat oral doses between 0.5 mg and 100 mg for up to 28 days have been well tolerated in subjects with CKD.

In a prior Phase IIa study, GSK1278863 was administered to Stage 5 HDD subjects who had been on rhEPO and switched to doses of 0.5 mg, 2 mg or 5 mg (Study PHI116582). In the study, switching from rhEPO to 5 mg GSK1278863 had a similar effect on maintaining Hgb over 4 weeks as continuing rhEPO. To avoid a potential rapid increase in hemoglobin that has been observed with repeat doses > 10 mg, a 5 mg dose is appropriate for PK investigation in this study.

Further, in a study (PHI115573) conducted in subjects with various stages of CKD, no safety concerns were found with a 5 mg oral dose.

Finally, a 5 mg dose is anticipated to lead to quantifiable plasma levels of parent and metabolites, permitting characterization of the pharmacokinetics.

### 3.3. Risk Management

Non-clinical data to date have not identified prohibitive risks associated with GSK1278863 at the exposures planned for this study. Overall, the compound has been generally well tolerated with no clinically significant safety-related findings observed to date following administration of up to 500 mg single dose and up to 100 mg once daily for 14 days in healthy subjects and up to 100 mg once daily for 28 days in CKD patients. Please refer to the GlaxoSmithKline Investigator's Brochure [GlaxoSmithKline Document Number. [RM2008/00267/07](#), 14 October 2015] and associated IB Supplements for GSK1278863 [GlaxoSmithKline Document Number [2015N266524\\_00](#), 17-Dec-2015; GlaxoSmithKline Document Number [2015N266524\\_01](#), 08-Apr-2016] for additional pre-clinical and clinical details.

To minimize risks to participants, eligibility criteria, safety monitoring, and stopping criteria are incorporated into the study design.

Based on the non-clinical studies, the primary areas of interest for GSK1278863 are related to GI tolerability (e.g., stomach erosions with bleeding) and potential for thrombosis and/or tissue ischemia secondary to excessive erythropoiesis.

In addition, several events of special interest have been identified based on clinical experience with ESAs including increased risk of cancer related morbidity and mortality

and increased risk of major cardiovascular events (e.g., death, stroke, myocardial infarction, congestive heart failure).

Lastly based on what is currently known of the possible roles for HIF-regulated pathways in mediating hypoxia associated pathophysiology, pulmonary artery hypertension, cardiomyopathy, and tissue neo-vascularization (e.g., retinal, joint synovium) have also been identified as areas of special interest.

Although no relevant safety findings related to these areas of special interest have been noted in animal or clinical studies conducted to date, where appropriate, specific eligibility criteria or monitoring instructions relevant to these theoretical concerns are included in the study protocol. For example, subjects who are at high risk for thrombotic events or malignancy, or who have underlying significant retinal vascular disorders, significant pulmonary disease (including pulmonary hypertension), or inflammatory conditions such as rheumatoid arthritis are not eligible to participate.

Hematologic parameters will be closely monitored throughout the dosing period with guidance provided regarding discontinuation of dosing. Stopping criteria or specific suggestions for diagnostic evaluations are also provided for gastrointestinal, visual, pulmonary, and joint related adverse events.

## **4. STUDY POPULATION**

### **4.1. Number of Subjects**

Approximately 24 subjects with ESRD may be enrolled (12 subjects in each cohort) considering high dropout in the study to ensure completion of 8 evaluable subjects complete dosing and critical assessments. If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor in consultation with the investigator.

### **4.2. Eligibility Criteria**

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on GSK1278863 that may impact subject eligibility is provided in the GSK1278863 IB [GlaxoSmithKline Document Number [RM2008/00267/07](#)] and associated IB Supplements for GSK1278863 [GlaxoSmithKline Document Number [2015N266524\\_00](#), 17-Dec-2015; GlaxoSmithKline Document Number [2015N266524\\_01](#), 08-Apr-2016].

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

#### 4.2.1. Inclusion Criteria

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

##### Safety

1. Satisfactory medical evaluation based upon medical history, medication history, physical examination, and clinical laboratory data obtained at the Screening visit. The determination of clinical significance will be made by the Investigator and the GSK Medical Monitor and will require that the finding is unlikely to introduce additional risk factors or interfere with the study procedures, or the integrity of the study.
2. QTc < 470 msec **OR** QTc < 480 msec in subjects with Bundle Branch Block. These should be based on average of triplicate values obtained over a brief recording period at Screening and on Day -1 and the single reading on Day 17. The same QT correction formula should be used to determine inclusion and discontinuation for any individual subject throughout the study.
3. Vitamin B12 and folate above the lower limit of normal at Screening.
4. AST, ALT, and bilirubin  $\leq 1.5 \times \text{ULN}$  (isolated bilirubin  $> 1.5 \times \text{ULN}$  is acceptable if bilirubin is fractionated and direct bilirubin  $< 35\%$ ).

##### Efficacy

5. A subject is eligible to enroll and participate in this study if he/she has ESRD and is on peritoneal dialysis for at least 2 months with a combined weekly (urine and peritoneal dialysis output) Kt/V urea  $> 1.7$  measured at any time within last 3 months.
6. No history of peritoneal dialysis-associated peritonitis, peritoneal catheter tunnel (exit site) infection or leakage for at least 3 months before study.
7. Meets the following erythropoiesis stimulating agent (ESA) criteria:
  - Is ESA naïve (i.e., no ESA use within the previous 12 weeks of screening)
  - OR**
  - Agrees to discontinue ESA (if currently using ESA) for at least 7 days prior to first dose of GSK1278863 until completion of Follow-up visit.
    - a. If the subject has a scheduled ESA interval which is  $\leq 7$  days, ESA treatment must be discontinued for at least 7 days prior to first dose of GSK1278863
    - b. If the subject has a scheduled ESA interval which is  $> 7$  days, ESA treatment must be discontinued for at least the scheduled interval length (e.g., if ESA interval is 14 days, then ESA must be discontinued for  $\geq 14$  days) prior to the first dose of GSK1278863
8. Has a hemoglobin value:
  - For ESA naïve subjects:  $< 10.0$  g/dL

- For subjects receiving ongoing ESA treatment: stable Hgb 9.0-11.5 g/dL.

**Other**

9. Subjects who are  $\geq 18$  years of age at the time of Screening.
10. A female subject is eligible to participate if she is of:
  - Childbearing potential, and agrees to use one of the contraception methods described in the protocol. This criterion must be followed from the time of Screening until completion of the Follow-up Visit.
  - Non-childbearing potential, defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (In questionable cases, a blood sample with simultaneous follicle stimulating hormone (FSH) 23.0-116.3 IU/L and estradiol  $\leq 10$  pg/mL (or  $\leq 37$  pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods described in the protocol 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. For most forms of HRT, at least 2 months must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.
11. Body weight  $> 45$  kg and  $< 140$  kg at Screening.
12. The subject is mentally and legally able to comply with the requirements and restrictions of the protocol and has provided signed informed consent prior to participation in any protocol-specific procedures, including Screening procedures.

**4.2.2. Exclusion Criteria**

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

**Safety**

1. A positive test for HIV antibody.
2. Uncontrolled hypertension (diastolic BP  $> 100$  mmHg or systolic BP  $> 170$  mmHg) at Screening.
3. History of drug abuse or dependence within 6 months of the study.
4. History of sensitivity to GSK1278863, or its components thereof or a history of drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor, contraindicates their participation.
5. History of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinical research unit uses heparin to maintain intravenous cannula patency).

6. History of thrombosis defined as deep vein thrombosis, stroke, pulmonary embolism or other thrombosis related condition within 3 months prior to Screening.
7. History of myocardial infarction or acute coronary syndrome within 3 months prior to Screening.
8. History of stroke or transient ischaemic attack within 3 months prior to Screening.
9. Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, and/or hepatic function that could interfere with the absorption, metabolism, and/or excretion of GSK1278863. Examples of conditions that could interfere with normal gastrointestinal anatomy or motility include gastrointestinal bypass surgery, partial or total gastrectomy, small bowel resection, vagotomy, malabsorption, Crohn's disease, ulcerative colitis, or celiac sprue. Examples of conditions that could interfere with hepatic function include Gilbert's syndrome.
10. Evidence of active peptic, duodenal or esophageal ulcer disease at Screening **OR** history of clinically significant GI bleeding within 3 months prior to Screening.
11. Subjects with chronic inflammatory disease that could impact erythropoiesis (e.g., scleroderma, systemic lupus erythematosus, rheumatoid arthritis, celiac disease).
12. Subjects with a history of symptomatic right heart failure.
13. Subjects with Class III or Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system.
14. Active malignancy or diagnosis of malignancy within 5 years prior to Screening (excluding successfully treated basal or squamous cell carcinoma).
15. History of proliferative vascular eye disease (e.g., choroidal or retinal disease, such as neovascular age-related macular degeneration, proliferative diabetic retinopathy or macular edema) based upon having had an ophthalmologic exam within 12 months prior to the end of the Screening period (The screening period is from the screening visit until Day -1).
16. Pregnant females as determined by positive serum -hCG test at Screening or Day -1.
17. Lactating females.
18. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period prior to first dose.
19. Consumption of red wine, grapefruit (juice), blood orange (juice), star fruit, onions, kale, broccoli, green beans, or apples from 7 days prior to the first dose of investigational product until the Follow-up visit, unless in the opinion of the Investigator and GSK Medical Monitor this will not interfere with the study procedures and compromise subject safety.
20. Use or planned use of any prescription or non-prescription drugs that are prohibited (see Section 5.10.2) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of GSK1278863 until completion of the follow-up visit, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

21. The following medications are specifically prohibited for the duration of the study (from Screening to the follow-up visit at the end of the study):

- Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of low dose ( $\leq 325$  mg/day) aspirin/acetylsalicylic acid. Occasional NSAID use is permitted (refer to Section 5.10.2.2).
- Immunosuppressant drugs and drugs used to treat malignancies (including corticosteroids at doses  $> 10$  mg prednisolone per day or equivalent) within 2 weeks of first dose of GSK1278863.

**Note:** Failed transplant subjects back on peritoneal dialysis are eligible for participating in this study but should not be on immunosuppressive medications within 3 months prior to Screening.

22. The subject has participated in a clinical trial and has received an experimental investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

### **Efficacy**

23. The most recent values of ferritin and transferrin within 3 months prior to Screening are:

- a. transferrin saturation  $< 20\%$
- b. serum ferritin  $< 100$   $\mu\text{g/L}$

### **Other**

24. A positive pre-dosing drug/alcohol screen. A minimum list of drugs that will be screened for include amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines. A positive pre-dosing screen for medications that are prescribed to a renal subject for pre-existing condition(s), may be allowed if in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

25. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of  $> 21$  units for males or  $> 14$  units for females. One unit is equivalent to 8 g of alcohol: a half-pint ( $\sim 240$  mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

26. History of regular use within 6 months of the study of tobacco- or nicotine-containing products in excess of 20 cigarettes per day or equivalent.

27. Unwillingness or inability to follow the procedures, or lifestyle and/or dietary restrictions outlined in the informed consent and as directed by site staff.

28. Subject is either an immediate family member of a participating Investigator, study coordinator, employee of an Investigator; or is a member of the staff conducting the study.

### 4.3. Lifestyle and/or Dietary Restrictions

#### 4.3.1. Contraception Requirements

##### 4.3.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Female subjects of childbearing potential with same sex partners (when this is their preferred and usual lifestyle) are not required to be abstinent or to use contraception.

##### Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

##### Contraceptive Methods with a Failure Rate of $\leq$ 1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- **Documented** male partner sterilization prior to **the female subject's entry** into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.

**NOTE:** 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 subjects understand how to properly use these methods of contraception.

#### 4.3.2. Meals and Dietary Restrictions

- Consumption of red wine, grapefruit (juice), blood orange (juice), star fruit, onions, kale, broccoli, green beans, or apples is prohibited from **7 days prior to the first dose** of GSK1278863 until the Follow-Up visit, unless in the opinion of the investigator and GSK Medical Monitor this will not interfere with the study procedures and compromise subject safety.

- Subjects will refrain from any food and drink (except water) at least 4 h before dosing on Day 1 and Day 14. On Day 1 and Day 14 subjects will be allowed a light snack (e.g., crackers and cheese or half a sandwich with a beverage which will not exceed 500 kcal) upon request.
- Subjects will be required to adhere to a balanced meal plan of the study site's choice while in the study site. The same meals served on Day 1 will also be served on Day 14.

#### **4.3.3. Caffeine, Alcohol, and Tobacco**

During each dosing session, subjects will abstain from ingesting caffeine- or xanthine containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 h prior to the start of dosing until collection of the final pharmacokinetic sample during each session.

During each dosing session, subjects will abstain from alcohol for 24 h prior to the start of dosing until collection of the final pharmacokinetic and/or pharmacodynamic sample during each session.

Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will **not** be permitted while they are in the clinical research unit.

#### **4.3.4. Activity**

Subjects will abstain from strenuous exercise for 48 h prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

#### **4.4. Screen and Baseline Failures**

Any subject who signs an Informed Consent Form but does not satisfy Inclusion/Exclusion criteria during the Screening Period will be considered a Screen Failure.

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

#### **4.5. Withdrawal Criteria and Procedures**

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or administrative reasons.

Refer to Section 5.3.3 for stopping criteria based on safety, tolerability, preliminary pharmacokinetic, and preliminary pharmacodynamic data and Section 5.3 for subject specific dose adaptation/stopping criteria including Liver Chemistry and QTc.

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). See Section 5.3.1 for details.

In the event that a subject withdraws or is withdrawn from the study, the investigator will make every effort to have the subject return to the clinic to complete follow up assessments.

A subject who withdraws from the study may be replaced with another subject (see Section 4.1).

All data will be listed and will be valid for clinical safety and tolerability evaluation.

#### 4.6. Subject Completion

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

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

## 5. STUDY TREATMENT

### 5.1. Investigational Product (GSK1278863)

	<b>Study Treatment</b>
<b>Product name:</b>	GSK1278863
<b>Dosage form:</b>	Tablet
<b>Unit dose strength(s)/Dosage level(s):</b>	5 mg/5 mg
<b>Route/Administration/ Duration:</b>	Oral, once daily in the morning for 14 days
<b>Dosing instructions:</b>	Take one tablet with approximately half a glass of water daily in the morning (Day 1 dosing time $\pm$ 1h). On Day 1 and Day14, the dose will be administered within 30 min after completion of night APD treatment or morning last fill of peritoneal dialysis fluid; on any other study days, the dose will be administered within 2 h after completion of night APD treatment or morning last fill of peritoneal dialysis fluid.
<b>Physical description:</b>	A round, biconvex, white film coated tablet
<b>Manufacturer:</b>	GlaxoSmithKline

## 5.2. Treatment Assignment

All subjects will be assigned to 5 mg GSK1278863 once daily.

For detail information about dosage and administration, refer to [Appendix 5](#).

## 5.3. Subject Specific Dose Adjustment/Stopping Criteria

### 5.3.1. Liver Chemistry Stopping Criteria

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

Study treatment will be stopped **for a subject** if the following liver chemistry stopping criteria is met:

- $ALT \geq 3xULN$

**NOTE:** Refer to [Appendix 1](#) for details of the required assessments if a subject meets the above criteria.

### 5.3.2. QTc Withdrawal Criteria

- A subject that meets any of the criteria below will be withdrawn from the study. The same QT correction formula should be used to determine inclusion and discontinuation for any individual subject throughout the study. Uncorrected QT >600 msec,
- Change from baseline: QTcB or QTcF >60 msec
- QTcB or QTcF  $\geq 500$  msec (for subjects without underlying bundle branch block)

For subjects with underlying bundle branch block the following withdrawal criteria should be used

Baseline QTc value (with underlying bundle branch block)	QTc withdrawal criteria
<470 msec	>500 msec
470-480 msec	>530 msec

Withdrawal of subjects is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

**Note:** The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.

For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.

### 5.3.3. Stopping Criteria

Dosing in the study may be stopped if **three or more** subjects receiving GSK1278863 experience any of the safety criteria listed below. An individual subject may also be withdrawn at the discretion of the Investigator and the GSK Medical Monitor for other safety reasons not listed below.

The subject will be followed at the discretion of the Investigator, and the GSK Medical Monitor will be notified. In the event one or more subjects are withdrawn, additional subjects may be enrolled (upon consultation with the GSK protocol contact, see Section 4.1) to ensure an adequate number of subjects complete the study. For an individual study participant, stopping criteria include, but are not limited to:

- Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g., ECG, vital signs, laboratory tests, etc), as judged by the Investigator in consultation with the Medical Monitor if necessary.
- Pregnancy.
- Active GI bleeding or new diagnosis of peptic or duodenal ulcer disease.
- Diagnosis of cancer, with the exception of squamous cell and basal cell carcinoma.
- Cardiovascular ischemic event or thrombotic events (e.g., myocardial infarction (MI), acute coronary syndrome, stroke, deep venous thrombosis, pulmonary embolism, new onset or worsening limb ischemia) excluding events associated with vascular access.
- New onset or clinically significant worsening right heart failure or right heart strain not explained by fluid intake.
- Treatment emergent pulmonary hypertension, new onset or worsening retinopathy (e.g., proliferative retinopathy or macular edema), or new onset or worsening nontraumatic joint inflammation (e.g., rheumatic or psoriatic arthritis).
- Subjects with new onset or worsening clinically-significant signs or symptoms affecting:
  - a. the gastrointestinal system (e.g., evidence of GI bleeding, new onset positive fecal occult blood test, abdominal pain other than transient, minor abdominal pain, etc.)

- b. vision (e.g., persistent blurred or diminished vision)
  - c. the pulmonary system (e.g., persistent significant dyspnea)
  - d. the musculoskeletal system (e.g., significant myalgias or joint inflammation)
- New onset or clinically significant worsening of hypertension inadequately responsive to change in anti-hypertensive therapy, **OR** BP  $\geq$ 180/110 mmHg (on a study visit day) which persists for >48 h despite optimal treatment.
  - Non-hypertensive subjects with normal baseline blood pressure that experience an increase in blood pressure to  $\geq$  160/100 mmHg that persists over 24 h. Any subject who demonstrates this increase in blood pressure will be followed to resolution, until any antihypertensive therapy is withdrawn.
  - Subjects with stable elevated blood pressure at baseline that further increases above baseline by either >20 mmHg systolic, >10 mmHg diastolic, or achieves  $\geq$  180/110 mmHg. To meet this criterion these elevations must persist longer than 24 h. Any subject who develops worsening hypertension requiring intervention will be followed to resolution, until any intervention therapy is withdrawn.
  - On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level > 11.0 g/dL, a second hemoglobin measurement will be obtained at the same study visit to confirm. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.
  - On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level of <8.5 g/dL, a second hemoglobin measurement will be obtained at the same study visit. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.
  - CPK level >5xULN without confirmed alternative etiology or if deemed clinically significant by the Investigator.

#### **5.4. Blinding**

This will be an open-label study.

#### **5.5. Packaging and Labeling**

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

#### **5.6. Preparation/Handling/Storage/Accountability**

A description of the methods and materials required for preparation of GSK1278863 is provided in [Appendix 5](#).

No special preparation of study treatment is required.

Study treatment will be dispensed or administered according to procedures described herein. Only subjects enrolled in the study will receive study treatment. Only authorized site staff will supply or administer study treatment.

All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff. Study treatment is to be stored to up 30°C (86°F). Maintenance of a temperature log (manual or automated) is required.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The Investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount administered to subjects. The required accountability unit for this study will be tablet. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the [Appendix 5](#).

GSK1278863 is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. Take adequate precautions to avoid direct eye or skin contact.

In the case of unintentional occupational exposure notify the study monitor, GSK Medical Monitor and/or protocol contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK. Precaution will be taken to avoid direct contact with GSK1278863.

## **5.7. Assessment of Compliance**

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

When subjects are dosed at the study site, they will receive study treatment directly from the Investigator or designee, under medical supervision.

The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

## 5.8. Treatment of Study Treatment Overdose

No specific antidote for GSK1278863 is known. The expected manifestations of GSK1278863 overdose 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 HD or PD is very low and these are not effective methods to enhance the elimination of GSK1278863. GSK1278863 metabolites are, in part, cleared via hemodialysis.

In the event of suspected overdose:

- collect blood samples for pharmacokinetics and safety laboratory immediately.
- 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.

## 5.9. Treatment after the End of the Study

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

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

## 5.10. Concomitant Medications and Non-Drug Therapies

All concomitant medications (including rhEPO) taken in the 4 weeks before and during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose administered and dates of administration are to be recorded.

*In vitro* characterization of GSK1278863 distribution and biotransformation has identified potential mechanisms for clinical drug-drug interactions. GSK1278863 is primarily metabolized via the CYP2C8 pathway, with minor involvement of the CYP3A4 pathway. Data from a study (PHI113634) to assess the interaction potential between GSK1278863 and a CYP2C8 inhibitor (gemfibrozil) showed a clinically-significant increase in GSK1278863 exposure following co-administration.

*In vitro* studies showed the potential for inhibition of CYP2C8 (IC<sub>50</sub>: 21 µM) by GSK1278863, while there was no evidence of concentration- or metabolism-dependent inhibitory potential towards human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4. In a recent drug-drug interaction, there was no apparent evidence of a drug interaction between GSK1278863, at doses up to 100 mg, with pioglitazone, a CYP2C8 substrate.

GSK1278863 was also observed to be an inhibitor of organic anion transporting polypeptide (OATP) 1B1 and 1B3 *in vitro* with IC<sub>50</sub>s of ~6 μM and ~11 μM, respectively. The average C<sub>max</sub> observed after single dose administration of 5 mg GSK1278863 to healthy subjects was 0.24 μM, suggesting a low risk of an interaction. In a recent drug-drug interaction, there was no apparent evidence of a drug interaction between GSK1278863, at doses up to 100 mg, with rosuvastatin, an OATP1B1 substrate.

GSK1278863 is a substrate of human breast cancer resistance protein (BCRP) *in vitro*. Therefore, there may be the potential for interactions when GSK1278863 is co-administered with drugs which are inhibitors of human-BCRP, however, GSK1278863 has moderate to high passive permeability, potentially mitigating any BCRP inhibition effects.

### **5.10.1. Permitted Medications**

Paracetamol or Acetaminophen, at doses of ≤ 2 grams/day is permitted for use from 48 h prior to the first dose of GSK1278863 and until completion of follow-up procedures.

Use of low dose (≤325mg/day) aspirin/acetylsalicylic acid is permitted for the duration of the study (from Screening to the follow-up visit at the end of the study).

Concomitant medications other than specified in Section 5.10 may be considered on a case by case basis by the Investigator in consultation with the GSK Medical Monitor.

Subjects receiving HRT and other drugs not specifically prohibited (see Section 5.10.2) are permitted to continue while on study.

#### **5.10.1.1. Inhibitors of BCRP**

Medications that are inhibitors of BCRP will be permitted in the study. These medications include omeprazole, lansoprazole, rabeprazole, and pantoprazole.

#### **5.10.1.2. Non-Drug Therapies**

Calcium, Vitamin D, and other vitamins and minerals may be permitted at the discretion of the Investigator or his/her designee. Refer to Study Procedural Manual (SPM) for an extended list.

### **5.10.2. Prohibited Medications and Non-Drug Therapies**

#### **5.10.2.1. Supplements**

Subjects must abstain from taking supplements (with the exception of vitamin or minerals), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of GSK1278863 until completion of the

follow-up visit, unless in the opinion of the Investigator and sponsor it will not interfere with the study.

#### **5.10.2.2. NSAIDs**

Chronic use of NSAIDs will **not** be permitted with the exception of low dose ( $\leq 325$ mg/day) aspirin/acetylsalicylic acid for the duration of the study (from Screening to the follow-up visit at the end of the study).

#### **5.10.2.3. Immunosuppressants**

Immunosuppressant drugs and drugs used to treat malignancies (including corticosteroids at doses  $>10$  mg prednisolone per day or equivalent) within 2 weeks of first dose of GSK1278863 are specifically prohibited from Screening through the follow-up visit.

**Note:** Failed transplant subjects who are on peritoneal dialysis are eligible for participation in this study but should not be on immunosuppressive medications within 3 months prior to Screening.

#### **5.10.2.4. Inhibitors and inducers of CYP2C8**

The primary route of metabolism of GSK1278863 involves CYP2C8.

Strong inhibitors and inducers of CYP2C8 are prohibited from 14 days prior to the first dose of GSK1278863 until 7 days after the last dose of GSK1278863. These medications include gemfibrozil, rifampin/rifampicin, phenytoin, hyperforin supplements (e.g., St John's Wort), Phenobarbital/phenobarbitone.

## **6. STUDY ASSESSMENTS AND PROCEDURES**

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section [6.1](#).

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order:

- 12-lead ECG
- vital signs
- blood draws

The timing of the assessments is required to allow the blood draw to occur as close as possible to the nominal time.

Protocol waivers or exemptions are **not allowed** with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those

specified in the Time and Events Table (Section 6.1), are essential and required for study conduct.

The timing and number of planned study assessments and procedures may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The change in timing or addition of time points for any planned study assessments must be approved and documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files. This will not constitute a protocol amendment.

The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF).

Additional safety tests (such as vital signs, physical exams, and clinical laboratory tests) may also be obtained during the course of the study based on newly available data, to ensure appropriate safety monitoring.

**No more than** 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

Refer to [Appendix 3](#) for details regarding PK sample time windows that will not be regarded as protocol deviations.

During the Follow-up Period, deviations of up to +2 days for clinical research unit visits will not be regarded as Protocol Deviations.

The actual date and time will be recorded for all procedures and the Investigator will make every effort to perform procedures at the scheduled nominal dates and times.

### 6.1. Time and Events Table

Informed consent for optional PGx (pharmacogenetics) research must be obtained before collecting a sample.

Protocol Activity	Screening (refer to Section 3.1)	Treatment														Follow Up (refer to Section 3.1)
	~Day -30	Day -1	Day 1	Day 2	Day 3	Day 4-6	Day 7	Day 8-10	Day 11	Day 12-13	Day 14	Day 15	Day 16	Day 17	Day 22	
<b>Window</b>															+2 days	
Informed Consent Process	X															
Demographics	X															
Medical/medication/drug/alcohol history	X															
<b>Safety Assessments</b>																
Concomitant Medications <sup>a</sup>		←=====X=====→														
Complete Physical	X															
Vital Signs	X	X												X	X	
12 - Lead ECG (refer to Section 6.3.3)	X	X												X		
Adverse Events Assessment/ SAE's <sup>a</sup>		←=====X=====→														
Brief Physical		X												X		
<b>Laboratory Assessments</b>																
Chemistry	X	X												X		
Hematology	X	X												X		
PGx Sampling		← collect one PGx sample after the start of dosing (preferably on Day 1) →														
Serum Pregnancy Test	X	X													X	

Protocol Activity	Screening (refer to Section 3.1)	Treatment														Follow Up (refer to Section 3.1)
	~Day -30	Day -1	Day 1	Day 2	Day 3	Day 4-6	Day 7	Day 8-10	Day 11	Day 12-13	Day 14	Day 15	Day 16	Day 17	Day 22	
<b>Window</b>															+2 days	
Hepatitis B Surface Antigen (HBsAg)	X															
Hepatitis C Antibody (HCVAb)	X															
Admission to Clinic (optional) <sup>b</sup>		X									X					
IP dosing (oral) <sup>c</sup>			X	X	X	X	X	X	X	X	X					
Discharge				X										X		
Blood PK samples			X <sup>d</sup>		X <sup>e</sup>		X <sup>e</sup>			X <sup>e</sup>	X <sup>d</sup>	X <sup>f</sup>	X <sup>g</sup>	X <sup>h</sup>		
Dialysate PK samples			X <sup>i</sup>								X <sup>i</sup>	X <sup>i</sup>				
Iron Binding Capacity (TIBC)	X															
Creatine Kinase (CPK) <sup>k</sup>				X		X		X		X		X				
ALT <sup>l</sup>				X		X		X		X		X				
Iron (Fe)	X															
Transferrin	X															
Ferritin	X															
Drug and Alcohol Screen <sup>m</sup>	X	X								X						
Estradiol (E2) (refer to Section 6.3.4)	X															
Follicle Stimulating Hormone (FSH) (refer to Section 6.3.4)	X															
Serum Vitamin B12 and folate	X															
EPO and Hepcidin			X <sup>d</sup>		X <sup>e</sup>		X <sup>e</sup>		X <sup>e</sup>		X <sup>d</sup>					
HIV Ab	X															
Hemoglobin (Hb) <sup>n</sup>				X		X		X								
Protein Binding											X <sup>d</sup>					

- a Both Adverse event monitoring and Concomitant Medication reviews will be conducted throughout the study starting from Day -1.
- b Subjects may remain in residence at the site from the afternoon of Day -1 through the last assessment on Day 17, at the discretion of the investigator or by request of the subject (refer to Section 3.1). Outpatients must return to the site for scheduled PK assessments.
- c Each dose will be administered within 30 min after completion of the night APD treatment or morning last fill of peritoneal dialysis fluid. Outpatients can self administer their daily dose
- d Sampling schedules within the day are given in Section 6.1.1.
- e Sample to be taken predose only.
- f Sample to be taken 24 h post Day 14 dose.
- g Sample to be taken 48 h post Day 14 dose.
- h Sample to be taken 72 h post Day 14 dose.
- i Aliquot of dialysate from the last drained dwell prior to dosing on Day 1. Aliquot for APD subjects may be collected from automated cycler drain/drain bag prior to dosing on Day 1.
- j In CAPD subjects, record volume and take aliquots of dialysate from each drain bag over 24 h dosing period starting at time of Day 14 dose. Aliquot for APD subjects is to be collected from APD collection drain bag over 24 h dosing period starting at time of Day 14 dose.
- k Measurement in addition to clinical chemistry assessment.
- l Measurement in addition to hematology assessment.
- m Test will be performed for drug and alcohol at Screening, Day-1, and Day 13 visits check-in for subjects who participate in the study as outpatient, and it must be negative prior to dosing.
- n Hemoglobin assessment will be by a HemoCue device.

**6.1.1. Study Procedures and Assessments for Plasma PK, EPO, Hepcidin & Protein Binding Sampling on Day 1 and Day 14**

Procedure	Time (in h relative to dosing)												
	Predose	0.5	1	2	3	4	6	8	12	16	24	48	72
<b>DAY 1</b>													
PK blood sample	X	X	X	X	X	X	X	X	X	X	X		
EPO and Hepcidin	X					X		X	X		X		
<b>DAY 14</b>													
PK blood sample	X	X	X	X	X	X	X	X	X	X	X	X	X
EPO and Hepcidin	X					X		X	X		X		
Protein Binding	X				X				X				

## 6.2. Demographic/Medical History Assessments

The following demographic parameters will be captured: date of birth (only year), gender, race and ethnicity.

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2.

Baseline assessments are defined as the last pre-dose timepoint of each assessment (except ECG, which will be the average of the 3 ECGs obtained at that timepoint).

## 6.3. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 6.1).

Additional time points for safety tests such as vital signs, physical exams and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

### 6.3.1. Physical Exams

- **A complete physical examination** will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.

Height and weight will also be measured and recorded.

- **A brief physical examination** will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

### 6.3.2. Vital Signs

- Vital sign measurements will be measured in supine position **after 5 min** rest and will include systolic and diastolic blood pressure, body temperature, and pulse rate.

### 6.3.3. Electrocardiogram (ECG)

- 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Subjects are required to rest quietly at supine position for **at least 10 min** before and during each ECG reading (subjects should remain comfortable).

Repeat measurements may be performed if there are any clinical abnormalities observed or if artifacts are present.

Below is the number of ECGs will be obtained at each timepoint:

- **Screening:** Three ECGs will be taken, at least 5 min apart. Take average of the three intervals to determine subject eligibility.
- **Day -1:** Three ECGs will be taken, at least 5 min apart. The average of the intervals from the three ECGs will determine the baseline (HR, PR, QRS, QTc).
- **Day 17:** A single ECG will be taken.

Refer to Section 5.3.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

### 6.3.4. Clinical Laboratory Assessments

Blood samples for Clinical Laboratory Assessments will be collected in the fasted state during the study at the time points indicated in the Time and Events Table (Section 6.1). Subjects are to be fasted for a minimum of 6 h prior to blood sample collections.

If screening results suggest that the blood sample was obtained without an appropriate fasting period, the clinical chemistry may be repeated once at the Investigator discretion.

The total volume of blood collected for planned Clinical Laboratory Assessments, pharmacodynamic and pharmacokinetic assessments from all subjects will **not exceed 500 mL** during the entire study period.

Hematology, clinical chemistry, and additional parameters to be tested are listed below.

Details for the preparation and shipment of samples will be provided by Quest.

Reference ranges for all safety parameters will be provided to the site by the laboratory.

If additional non-protocol specified laboratory assessments are performed at the site's local laboratory and result in a change in subject management or are considered clinically significant by the Investigator (for example SAE or AE or dose modification) the results must be captured and sent to GSK along with other study data as defined in [Appendix 4](#).

Hematology, clinical chemistry, and additional parameters to be tested are listed below:

#### Hematology

	<i>RBC Indices:</i>	<i>Automated WBC Differential:</i>
Platelet Count		
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

## Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting	Total CO <sub>2</sub>	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
CPK			

**NOTE:** Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 5.3.1.

### Other screening/lab tests

HIV	
Hepatitis B (HBsAg)	
Hepatitis C (Hep C antibody – if second generation Hepatitis C antibody positive, a hepatitis C RNA assay (or other third generation immunoassay) should be reflexively performed <b>on the same sample</b> to confirm the result)	
FSH and Estradiol (as needed in women of non-child bearing potential only)	
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).	
Erythropoietin	
TIBC	Serum iron
Serum Ferritin	Serum transferrin
Vitamin B-12	Folate

Out of range laboratory results may be repeated at the discretion of the Investigator.

When hemoglobin values achieve the threshold values defined in Section 5.3.3 (Safety Stopping Criteria), appropriate procedures (e.g., venesection or erythrocytapheresis) will be considered and implemented at the discretion of the Investigator until the values return below the thresholds.

## 6.4. Pharmacokinetics

### 6.4.1. Blood Sample Collection

Blood samples (approximately 3 mL) for pharmacokinetic analysis of GSK1278863 and metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), and GSK2531401 (M13)) will be collected at the time points indicated in Section 6.1, Time and Events Table.

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Additional blood (approximately 3 mL) will be collected for assessment of protein binding of GSK1278863 and metabolites, M4 (GSK2487818) and M5 (GSK2506102), at the time points indicated in the Time and Events Table in Section 6.1.

Processing, storage and shipping procedures are provided in the SPM.

#### **6.4.2. Dialysate Sample Collection**

Peritoneal dialysate samples for pharmacokinetic analysis of GSK1278863 and metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), and GSK2531401 (M13)) will be collected on the days listed in Section 6.1, Time and Events Table.

##### **On Day 1:**

After mixing, approximately 1.5 mL aliquot of dialysate from the last drained dwell prior to GSK1278863 dosing will be collected (aliquot for APD subjects may be collected from automated cycler drain/drain bag).

##### **On Day 14:**

All drained dialysate will be collected over a 24 h period, starting at the time of GSK1278863 dosing. The volume of each drained dwell needs to be recorded, and an aliquot taken for analysis.

CAPD subjects: After mixing and measurement of drained dialysate volume, approximately 1.5 mL aliquot of dialysate from each drained dwell will be collected.

APD subjects: After mixing and measurement of drained dialysate volume, approximately 1.5 mL aliquot of dialysate from the cycler drain bag (and any manual peritoneal dialysis exchanges during the day) will be collected.

Details of PK dialysate sample processing, storage and shipping procedures are provided in the SPM.

#### **6.4.3. Sample Analysis**

All samples will be shipped at the end of dosing period and appropriately analyzed for plasma or dialysate GSK1278863 and metabolite concentrations and protein binding (free fraction, plasma if technically feasible) using validated methods.

Once the plasma has been analyzed for GSK1278863 and metabolites, and protein binding, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK, GlaxoSmithKline protocol.

#### **6.5. Pharmacodynamic (PD) Markers**

##### **6.5.1. PD Sample Collection (EPO and Heparin)**

Blood samples for PD analysis of EPO and heparin will be collected at the time points indicated in the Time and Events Table in Section 6.1.

The actual date and time of each blood sample collection will be recorded. Details of PD blood sample collection, processing, storage, and shipping procedures are provided in the SPM.

## **6.6. Pharmacogenetics**

Information regarding pharmacogenetic (PGx) research is included in [Appendix 2](#)

The IRB/IEC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site.

In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and in most cases, the study, except for PGx assessments, can be initiated.

When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

## **7. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, PREGNANCY AND MEDICAL DEVICES INCIDENTS**

### **7.1. Adverse Events (AE) and Serious Adverse Events (SAEs)**

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### **7.1.1. Time period for collecting AE and SAE information**

AEs will be collected from the start of Study Treatment and until the follow-up contact. 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 CRF.

SAEs will be collected over the same time period as stated above for AEs. However, 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 h, as indicated in [Appendix 4](#).

Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 would promptly notify GSK.

NOTE: The method of, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in [Appendix 4](#).

### 7.1.2. 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?”

### 7.1.3. Definition of Adverse Events

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 the definition of an AE **include**:

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

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

#### **7.1.4. Definition of Serious Adverse Events**

If an event is not an AE per Section 7.1.3, 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).

An SAE is any untoward medical occurrence that, at any dose:

- a. Results in death
- b. Is life-threatening

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

- c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- d. Results in disability/incapacity, or

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

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

### 7.1.5. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools 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

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

### **7.1.6. Death Events**

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

### **7.1.7. Prompt Reporting of SAEs to GSK**

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK within 24 h. Any follow-up information on a previously reported SAE will also be reported to GSK within 24 h.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in [Appendix 4](#).

### **7.1.8. Regulatory Reporting Requirements for SAEs**

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects 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 regulatory authorities, IRBs/IECs 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 an 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.

## **7.2. Pregnancy**

### **7.2.1. Time period for collecting pregnancy information**

All pregnancies in female subjects will be collected after the start of dosing and until the time period that is 5 terminal half-lives after the last dose.

### **7.2.2. Action to be taken if pregnancy occurs**

The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The Investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to GSK1278863 by the Investigator, will be reported to GSK as described in Section 7.1.7. 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 GSK1278863.

## **8. DATA MANAGEMENT**

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. eCRFs (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. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS**

Statistical analyses of the pharmacokinetic data will be provided by, or under the direct auspices of Quantitative Sciences (QSci), GSK.

## **9.1. Hypotheses and Treatment Comparisons**

This study is designed to estimate pharmacokinetic endpoints of GSK1278863 and metabolites in ESRD patients undergoing peritoneal dialysis following repeat administration of 5 mg once daily GSK1278863.

There will be two cohorts of subjects in this study: subjects with CAPD and subjects with APD.

No formal statistical hypotheses will be tested. An estimation approach will be used to evaluate the comparisons of interest, with point estimates and associated 90% confidence intervals presented to provide a range of plausible values for the comparisons.

## **9.2. Sample Size Considerations**

### **9.2.1. Sample Size Assumptions**

As this study is descriptive in nature and no formal statistical comparisons of PK data will be performed, the sample size of 24 subjects (12 in each cohort) will be recruited such that at least 8 subjects complete the trial. Based on PK parameter CV% of ~50% in subjects with renal impairment or ESRD [refer to GlaxoSmithKline Document Number [RM2008/00267/07](#), 14-Oct-2015.GSK1278863 IB and associated IB supplements for GSK1278863 [GlaxoSmithKline Document Number [2015N266524\\_00](#), 17-Dec-2015; GlaxoSmithKline Document Number [2015N266524\\_01](#), 08-Apr-2016]] for a sample size of at least 8 statistically evaluable subjects, the half width of the 90% confidence interval will be within 56% of the point estimate.

### **9.2.2. Sample Size Sensitivity**

Not applicable.

### **9.2.3. Sample Size Re-estimation**

No sample size re-estimation will be performed.

### **9.3. Data Analysis Considerations**

#### **9.3.1. Analysis Populations**

##### **All Screened Population**

The “All Screened” population will be defined as all subjects screened.

##### **All Subjects Population**

The ‘All Subjects Population’ is defined as all subjects who receive at least one dose of study treatment. This population will be used for the study population and safety analyses.

##### **Pharmacokinetic Population**

The ‘PK Population’ is defined as subjects in the ‘All Subjects’ population for whom a pharmacokinetic sample was obtained and analyzed. This will be the population used for all the pharmacokinetic displays.

#### **9.3.2. Interim Analysis**

Informal PK reviews will be conducted throughout the study to assist Phase III development of the compound

##### **9.3.2.1. Final Analyses**

Descriptive statistics (n, arithmetic mean and associated 95% confidence interval (CI), standard deviation, minimum, median, maximum) will be calculated for all pharmacokinetic endpoints of GSK1278863 and metabolites separately by cohort and overall (CAPD, APD, and both combined)

In addition, geometric means, associated 95% CIs, and estimates of between-subject CVs (CVb(%)) will be calculated for AUC (0- $\tau$ ), AUC (0- $\infty$ ), C<sub>max</sub>, clearance, and t<sub>1/2</sub> where

$$\text{Geometric mean} = \exp(\text{mean on } \log_e \text{ scale})$$

$$\text{CVb}(\%) = \text{SQRT}(\exp(\text{SD}^2 - 1)) * 100, \text{ where SD is the standard deviation of the } \log_e\text{-transformed data.}$$

Similar descriptive summaries will be created for the steady-state GSK1278863 and metabolite unbound concentration and free fraction, erythropoietin, and hepcidin plasma concentration.

At a minimum, descriptive statistics (n, mean and associated 95% CI, standard deviation, minimum, median, maximum) will be calculated at each relevant time point.

### 9.3.2.2. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to CDISC standards.

### 9.3.2.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GSK.

Plasma GSK1278863 and metabolites GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), and GSK2531401 (M13) concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin Version 6.3 or higher. Calculations will be based on the actual sampling times recorded during the study.

Pharmacokinetic data will be listed and may be presented in graphical form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GSK, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GSK.

#### 9.3.2.3.1. Plasma PK Parameters

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit

**Day 1:** Maximum observed plasma concentration ( $C_{max}$ ), time to  $C_{max}$  ( $t_{max}$ ), area under the plasma concentration-time curve  $AUC(0-\tau)$  and  $AUC(0-\infty)$ , and apparent terminal phase half-life ( $t_{1/2}$ ).

**Day 14:**  $C_{max}$ ,  $t_{max}$ ,  $AUC(0-\tau)$ , and apparent terminal phase half-life ( $t_{1/2}$ ).

$AUC(0-\infty)$ ,  $AUC(0-\tau)$  and  $C_{max}$  following single (Day 1) and repeat doses (Day 14) will be used for determination of accumulation and time-invariance ratios.

**Day 12 to 15:** Trough concentration ( $C_{tau}$ , or  $C_{\tau}$ ) samples collected on Days 12 to 15 will be used to assess attainment of steady state.

**Other Plasma PK Analyses:** GSK1278863 and metabolite unbound concentration and free fraction (as a percentage) will be presented in tabular form and will be summarized descriptively. Metabolite-to-parent exposure ratios (corrected for molecular weight) will also be calculated and summarized descriptively.

#### Steady State Assessment

Trough concentration ( $C_{\tau}$ ) samples collected on the specified days will be used to assess attainment of steady state. Individual trough concentration data  $C_{\tau}$  will be plotted and

listed.  $C\tau$  will be summarized by day and cohort, and the mean and median plots will be provided.

Steady state will be assessed separately for GSK1278863 and metabolites in each cohort.

A linear mixed effects ANOVA model will be used to evaluate steady state for GSK1278863 and each metabolite. The dependent variable will be log-transformed pre-dose (trough) concentrations ( $C\tau$ ) on Days 12 to 15. Independent variables in the model include day (as a continuous variable) as a fixed effect and subject as a random effect.

Assessment of plasma GSK1278863 and metabolites steady state will be assessed by evaluating the estimated slope for the day parameter and associated 90% CI for both the cohorts combined.

### **Secondary Comparisons:**

#### **Assessment of Accumulation**

To estimate the extent of accumulation for GSK1278863 and metabolites after repeat dosing, the observed accumulation ratio  $R_0$  will be determined.

$$R_0 = \frac{AUC(0-\tau)_{ss}}{AUC(0-\tau)}$$

where  $AUC(0-\tau)_{ss}$  is AUC from time zero to  $t$  h under steady state and  $AUC(0-\tau)$  is AUC from time zero to *dosing interval* at Day 1.

To evaluate the accumulation ratio, statistical analysis of GSK1278863 and metabolites for both the cohorts combined will be performed after a log transformation of the data.

A mixed effect model will be fitted with day (single and repeat dose), as fixed effects and subject as a random effect. Day 14 will be compared to Day 1 in order to estimate the accumulation ratios,  $R_0 = (AUC(0-\tau, \text{Day14}) : AUC(0-\tau, \text{Day1}))$ . The ratios will be calculated by back-transforming the difference between the LS means.

Using the pooled estimate of variance, 90% confidence intervals will be calculated for  $R_0$ , and back-transformed to the original scale.

#### **Assessment of Time Invariance**

To evaluate the time invariance ratio, statistical analysis of  $(AUC(0-\infty) \text{ Day 1})$  and  $AUC(0-\tau) \text{ (Day14)}$ , of GSK1278863 and metabolites for both the cohorts combined will be performed after a log transformation of the data.

A mixed effect model will be fitted with day as fixed effects and subject as a random effect. Day 14  $AUC(0-\tau)$  will be compared to Day 1  $AUC(0-\infty)$  in order to estimate the

time invariance ratios,  $R_S = \text{AUC}(0-\tau, \text{Day 14}) : \text{AUC}(0-\infty, \text{Day 1})$ . The ratios will be calculated by back-transforming the difference between the LS means.

**9.3.2.3.2. *Using the pooled estimate of variance, 90% confidence intervals will be calculated for  $R_S$ , and back-transformed to the original scale.* Dialysate PK Parameters**

Peritoneal dialysis excretion amounts and clearance of GSK1278863 and metabolites will be calculated from Day 14 dialysate excretion data (total amount excreted over 24 h) divided by plasma  $\text{AUC}(0-\tau)$ .

**9.3.2.4. Pharmacodynamic/Biomarker Analyses**

Plasma erythropoietin and hepcidin concentrations will be presented in graphical and/or tabular form and will be summarized descriptively.

**9.3.2.5. Pharmacogenetic Analysis**

Samples will be collected and stored. No prospective analyses will be performed.

## **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 enrolment of subjects begins.

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

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

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki.

This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) must be obtained for each subject before participation in the study

Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to IRB/IEC).

Detailed information regarding pharmacogenetic research conduct is included in Section 6.6 and in [Appendix 2](#).

### **10.2.1. Urgent Safety Measures**

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of subjects, the sponsor and the Investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The sponsor will work with the Investigator to ensure the IEC/IRB is notified.

### **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 eCRFs 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 monitor will conduct site closure activities with the Investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, 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 this with the Investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, GSK will provide advance notification to the Investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform Investigators or the head of the medical institution (where applicable) and the 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 by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and 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 assure 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, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

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 leaves 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.

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

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

## 11. REFERENCES

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## 12. APPENDICES

### 12.1. Appendix 1: Liver Safety Process

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 5.3.1:

- Immediately withdraw the subject from study treatment
- Notify the GSK medical monitor within 24 h of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 7.1.4), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required
- Do not restart study treatment
- Refer to the Flow chart for a visual presentation of the procedures listed below.

#### **Safety Follow-Up Procedures for subjects with ALT $\geq$ 3xULN:**

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

#### **Safety Follow-Up Procedures for subjects with ALT $\geq$ 3xULN and total bilirubin $\geq$ 2xULN (>35% direct bilirubin); or ALT $\geq$ 3xULN and INR<sup>1</sup> > 1.5:**

- This event is considered an SAE (see Section 7.1.4. Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 h for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

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

- Viral hepatitis serology including:

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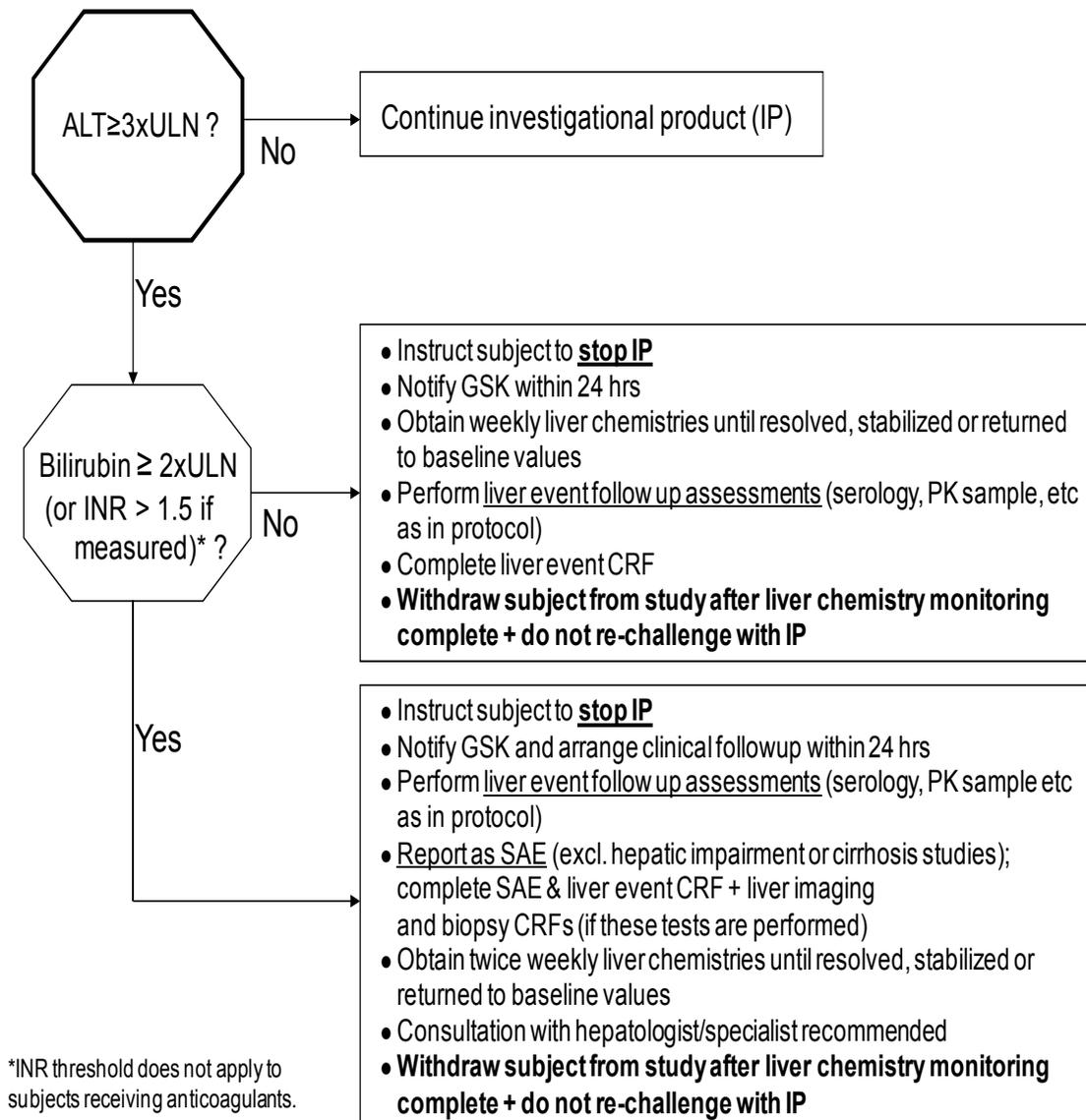
<sup>1</sup> INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

- Hepatitis A IgM antibody.
- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
- Hepatitis C RNA.
- Cytomegalovirus IgM antibody.
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
- Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 24 h of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin  $\geq 2xULN$ .
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

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

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week (James, 2009).
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

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



## 12.2. Appendix 2: Pharmacogenetic research

### Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
<b>Abacavir</b>	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	HLA-B* 57:01 (Human Leukocyte Antigen B)	Carriage of the HLA-B*57:01 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B*57:01 screening and exclusion of HLA-B*57:01 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B*57:01 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*57:01 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
<b>Carbamazepine</b>	Seizure, Bipolar disorders & Analgesia Chung, 2010; Ferrell, 2008	HLA-B*15:02	Independent studies indicated that patients of East Asian ancestry who carry HLA-B*15:02 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*15:02 prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to [insert the name of the study treatment].

### Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to GSK1278863 . If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK1278863, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

### Study Population

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

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

## Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

- The PGx sample is labelled (or “coded”) with a study specific number that 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). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of GSK1278863 has been completed and the clinical study data reviewed. In some cases, the samples may not be studied; e.g., no questions are raised about how people respond to GSK1278863.

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 use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

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

## Subject Withdrawal from Study

If a subject who has consented to participate in PGx 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 PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx 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. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time

when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

### **Screen and Baseline Failures**

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx 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.

### **Pharmacogenetics Analyses**

#### Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to [insert the name of the study treatment]. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

### **Informed Consent**

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

## Provision of Study Results and Confidentiality of Subject's PGx Data

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

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, 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 PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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**12.3. Appendix 3: PK, EPO, Heparin, and Protein Binding Sampling Scheduled Times and Allowed Deviations**

<b>Procedures</b>	<b>Time</b>	<b>Allowed deviation</b>
<b>For PK, EPO /hepcidin, and protein binding samples</b>	Pre-dose	within 1 h of dosing
	0.5 h post dose	± 10 min
	1 h post dose	± 10 min
	2 h post dose	± 15 min
	3 h post dose	± 15 min
	4 h post dose	± 15 min
	6 h post dose	± 30 min
	8 h post dose	± 30 min
	12 h post dose	± 30 min
	16 h post dose	± 30 min
	24 h post dose	± 30 min
	48 h post dose	± 60 min
	72 h post dose	± 60 min

## **12.4. Appendix 4: Procedures for Detection, Evaluation, Follow-Up and Reporting of Adverse Events and Medical Device Incidents**

### **Recording of AEs and SAEs**

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 appropriate data collection tool.

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 data collection tool. However, 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.

Subject-completed health outcomes questionnaires and the collection of AE data are independent components of the study. Responses to each question in the health outcomes 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.

### **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 discomfoting 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

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

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 data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

## Reporting of SAEs to GSK

The primary mechanism for reporting SAEs to GSK will be the electronic data collection tool. If the electronic system is unavailable for greater than 24 hr, the site will use the paper SAE data collection tool and fax it to the GSK Medical Monitor and/or protocol

contact. Then the site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant 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 their GSK protocol contact by telephone.

GSK contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

GSK contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.

## **12.5. Appendix 5: Investigational Product (GSK1278863) Information**

### **Shipping, Receipt, and Storage of GSK1278863**

The shipment of GSK1278863 will contain a Clinical Supplies Shipping Invoice.

Upon receipt of a shipment, check that the contents correspond to the form. If all of the contents are present exactly as listed on the form, the pharmacist or designee signs and dates the form. The form will be retained in the pharmacy and/or study site records.

The initial shipment of GSK1278863 will only occur after all of the appropriate regulatory and IRB documents have been received and reviewed for completeness by GSK.

In the event additional GSK1278863 supplies are needed, contact the GSK protocol contact and allow a minimum of 5 days for delivery.

GSK1278863 tablets are to be stored at up to 30°C, and in the original container(s), unless being prepared for administration.

### **Dosage and Administration**

GSK1278863 will be supplied in 5 mg tablet strength, supplied as 35 tablets per bottle in a white, HDPE 45cc bottle with CR cap. Each bottle will be labelled with an open label, single panel label without container numbers.

The tablets are packaged for the site to dispense the medication to the subjects daily while at the clinic.

Study drug will be administered with small amount of water.

Subjects need to refrain from any food and drink (except water) at least 4 h before dosing and 4 h after dosing on Day 1 and Day14.

### **Drug Accountability and Reconciliation**

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for GSK1278863 accountability, reconciliation, and record maintenance.

In accordance with all applicable regulatory requirements, the Investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain GSK1278863 accountability records throughout the course of the study.

The responsible person(s) will document the amount of GSK1278863 received from and returned to GSK (when applicable), the amount supplied and/or administered to and returned by subjects, if applicable.

**GSK1278863 Returns**

At the conclusion of the study, a final inventory will be performed by a Study Monitor and site pharmacy staff.

Unused bottles of GSK1278863 must be destroyed locally according to local requirements after full review and reconciliation of GSK1278863 accountability records.

## 12.6. Appendix 6: Protocol Amendment Changes

### AMENDMENT 1

**This amendment will apply to all the study sites and all countries.**

This amendment will serve to implement

#### Summary of Amendment Changes with Rationale

##### List of Specific Changes

Section 4.2.1. Inclusion Criteria, Inclusion#8,

Hemoglobin levels are updated based on the feedback received from FDA. It was  $\leq 11.0$  g/dL for ESA naïve subjects, it is updated as  $< 10.0$  g/dL; it was  $\leq 12.0$  g/dL for subjects receiving ongoing ESA treatment, it is updated as  $\leq 11.0$  g/dL.

##### PREVIOUS TEXT

Inc#8: Has a hemoglobin value:

- For ESA naïve subjects:  $\leq 11.0$  g/dL
- For subjects receiving ongoing ESA treatment:  $\leq 12.0$  g/dL at Screening with a re-check value of  $\leq 11.0$  g/dL after appropriate discontinuation according to Inclusion Criterion #7 and prior to commencing GSK1278863 dosing.

##### REVISED TEXT

Inc# 8: Has a hemoglobin value:

- For ESA naïve subjects:  $< 10.0$  g/dL
- For subjects receiving ongoing ESA treatment:  $\leq 11.0$  g/dL at Screening.

Section 4.2.2. Exclusion Criteria,

The numbering of exclusion criteria was incremented from previous section. The numbering now is updated and starts from “1”.

##### PREVIOUS TEXT

The numbering was from 13 through 40.

##### REVISED TEXT

The numbering now starts from 1 and goes up to 28.

### Section 5.3.3. Stopping Criteria

The stopping criteria related to the hemoglobin level is updated per the FDA's feedback received. A previous criterion required subjects to have their absolute hemoglobin level  $\geq 13.0$  g/dL to stop the dosing. The hemoglobin level for stopping the dosing is now updated as  $>11.0$  g/L.

#### PREVIOUS TEXT

- On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level  $\geq 13.0$  g/dL, a second hemoglobin measurement will be obtained at the same study visit to confirm. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.

#### REVISED TEXT

- On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level  $> 11.0$  g/dL, a second hemoglobin measurement will be obtained at the same study visit to confirm. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.

### Section 6.1. Time and Events Table,

Protocol Activity "Urine Drug and Alcohol Screen" is updated as "Drug and Alcohol Screen" with a new footnote "m". Majority of subjects with ESRD undergoing peritoneal dialysis will not be able to produce urine samples. For these subjects this screening test will be serum-based.

#### PREVIOUS TEXT

Urine Drug and Alcohol Screen

#### REVISED TEXT

Drug and Alcohol Screen<sup>m</sup>

Footnote m: "Urine test will be performed for drug and alcohol screening at Screening (it must be negative prior to dosing) and Day-1 visits. For subjects who are not able to produce the required amount of urine sample, serum based test will be performed as an alternative."

### Section 6.3.2. Vital Signs

Body temperature measurement was not included under vital signs assessment. It is now included as a part of vital signs assessment since it is a measurement performed as a standard practice at the site.

## PREVIOUS TEXT

- Vital sign measurements will be measured in supine position **after 5 min** rest and will include systolic and diastolic blood pressure, and pulse rate.

## REVISED TEXT

- Vital sign measurements will be measured in supine position **after 5 min** rest and will include systolic and diastolic blood pressure, body temperature, and pulse rate.

## Section 6.3.3. Electrocardiogram (ECG)

On Day -1, ECG measurement will be taken; however, it indicated that this ECG measurement should be taken 2 h prior to dosing.

The first dosing will take place on Day 1, and there will be no ECG measurement on that day. This logical error is now corrected.

## PREVIOUS TEXT

**Day -1:** Three ECGs will be taken, at least 5 min apart within 2 h prior to dosing.

## REVISED TEXT

**Day -1:** Three ECGs will be taken, at least 5 min apart.

## AMENDMENT 2

**This amendment will apply to all the study sites and all countries.**

This amendment will serve to implement

### Summary of Amendment Changes with Rationale

#### List of Specific Changes

Section 6.1. Time and Events Table, Footnote m

Section 6.1. Time and Events Table, Footnote m is revised to make the Drug and Alcohol test type flexible. At screening and on Day -1, this test would have been performed urine based or alternatively serum based. However, it was recognized that each site has their standard tests for this assessment. At the discretion of the investigator, sites will be able to use their standard test in order to ensure that the test results will be ready for an evaluation prior the dosing. Test will also be performed on Day 13.

#### PREVIOUS TEXT

Urine test will be performed for drug and alcohol screening at Screening (it must be negative prior to dosing) and Day-1 visits. For subjects who are not able to produce the required amount of urine sample, serum based test will be performed as an alternative.

#### REVISED TEXT

Test will be performed for drug and alcohol at Screening, Day-1, and Day 13 visits check-in for subjects who participate in the study as outpatient, and it must be negative prior to dosing.

Section 6.1. Time and Events Table, Footnote

A new footnote, footnote n, is included to clarify how hemoglobin can be assessed on Day 3, Day 7, and Day 11 visits.

#### PREVIOUS TEXT

N/A

#### REVISED TEXT

Hemoglobin assessment will be by a HemoCue device.

## **AMENDMENT 3**

**This amendment will apply to all the study sites and all countries.**

This amendment will serve to implement

### **Summary of Amendment Changes with Rationale**

#### **List of Specific Changes**

Section 4.2.2., Inclusion and Exclusion Criteria, the numbering of each criterion was inadvertently changed starting from subtitles “Efficacy” and “Other”. After subtitle “Safety”, the numbering was not consecutively increasing for the remaining inclusion and exclusion criteria. The inclusion and exclusion criteria numbers were changed to be consecutive. Inclusion criteria numbers now starts from 1 and goes up to 12, exclusion criteria numbers start from 1 and goes up to 28.

#### **PREVIOUS TEXT**

After the subtitle “Safety”, the numbering for the additional inclusion and exclusion criteria under the next subtitles “Efficacy” and “Other” was starting from 1 again, and was not consecutive.

#### **REVISED TEXT**

Numbering of both inclusion and exclusion criteria is updated after the subtitle “Safety”. It is now starting from 1 and goes up to 12 for inclusion criteria and it start from 1 and goes up to 28 for exclusion criteria.

Section 4.3.3. Caffeine, Alcohol, and Tobacco, the word “sample” was missing after the word “the final pharmacokinetic” in the last part of first sentence, this is now included.

#### **PREVIOUS TEXT**

During each dosing session, subjects will abstain from ingesting caffeine- or xanthine containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 h prior to the start of dosing until collection of the final pharmacokinetic during each session.

#### **REVISED TEXT**

During each dosing session, subjects will abstain from ingesting caffeine- or xanthine containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 h prior to the start of dosing until collection of the final pharmacokinetic sample during each session.

## AMENDMENT 4

**This amendment will apply to all the study sites and all countries.**

This amendment will serve to implement

### Summary of Amendment Changes with Rationale

#### List of Specific Changes

List of Abbreviations

The abbreviation for kilocalorie, kcal, is included in the list.

PREVIOUS TEXT

The abbreviation kcal was not listed.

REVISED TEXT

The abbreviation kcal is now listed.

Regulatory Agency Identifying Number(s), the EudraCT number was provided as 2013-002681-39. The EudraCT number is now updated as “2014-001197-34” which is the correct number for this specific protocol.

PREVIOUS TEXT

EudraCT: 2013-002681-39

REVISED TEXT

EudraCT: 2014-001197-34

Section 4.2.1 Inclusion Criteria, Efficacy, inclusion criteria#5

The urine output and Kt/V values were revised for subject’s eligibility after study investigators provided further information gathered about these conditions for the subjects who are on peritoneal dialysis.

PREVIOUS TEXT

Inclusion#5: A subject is eligible to enroll and participate in this study if he/she has ESRD and is on peritoneal dialysis for at least 2 months with estimated minimal residual kidney function (average urine output < 100 mL/daily) with stable Kt/V urea > 1.7 weekly.

REVISED TEXT

Inclusion#5: A subject is eligible to enroll and participate in this study if he/she has ESRD and is on peritoneal dialysis for at least 2 months with an average urine output of <

750 mL/daily with a combined weekly (urine and peritoneal dialysis output) Kt/V urea > 1.7 measured at any time within last 3 months.

#### Section 4.2.1. Inclusion Criteria, Efficacy, inclusion#8

Hemoglobin levels are updated to meet with country specific requirements. **For UK only site(s)**, hemoglobin value is updated as  $\leq 11$  g/dL for ESA naïve subjects and as  $\leq 12.0$  g/dL for subjects receiving ongoing ESA treatment.

#### PREVIOUS TEXT

##### Inclusion#8

Has a hemoglobin value:

- For ESA naïve subjects:  $< 10.0$  g/dL For subjects receiving ongoing ESA treatment:  $\leq 11.0$  g/dL at Screening.

#### REVISED TEXT

##### Inclusion#8

Has a hemoglobin value:

- For ESA naïve subjects:  $< 10.0$  g/dL (**UK site(s) only:**  $\leq 11.0$  g/dL)
- For subjects receiving ongoing ESA treatment:  $\leq 11.0$  g/dL at Screening (**UK site(s) only:**  $\leq 12.0$  g/dL at Screening).

#### Section 4.2.2. Exclusion Criteria, Safety, exclusion criteria#15

The exclusion criteria was revised to be flexible for those subjects who have not received their ophthalmology exam within 12 months prior to Screening, so they may take their exam with a referral from the study investigators during Screening period.

#### PREVIOUS TEXT

Exclusion#15: History of proliferative vascular eye disease (e.g., choroidal or retinal disease, such as neovascular age-related macular degeneration, proliferative diabetic retinopathy or macular edema) based upon having had an ophthalmologic exam within 12 months prior to Screening.

#### REVISED TEXT

Exclusion#15: History of proliferative vascular eye disease (e.g., choroidal or retinal disease, such as neovascular age-related macular degeneration, proliferative diabetic retinopathy or macular edema) based upon having had an ophthalmologic exam within 12

months prior to the end of the Screening period (The screening period is from the screening visit until Day -1).

#### Section 4.3.2 Meals and Dietary Restrictions

It was stated that subjects would not consume any food and drinks (except water) during 4 h fasting period after dosing on Day 1 and Day 14. Based on the initial feedback from one of study sites, some subjects on peritoneal dialysis are very hungry after they finish night portion therapy on peritoneal dialysis cycler. This is most likely due to the relatively high insulin dose required to mitigate high dextrose content in the peritoneal dialysis fluid needed to achieve adequate ultrafiltration. Thus this section was revised to allow subjects to have some light snacks during this 4 h fasting period after dosing.

#### PREVIOUS TEXT

Subjects will refrain from any food and drink (except water) at least 4 h before dosing and 4 h after dosing on Day 1 and Day 14.

#### REVISED TEXT

Subjects will refrain from any food and drink (except water) at least 4 h before dosing on Day 1 and Day 14. On Day 1 and Day 14 subjects will be allowed a light snack (e.g., crackers and cheese or half a sandwich with a beverage which will not exceed 500 Kcal) upon request.

#### Section 5.3.3. Stopping Criteria;

The stopping criteria related to the hemoglobin level is updated to meet with country specific requirements. **For UK only site(s)**, stopping criteria for absolute hemoglobin level now is  $\geq 12.0$  g/dL to stop the dosing.

#### PREVIOUS TEXT

- On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level  $> 11.0$  g/dL, a second hemoglobin measurement will be obtained at the same study visit to confirm. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.

#### REVISED TEXT

- On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level  $> 11.0$  g/dL (**UK site(s) only**:  $\geq 12.0$  g/dL), a second hemoglobin measurement will be obtained at the same study visit to confirm. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.

Section 6.4.2. Dialysate Sample Collection, on Day 1 and Day 14, the volume of dialysate solution to be collected for analysis was specified as 10 mL aliquot. This is revised to 1.5 mL.

## PREVIOUS TEXT

On Day 1 and Day 14, “..approximately 10 mL aliquot of dialysate from..”

## REVISED TEXT

On Day 1 and Day 14, “..approximately 1.5 mL aliquot of dialysate from..”

Section 6.1, Time and Events Table, there was a typo error on the Day of Follow-up visit. It was entered as Day 23. This is now corrected as Day 22.

## PREVIOUS TEXT

Column “Follow Up (refer to Section 3.1)”, Protocol Activity, Day 23

## REVISED TEXT

Column “Follow Up (refer to Section 3.1)”, Protocol Activity, Day 22

## AMENDMENT 5

**This amendment will apply to all the study sites and all countries.**

This amendment will serve to implement

### Summary of Amendment Changes with Rationale

#### List of Specific Changes

##### List of Abbreviations

##### PREVIOUS TEXT

APD	Ambulatory peritoneal dialysis
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##### REVISED TEXT

APD	Automated peritoneal dialysis
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##### Section 4.1 Number of Subjects

##### PREVIOUS TEXT

Approximately 30 subjects with ESRD will be enrolled (15 subjects in each cohort) considering high dropout in the study to ensure completion of 12 evaluable subjects such that 6 CAPD subjects and 6 APD subjects complete dosing and critical assessments.

##### REVISED TEXT

Approximately 30 subjects with ESRD may be enrolled (15 subjects in each cohort) considering high dropout in the study to ensure completion of 12 evaluable subjects such that 6 CAPD subjects and 6 APD subjects complete dosing and critical assessments. However, if during the informal review of the available PK data it is determined that there are no clinically-significant differences in PK between the CAPD and APD populations, the planned number of subjects may be reduced.

##### Section 4.2.1 Inclusion Criteria

##### PREVIOUS TEXT

5. A subject is eligible to enroll and participate in this study if he/she has ESRD and is on peritoneal dialysis for at least 2 months with an average urine output of < 750 mL/daily with a combined weekly (urine and peritoneal dialysis output) Kt/V urea > 1.7 measured at any time within last 3 months.

## REVISED TEXT

5. A subject is eligible to enroll and participate in this study if he/she has ESRD and is on peritoneal dialysis for at least 2 months with a combined weekly (urine and peritoneal dialysis output) Kt/V urea > 1.7 measured at any time within last 3 months.

Section 4.2.2 Exclusion Criteria

## PREVIOUS TEXT

23. The values of ferritin and transferrin within 3 months prior to Screening are:
- transferrin saturation < 20%
  - serum ferritin < 100 µg/L

## REVISED TEXT

23. The most recent values of ferritin and transferrin within 3 months prior to Screening are:
- transferrin saturation < 20%
  - serum ferritin < 100 µg/L

Section 4.3.2 Meals and Dietary Restrictions

## PREVIOUS TEXT

Consumption of red wine, grapefruit (juice), blood orange (juice), star fruit, onions, kale, broccoli, green beans, or apples is prohibited from **7 days prior to the first dose** of GSK1278863 and throughout the study until Day 14.

## REVISED TEXT

Consumption of red wine, grapefruit (juice), blood orange (juice), star fruit, onions, kale, broccoli, green beans, or apples is prohibited from **7 days prior to the first dose** of GSK1278863 until the Follow-Up visit, unless in the opinion of the investigator and GSK Medical Monitor this will not interfere with the study procedures and compromise subject safety.

Section 5.10 Concomitant Medications

## PREVIOUS TEXT

All concomitant medications taken during the study will be recorded in the eCRF.

## REVISED TEXT

All concomitant medications (including rhEPO) taken in the 4 weeks before and during the study will be recorded in the eCRF.

## PREVIOUS TEXT

While no other studies have been performed specifically to evaluate potential interactions with drugs that ma

y be co-administered with GSK1278863, *in vitro* studies showed the potential for inhibition of CYP2C8 (IC<sub>50</sub>: 21 µM) by GSK1278863, while there was no evidence of concentration- or metabolism-dependent inhibitory potential towards human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4.

## REVISED TEXT

There are ongoing clinical studies to evaluate potential interactions with drugs that may be co-administered with GSK1278863. *In vitro* studies showed the potential for inhibition of CYP2C8 (IC<sub>50</sub>: 21 µM) by GSK1278863, while there was no evidence of concentration- or metabolism-dependent inhibitory potential towards human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4

## PREVIOUS TEXT

GSK1278863 is a substrate of murine breast cancer resistance protein (Bcrp) 1 *in vitro*.

## REVISED TEXT

GSK1278863 is a substrate of human breast cancer resistance protein (BCRP) *in vitro*.

Section 4.4 Screen and Baseline Failures

## PREVIOUS TEXT

Data for screen failures will be collected in source documentation at the site but will not be transmitted to GSK.

## REVISED TEXT

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

Section 9.3.1 Analysis Populations

## PREVIOUS TEXT

Not applicable.

REVISED TEXT – New Section in Protocol.

### **All Screened Population**

The “All Screened” population will be defined as all subjects screened.

### **All Subjects Population**

The ‘All Subjects Population’ is defined as all subjects who receive at least one dose of study treatment. This population will be used for the study population and safety analyses.

### **Pharmacokinetic Population**

The ‘PK Population’ is defined as subjects in the ‘All Subjects’ population for whom a pharmacokinetic sample was obtained and analyzed. This will be the population used for all the pharmacokinetic displays.

### Section 9.3.1 Analysis Populations (Section 9.3.1 in Previous Amendments)

#### PREVIOUS TEXT

No formal interim analysis will be performed.

#### REVISED TEXT

Informal PK reviews will be conducted throughout the study to assist Phase III development of the compound.

## AMENDMENT 6

**This amendment will apply to all the study sites and all countries.**

This amendment will serve to implement

### Summary of Amendment Changes with Rationale

#### List of Specific Changes

#### Sponsor/Medical monitor information page

##### PREVIOUS TEXT

Primary & Secondary Medical monitor: fax number: PPD Address:  
GlaxoSmithKline, N0410  
2301 Renaissance Blvd, Bldg #510, PO Box 61540, King of Prussia, PA 19406

##### REVISED TEXT

Primary & Secondary Medical monitor: PPD Address: GlaxoSmithKline,  
UP4400, 1250 S. Collegeville Rd. Collegeville, PA 19426

#### SECTION 1.1.1

##### PREVIOUS TEXT

Additional paragraph added at the end of this section

##### REVISED TEXT

The effective date of the original protocol is 11-APR-2014. In the 2 years that the study has been active, only 4 subjects have completed the study. This includes 1 CAPD and 3 APD subjects. Considering the difficulties with recruitment in general, and the CAPD population in particular, this protocol will be amended to enroll ESRD subjects undergoing peritoneal dialysis of either modality (i.e., CAPD or APD). In addition, in a previous study (PHI115573), the pharmacokinetic properties of daprodustat and the predominant metabolites were able to be adequately characterized in an ESRD population undergoing hemodialysis with 8 subjects. Finally, preliminary results from this study has shown that a subject using CAPD had similar PK to the 3 subjects using APD suggesting that, if there are differences in the PK of daprodustat depending upon the peritoneal dialysis modality, they are likely to be not considered clinically significant.

#### SECTION 1.3

##### PREVIOUS TEXT

As of 28 February 2014, GSK1278863 has been administered as single oral doses ranging from 2 to 300 mg to 175 healthy, adult male and female subjects in five completed Clinical Pharmacology studies (PHX111427, PHI112843, PHI113634, PHI114703,

PHI115385) and administered once daily (15 to 100 mg) or 25 mg twice daily for up to 14 days duration to 20 healthy subjects in completed study PHI112842.

Details of the completed studies, as well as available safety, pharmacokinetic and pharmacodynamic (PD) data, may be found in the Investigator's Brochure (IB) for GSK1278863 (GlaxoSmithKline Document Number RM2008/00267/06).

#### REVISED TEXT

As of 28 August 2015, GSK1278863 has been administered as single oral doses ranging from 2 to 500 mg to 235 healthy, adult male and female subjects in nine completed Clinical Pharmacology and Biopharmaceutical studies (PHX111427, PHI112842, PHI112843, PHI116008, PHI115573, PHI113635, PHI113634, PHI114703, PHI115385) and administered once daily (15 to 100 mg) or 25 mg twice daily for up to 14 days duration to 20 healthy subjects in completed study PHI112842.

Details of the completed studies, as well as available safety, pharmacokinetic and pharmacodynamic (PD) data, may be found in the Investigator's Brochure (IB) for GSK1278863 [GlaxoSmithKline Document Number RM208/00267/07] and associated IB Supplements [GlaxoSmithKline Document Number 2015N266524\_00, GlaxoSmithKline Document Number 17-Dec-2015; GlaxoSmithKline Document Number 2015N266524\_01, 08-Apr-2016].

### **SECTION 3.1**

#### PREVIOUS TEXT

- **Cohort 1** will enrol approximately 15 subjects such that at least 6 subjects on continuous ambulatory peritoneal dialysis (CAPD) will complete all dosing and critical assessments
- **Cohort 2** will enrol approximately 15 subjects such that at least 6 subjects on automated peritoneal dialysis (APD) will complete all dosing and critical assessments.

#### REVISED TEXT

- **Cohort 1** will enrol subjects on continuous ambulatory peritoneal dialysis (CAPD) to complete all dosing and critical assessments
- **Cohort 2** will enrol subjects on automated peritoneal dialysis (APD) to complete all dosing and critical assessments.

Once a total of 8 subjects across both cohorts collectively have completed the trial, enrolment will be stopped and the study will be concluded.

A sufficient number of ESRD subjects undergoing peritoneal dialysis will be enrolled in this study in order to ensure that at least 8 subjects total complete dosing and all critical assessments. However, if during an informal review of available PK data it is determined that the PK appears to be adequately characterized, the planned number of subjects may be reduced.

## PREVIOUS TEXT

Subjects will be offered to stay in residence at the study site (inpatient) or they are allowed to remain at home (outpatient) throughout the study. Regardless of whether subjects remain in residence or not, all subjects are to be at the site every morning for administration of GSK1278863 and for receiving any scheduled assessments. If a subject prefers to participate in the study as an outpatient, subjects will be released from the clinic after dosing or completion of any scheduled assessments.

## REVISED TEXT

Subjects will be offered to stay in residence at the study site (inpatient) or they are allowed to remain at home (outpatient) throughout the study. For subjects that choose to participate in the study as an outpatient, they will be released from the clinic and must return to the clinic for scheduled assessments.

## PREVIOUS TEXT

At a minimum, study staff must ensure that subjects are in residence at the site on full PK Days (**Day 1** and **Day 14**), as well as Days 15, and 16 for 48 and 72 h PK sampling.

## REVISED TEXT

At a minimum, study staff must ensure that subjects are in residence at the site on full PK Days (**Day 1** and **Day 14**), as well as on Days 15, and 16 for 48 and 72 h PK sampling.

**SECTION 3.3**

## PREVIOUS TEXT

Please refer to the GlaxoSmithKline Investigator's Brochure for GSK1278863 for additional pre-clinical and clinical details (GlaxoSmithKline Document Number. RM2008/00267/06, 04 March 2014).

## REVISED TEXT

Please refer to the GlaxoSmithKline Investigator's Brochure [GlaxoSmithKline Document Number. RM2008/00267/07, 14 October 2015] and associated IB Supplements for GSK1278863 [GlaxoSmithKline Document Number 2015N266524\_00, 17-Dec-2015; GlaxoSmithKline Document Number 2015N266524\_01, 08-Apr-2016] for additional pre-clinical and clinical details.

## PREVIOUS TEXT

Based on the non-clinical studies, the primary areas of interest for GSK1278863 are related to GI tolerability (e.g., stomach erosions with bleeding) and potential for thrombosis with ischaemia secondary to erythrocytosis (excessive erythropoiesis).

## REVISED TEXT

Based on the non-clinical studies, the primary areas of interest for GSK1278863 are related to GI tolerability (e.g., stomach erosions with bleeding) and potential for thrombosis and/or tissue ischemia secondary to excessive erythropoiesis.

**PREVIOUS TEXT**

In addition, several events of special interest have been identified based on clinical experience with ESAs including increased risk of cancer related morbidity and mortality and increased risk of major cardiovascular events (e.g., stroke, myocardial infarction, congestive heart failure).

Lastly based on what is currently known of the possible roles for HIF-regulated pathways in mediating hypoxia associated pathophysiology, pulmonary artery hypertension and tissue neo-vascularization (e.g., retinal, joint synovium) have also been identified as areas of special interest.

**REVISED TEXT**

In addition, several events of special interest have been identified based on clinical experience with ESAs including increased risk of cancer related morbidity and mortality and increased risk of major cardiovascular events (e.g., death, stroke, myocardial infarction, congestive heart failure).

Lastly based on what is currently known of the possible roles for HIF-regulated pathways in mediating hypoxia associated pathophysiology, pulmonary artery hypertension, cardiomyopathy, and tissue neo-vascularization (e.g., retinal, joint synovium) have also been identified as areas of special interest.

**SECTION 4.1****PREVIOUS TEXT**

Approximately 30 subjects with ESRD may be enrolled (15 subjects in each cohort) considering high dropout in the study to ensure completion of 12 evaluable subjects such that 6 CAPD subjects and 6 APD subjects complete dosing and critical assessments. However, if during the informal review of the available PK data it is determined that there are no clinically-significant differences in PK between the CAPD and APD populations, the planned number of subjects may be reduced.

**REVISED TEXT**

Approximately 24 subjects with ESRD may be enrolled (12 subjects in each cohort) considering high dropout in the study to ensure completion of 8 evaluable subjects complete dosing and critical assessments. If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor in consultation with the investigator.

**SECTION 4.2****PREVIOUS TEXT**

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on GSK1278863 or other study treatment that may impact subject eligibility is provided in the GSK1278863 IB [GlaxoSmithKline Document Number RM2008/00267/06].

**REVISED TEXT**

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on GSK1278863 that may impact subject eligibility is

provided in the GSK1278863 IB [GlaxoSmithKline Document Number RM2008/00267/07] and associated IB Supplements for GSK1278863 [GlaxoSmithKline Document Number 2015N266524\_00, 17-Dec-2015; GlaxoSmithKline Document Number 2015N266524\_01, 08-Apr-2016].

### **SECTION 4.2.1**

Inclusion criteria #8

PREVIOUS TEXT

Has a hemoglobin value:

- For ESA naïve subjects: <10.0 g/dL (**UK site(s) only**: ≤11.0 g/dL)
- For subjects receiving ongoing ESA treatment: ≤11.0 g/dL at Screening (**UK site(s) only**: ≤12.0 g/dL at Screening).

REVISED TEXT

Has a hemoglobin value:

- For ESA naïve subjects: <10.0 g/dL
- For subjects receiving ongoing ESA treatment: stable Hgb 9.0-11.5 g/dL.

### **SECTION 5.3.3**

PREVIOUS TEXT

- On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level > 11.0 g/dL (**UK site(s) only**: ≥ 12.0 g/dL), a second hemoglobin measurement will be obtained at the same study visit to confirm. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.

REVISED TEXT

- On Days 3, 7 and 11, subject's hemoglobin will be assessed prior to dosing using a HemoCue device. Should subjects have an absolute hemoglobin level > 11.0 g/dL, a second hemoglobin measurement will be obtained at the same study visit to confirm. If confirmed, permanently discontinue GSK1278863 and withdraw subject from the study.

### **SECTION 5.8**

PREVIOUS TEXT

No specific antidote for GSK1278863 is known. Any signs or symptoms of possible overdose are to be treated supportively. In the event of suspected overdose, collect blood samples for pharmacokinetics and safety laboratory immediately. GSK does not recommend specific treatment for an overdose. The Investigator is to use clinical judgment to treat any overdose.

**REVISED TEXT**

No specific antidote for GSK1278863 is known. The expected manifestations of GSK1278863 overdose 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 HD or PD is very low and these are not effective methods to enhance the elimination of GSK1278863. GSK1278863 metabolites are, in part, cleared via hemodialysis.

In the event of suspected overdose:

- collect blood samples for pharmacokinetics and safety laboratory immediately.
- 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.

**SECTION 5.10****PREVIOUS TEXT**

There are ongoing clinical studies to evaluate potential interactions with drugs that may be co-administered with GSK1278863. *In vitro* studies showed the potential for inhibition of CYP2C8 (IC<sub>50</sub>: 21 µM) by GSK1278863, while there was no evidence of concentration- or metabolism-dependent inhibitory potential towards human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4.

GSK1278863 was also observed to be an inhibitor of organic anion transporting polypeptide (OATP) 1B1 and 1B3 *in vitro* with IC<sub>50</sub>s of ~6 µM and ~11 µM, respectively. The average C<sub>max</sub> observed after single dose administration of 5 mg GSK1278863 to healthy subjects was 0.24 µM, suggesting a low risk of an interaction.

**REVISED TEXT**

*In vitro* studies showed the potential for inhibition of CYP2C8 (IC<sub>50</sub>: 21 µM) by GSK1278863, while there was no evidence of concentration- or metabolism-dependent inhibitory potential towards human CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4. In a recent drug-drug interaction, there was no apparent evidence of a drug interaction between GSK1278863, at doses up to 100 mg, with pioglitazone, a CYP2C8 substrate.

GSK1278863 was also observed to be an inhibitor of organic anion transporting polypeptide (OATP) 1B1 and 1B3 *in vitro* with IC<sub>50</sub>s of ~6 µM and ~11 µM, respectively. The average C<sub>max</sub> observed after single dose administration of 5 mg GSK1278863 to healthy subjects was 0.24 µM, suggesting a low risk of an interaction. In a recent drug-drug interaction, there was no apparent evidence of a drug interaction between GSK1278863, at doses up to 100 mg, with rosuvastatin, an OATP1B1 substrate.

**SECTION 5.10.1.1****PREVIOUS TEXT**

As there are limited data on the potential for pharmacokinetic interactions with

GSK1278863, substrates of OATP1B1/1B3 and CYP2C8 should be used with caution and subjects should be monitored for any signs of (increased) toxicity (e.g., liver function tests and creatinine phosphokinase for ‘statins’).

A reduction in dose of the OATP1B1/1B3 or CYP2C8 substrate may be considered if appropriate. Consideration should be given to have statin or other OATP1B1/1B3 substrate dosing held until 12 h after GSK1278863 administration on a case by case basis.

CYP2C8 substrates not described in the prohibited medications section, e.g., including rosiglitazone, pioglitazone, and torsemide are permitted for use during the study, as long as subjects have been taking a stable dose for more than 3 months.

#### REVISED TEXT

This section was deleted and amended in Section 5.10

### **SECTION 6.1 Time and Events Table - footnotes**

#### PREVIOUS TEXT

b Subjects may remain in residence at the site from the afternoon of Day -1 through the last assessment on Day 17, at the discretion of the investigator or by request of the subject (refer to Section 3.1).

c Each dose will be administered within 30 min after completion of the night APD treatment or morning last fill of peritoneal dialysis fluid.

#### REVISED TEXT

b Subjects may remain in residence at the site from the afternoon of Day -1 through the last assessment on Day 17, at the discretion of the investigator or by request of the subject (refer to Section 3.1). Outpatients must return to the site for scheduled PK assessments.

c Each dose will be administered within 30 min after completion of the night APD treatment or morning last fill of peritoneal dialysis fluid. Outpatients can self administer their daily dose, following discussion with the investigator.

### **SECTION 9.2.1**

#### PREVIOUS TEXT

As this study is descriptive in nature and no formal statistical comparisons of PK data will be performed, the sample size of 30 subjects (15 in each cohort) will be recruited such that at least 12 subjects (6 in each cohort) complete the trial. Based on PK parameter CV% of ~50% in subjects with renal impairment or ESRD (refer to GlaxoSmithKline Document Number RM2008/00267/06.GSK1278863 IB) a sample size of at least 6 subjects, the lower and upper bounds of the 95% confidence interval for a PK parameter geometric mean would be within 50% and 202% of the estimate and for sample size of at least 12 subjects, the lower and upper bounds of the 95% confidence interval for a PK parameter geometric mean would be within 65% and 153% of the estimate.

## REVISED TEXT

As this study is descriptive in nature and no formal statistical comparisons of PK data will be performed, the sample size of 24 subjects (12 in each cohort) will be recruited such that at least 8 subjects complete the trial. Based on PK parameter CV% of ~50% in subjects with renal impairment or ESRD [refer to GlaxoSmithKline Document Number RM2008/00267/07, 14-Oct-2015.GSK1278863 IB and associated IB supplements for GSK1278863 [GlaxoSmithKline Document Number 2015N266524\_00, 17-Dec-2015; GlaxoSmithKline Document Number 2015N266524\_01, 08-Apr-2016] for a sample size of at least 8 statistically evaluable subjects, the half width of the 90% confidence interval will be within 56% of the point estimate.

**SECTION 9.3.3.2.1****Steady State Assessment**

## PREVIOUS TEXT

Assessment of plasma GSK1278863 and metabolites steady state will be assessed by evaluating the estimated slope for the day parameter and associated 90% CI within each cohort.

## REVISED TEXT

Assessment of plasma GSK1278863 and metabolites steady state will be assessed by evaluating the estimated slope for the day parameter and associated 90% CI for both the cohorts combined.

**Secondary Comparisons: Assessment of Accumulation**

## PREVIOUS TEXT

To evaluate the accumulation ratio, statistical analysis of GSK1278863 and metabolites will be performed separately after a log transformation of the data.

A mixed effect model will be fitted with day (single and repeat dose), as fixed effects and subject as a random effect. Day 14 will be compared to Day 1 in order to estimate the accumulation ratios,  $R_o = \frac{AUC(0-\tau, Day14)}{AUC(0-\tau, Day1)}$ . The ratios will be calculated by back-transforming the difference between the LS means.

Using the pooled estimate of variance, 90% confidence intervals will be calculated for the primary comparisons, and back-transformed to the original scale.

## REVISED TEXT

To evaluate the accumulation ratio, statistical analysis of GSK1278863 and metabolites for both the cohorts combined will be performed after a log transformation of the data.

A mixed effect model will be fitted with day (single and repeat dose), as fixed effects and subject as a random effect. Day 14 will be compared to Day 1 in order to estimate the accumulation ratios,  $R_o = \frac{AUC(0-\tau, Day14)}{AUC(0-\tau, Day1)}$ . The ratios will be calculated by back-transforming the difference between the LS means.

Using the pooled estimate of variance, 90% confidence intervals will be calculated for  $R_o$ , and back-transformed to the original scale.

### **Assessment of Time Invariance**

#### **PREVIOUS TEXT**

To evaluate the time invariance ratio, statistical analysis of (AUC (0- $\infty$ ) Day 1) and AUC (0-  $\tau$ ) (Day14), of GSK1278863 and metabolites for each cohort will be performed separately after a log transformation of the data.

A mixed effect model will be fitted with day as fixed effects and subject as a random effect. Day 14 AUC (0-  $\tau$ ) will be compared to Day 1 AUC (0- $\infty$ ) by cohort in order to estimate the time invariance ratios,  $R_{S=}$  AUC (0-  $\tau$ , Day 14): AUC (0- $\infty$ , Day 1). The ratios will be calculated by back-transforming the difference between the LS means.

Using the pooled estimate of variance, 90% confidence intervals will be calculated for the primary comparisons, and back-transformed to the original scale.

#### **REVISED TEXT**

To evaluate the time invariance ratio, statistical analysis of (AUC (0- $\infty$ ) Day 1) and AUC (0-  $\tau$ ) (Day14), of GSK1278863 and metabolites for both the cohorts combined will be performed after a log transformation of the data.

A mixed effect model will be fitted with day as fixed effects and subject as a random effect. Day 14 AUC (0-  $\tau$ ) will be compared to Day 1 AUC (0- $\infty$ ) in order to estimate the time invariance ratios,  $R_{S=}$  AUC (0-  $\tau$ , Day 14): AUC (0- $\infty$ , Day 1). The ratios will be calculated by back-transforming the difference between the LS means.

Using the pooled estimate of variance, 90% confidence intervals will be calculated for  $R_s$ , and back-transformed to the original scale.