Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 204836: A 29-day, randomized, double-blinded, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of GSK1278863 in hemodialysis-dependent subjects with anemia associated with chronic kidney disease who are switched from a stable dose of an erythropoiesis-stimulating agent
Compound Number	:	GSK1278863
Effective Date	:	14-FEB-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204836.
- This RAP is intended to describe the analyses of efficacy, safety and pharmacokinetics required for the study.
- This RAP will be provided to the study team members and CRO (PPD) to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe: • The planned analyses of haemoglobin (Hgb) dose-response relationship for three times weekly dosing of GSK1278863 at 29 days in order to describe the efficacy relationship between once-daily (QD) and three-times weekly (TIW) administration. • Other planned analyses and outputs required for the final Clinical Study Report (CSR) for study 204836.
Protocol	• This RAP is based on the protocol amendment number 01 (Dated: 11-MAY-2016) of study 204836 (GlaxoSmithKline Document Number 2015N241222_01) and eCRF Version 4.00
Primary Objective	• Characterize the dose-response relationship between GSK1278863 administered three-times weekly and Hgb at Day 29
Primary Endpoint	• Hgb change from baseline at Day 29
Study Design	• A randomized, double-blinded, dose-ranging, placebo-controlled, parallel group study. • There is a 28-day Screening period, a 29-day Treatment period, and a Follow-up visit 14 ± 3 days after completing treatment. • Subjects will be randomized 1:1:1:1:1 to receive one of four three-times weekly doses (10 mg, 15 mg, 25 mg, 30 mg), or placebo on a dialysis day. • Subjects will be stratified by prior ESA dose based on the average weekly (for epoetins or darbepoetin) or monthly (for methoxy PEG-epoetin beta) dosing during the 12 weeks prior to randomization (Day 1) • Approximately 200 subjects will be screened to achieve approximately 90 randomized and 75 evaluable subjects, with approximately 15 evaluable subjects per treatment group.
Planned Analyses	• No interim analysis is planned. • Planned final analyses will be performed after all subjects have completed the study, database freeze has been declared, and study treatment has been unblinded.
Analysis Populations	• All Screened population comprises all subjects who consented to participate in the clinical trial and were screened. • All Randomized population comprises all randomized subjects regardless of whether they took study drug. This population will be based on the treatment to which the subject was randomized. • The Intent-to-Treat (ITT) population comprises all randomized subjects who received at least one dose of study treatment, had a baseline and at least one corresponding on treatment assessment, including Hgb (Quest or HemoCue). This population will be used to summarize subject disposition, baseline and demographic data and will be the primary population used in the efficacy analyses. Subjects will be classified according to the treatment group to which they were randomized.

Overview	Key Elements of the RAP
	• The Safety population comprises all subjects who received at least one dose of study treatment. This population will be based on the treatment and the actual dose the subject received, and will be used for all assessments of safety and tolerability. • The Per Protocol (PP) population comprises all ITT subjects who were not major protocol violators with regards to inclusion/exclusion criteria, investigational product compliance and concomitant medication instructions. The Per-Protocol population will be used for sensitivity analyses. The PP population will not be analyzed if this population comprises more than 80% of the ITT population. • The Completers population comprises all ITT subjects who fully completed the Day 29 study assessments without prematurely discontinuing study drug. The Completers Population will be used for sensitivity analyses • Pharmacokinetic population comprises all subjects from whom a pharmacokinetic sample has been obtained and analyzed.
Hypothesis	• No formal hypothesis will be tested.
Primary Analyses	• A three-parameter Emax model is planned to model the dose-response relationship. The Emax model will be fitted using Bayesian statistical methods. • If problems are encountered fitting a three parameter Emax model or if the Emax shape is a poor fit for the data and a linear relationship looks plausible across the three-times weekly dose range, then a linear model will be considered. Alternative models will also be investigated until an appropriate model can be chosen (e.g., quadratic model, log-transformed dose *et al.*).
Secondary Analyses	• Efficacy: In general, all planned secondary analyses of efficacy endpoints (i.e. hepcidin, hematocrit, RBC count, reticulocyte count, reticuloctye Hgb, EPO, and VEGF) are descriptive and estimation based. • Safety: Overall safety evaluations will be descriptive using the Safety Population. Graphical and tabular displays will be presented to facilitate safety data review.
PK/PD Analyses	• Daprodustat (GSK1278863) and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) plasma pharmacokinetic concentration will be summarized by visit and planned collection time point for each dose level of daprodustat, will be plotted appropriately, and will be listed. Plasma concentration-time data for daprodustat and its six metabolites will be analyzed by non-compartmental methods. Pharmacokinetic parameters (AUC(0-t), AUC(0-∞), C_{max}, t_{max}, $t_{1/2}$) will be determined from the plasma concentration-time data for daprodustat and its six predominant metabolites, as data permits. Pharmacokinetic parameters will be summarized by treatment group using descriptive statistics, and will be listed. • The relationship between plasma concentrations of daprodustat and selected endpoints may be explored using appropriate pharmacokinetic/ pharmacodynamic models. Exploratory modeling of the plasma EPO, VEGF and/or hepcidin concentrations also may be conducted, as a function of

Overview	Key Elements of the RAP
	daprodustat dose or PK, and may be used to further characterize the effect of daprodustat. Other PD data such as iron parameters and RBC indices may also be included if relevant to characterize the PD response. Relevant measures of the secondary and exploratory endpoints (if meaningful) will be initially explored graphically and where appropriate modeling approaches will be used. Pharmacokinetic/Pharmacodynamic exploratory analysis will be the responsibility of CPMS. If additional details are needed, they will be included in a separate PK/PD RAP. The results of the PK/PD analyses may be reported in separate PK/PD report(s).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

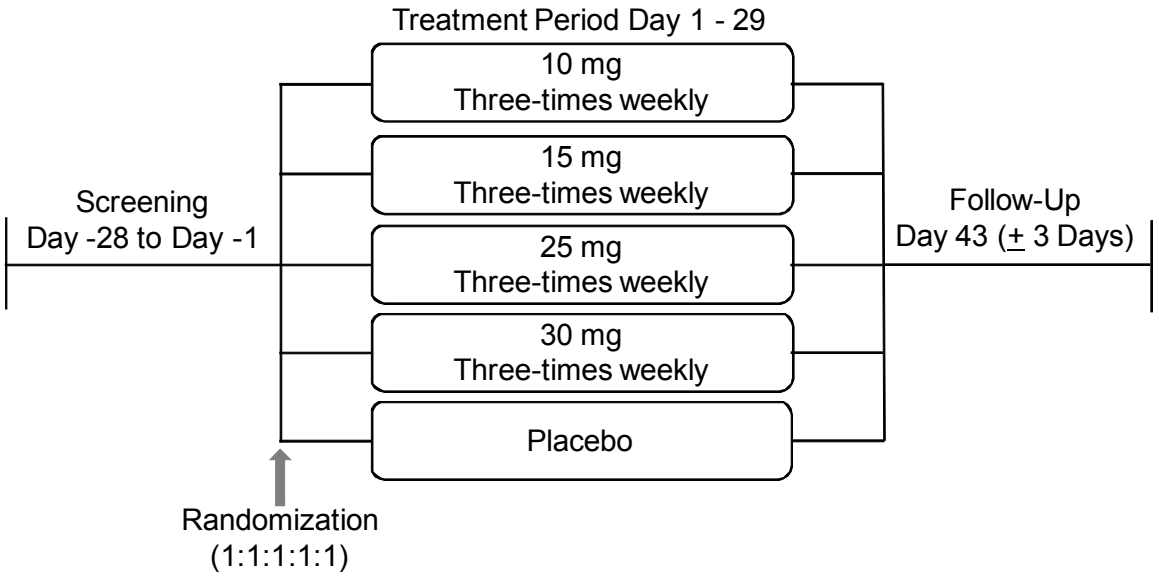
Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• For Hgb Day 1 measurement using central lab Quest will serve as the baseline value. (Section 7.3)	• For Hgb the average of Hgb measured by the central lab, Quest, at Week -2 and Day 1 visits will serve as the baseline value.	• Average of Hgb measured by the central lab, Quest, at Week -2 and Day 1 visits will reflect the overall pre-treatment stable Hgb level.

2.2. Study Objective(s) and Endpoint(s)

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

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• A randomized, double-blinded, dose-ranging, placebo-controlled, parallel group study. • There is a 28-day Screening period, a 29-day Treatment period, and a Follow-up visit 14 ±3 days after completing treatment.

Dosing	• Subjects who meet eligibility criteria will be randomized and begin dosing on Day 1. Subjects will discontinue their current ESA therapy and will be randomized to receive one of four three-times weekly doses (10 mg,15 mg, 25 mg, or 30 mg of GSK1278863), or placebo on a dialysis day.
	  • This should be timed such that randomization (Day 1) occurs on the date that would have been the next scheduled dose of ESA (or as close as practicable).
	  • For subjects with a three-times weekly dialysis schedule, Day 1 must not occur on the first dialysis session of the week (e.g., if Monday-Wednesday-Friday schedule, the study visit cannot be on Monday).
	  • For subjects with a four- to five-times weekly dialysis schedule, Day 1 can be on any hemodialysis session of the week.
	• The treatment period will be for a total of 29 days.

Treatment Assignment	• Approximately 200 subjects will be screened to achieve approximately 90 randomized and 75 evaluable subjects, with approximately 15 evaluable subjects per treatment group. • Subjects will be randomized 1:1:1:1:1 to receive one of four three-times weekly doses (10 mg, 15 mg, 25 mg, 30 mg), or placebo on a dialysis day

Overview of Study Design and Key Features	
	• Randomization schedule will be computer generated by PPD using the randomization system Prism. • Subjects will be stratified by prior ESA dose based on the average weekly (for epoetins or darbepoetin) or monthly (for methoxy PEG-epoetin beta) dosing during the 12 weeks prior to randomization (Day 1). • Central randomization and PPD's Interactive Voice/Web Response System (IVWRS) will be used for treatment allocation.
Interim Analysis	• No interim analysis is planned.

2.4. Statistical Hypotheses

No formal hypothesis will be tested. This study is designed to estimate the relationship between three-times weekly doses of GSK1278863 and Hgb response after 29 days of treatment in hemodialysis-dependent subjects with anemia associated with chronic kidney disease who are switched from a stable dose of an erythropoiesis-stimulating agent. To achieve this, a model-based dose-response analysis is planned with the primary endpoint of change in Hgb from baseline at Day 29. It is anticipated that the data and the estimated parameters generated from this model will enable conversion of QD starting and maintenance dose regimens to three-times weekly doses/regimens.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed or withdrawn from the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by both PPD and GSK Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to GSK and PPD procedures.

The final analyses with the exception of the dose-response analysis will be performed by PPD. All dose-response analyses as described in Section 7.1.2 will be carried out by GSK.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screened	• Comprise all subjects who consented to participate in the clinical trial and were screened.	• Summarize the screen failure subjects
All Randomized	• Comprise all randomized subjects regardless of whether they took study drug. • This population will be based on the treatment to which the subject was randomized. • Any subject who received a treatment randomization number will be considered to have been randomized.	• Describe the breakdown of Study Populations • Study Population • Selected listings
Safety	• Comprise all subjects who received at least one dose of study treatment. • This population will be based on the treatment and the actual dose the subject received. Note: (1) If a subject randomized to the placebo arm, temporarily received daprodustat by mistake during the study, then the subject would be included in the corresponding daprodustat arm in the Safety population. (2) If a subject randomized to one of the daprodustat arms, temporarily received placebo by mistake during study, then the subject would remain in the randomized daprodustat arm in the Safety population.(3) If a subject randomized to one of the daprodustat arms, received a wrong dose of daprodustat by mistake throughout the study, then the subject will be included in the daprodustat arm in the Safety population based on the actual daprodustat dose received.(4) If a subject randomized to one of the daprodustat arms, temporarily received wrong dose of daprodustat by mistake during study, then the subject would be included in the daprodustat arm from which the subject received >50% of the study medication.	• Study Population • Safety and tolerability
Intent-To-Treat	• Comprise all randomized subjects who received at least one dose of study treatment, had a baseline and at least one corresponding on treatment assessment, including Hgb (Quest or HemoCue) • This population will be based on the treatment to which the subject was randomized.	• Efficacy
Per-Protocol	• Comprise all Intent-To-Treat subjects who	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
	were not major protocol violators with regards to inclusion/exclusion criteria, investigational product compliance and concomitant medication instructions. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population). • The Per-Protocol population will be used for sensitivity analyses. The Per-Protocol population will not be analyzed if this population comprises more than 80% of the Intent-To-Treat population.	
Completer	• Comprise all Intent-To-Treat subjects who fully completed the Day 29 study assessments without prematurely discontinuing study drug. • The Completer Population will be used for sensitivity analyses.	• Efficacy
Pharmacokinetic Population	• Comprises all subjects from whom a pharmacokinetic sample has been obtained and analyzed.	• PK

NOTES :

- Please refer to Appendix 14: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

- Important/significant protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Important/significant deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

  All protocol deviations, including significant protocol deviation, will be tracked in PPD CTMS (Clinical Trial Management System), and will be reviewed by PPD and GSK study team throughout the conduct of the study in accordance with PPD's Study Deviation Rules Document.

  - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.

  - This dataset will be the basis for the summaries and listings of protocol deviations.

- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

- There are planned examination of covariates and subgroups.
- There are no planned adjustments made for multiple centres in this study.
- There are no planned adjustments for multiple comparisons or multiplicity.

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
Section 11.2	Appendix 2: Time & Events
Section 11.3	Appendix 3: Assessment Windows
Section 11.4	Appendix 4: Treatment States and Study Phases
Section 11.5	Appendix 5: Data Display Standards & Handling Conventions
Section 11.6	Appendix 6: Derived and Transformed Data
Section 11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
Section 11.8	Appendix 8: Values of Potential Clinical Importance
Section 11.9	Appendix 9: Multicenter Studies
Section 11.10	Appendix 10: Examination of Covariates and Subgroups
Section 11.11	Appendix 11: Multiple Comparisons & Multiplicity
Section 11.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Section 11.13.	Appendix 13: Abbreviations & Trade Marks
Section 11.14	Appendix 14: List of Data Displays
Section 11.15	Appendix 15: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on either the Safety population, the ITT population or the All Randomized population, unless otherwise specified. All summary tables will include a Total column and a Dapro Total column, unless otherwise specified.

Table 3 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 3 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y		
Reasons for Screening Failure	Y		Y
Study Treatment Discontinuation	Y		Y
Reasons for Study Withdrawal			Y
Subjects for Whom the Treatment Blind was Broken			Y
Randomized and Actual Treatment Assignment			Y
Subjects at Each Visit	Y		
Protocol Deviations			
Important Protocol Deviations	Y		Y
Deviations Leading to Exclusions from Per Protocol Population	Y		[1]
Subjects with Inclusion/Exclusion Criteria Deviations	Y		Y
Populations Analyzed			
Study Populations	Y		Y
Number of Subjects by Center	Y		
Subjects Excluded from Any Population			Y
Demography			
Demographic and Other Baseline Characteristics	Y		Y
Race & Racial Combinations	Y		Y [2]
Summary of Race and Racial Combination Details	Y		Y[2]
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)	Y		Y
Concomitant Medication	Y		Y
Relationship Between ATC Level 1, Ingredients And Verbatim Text			Y
Cardiovascular Risk Assessment			Y
Family History of Cardiovascular Risk	Y		

Display Type	Data Displays Generated		
	Table	Figure	Listing
Substance Use History	Y		Y
Baseline Hemodialysis	Y		Y
Prior Erythropoiesis-Stimulating Agents	Y	Y	Y
Erythropoiesis Stimulating Agents Medications			Y
Standardized Prior Recombinant Human Erythropoietin Dose		Y	
Concomitant Erythropoiesis-Stimulating Agents	Y		
Pre-therapy Average Iron Dose	Y		
On-therapy Average Iron Dose	Y		
Subjects Using IV Iron Dose Between Study Treatment Start and Final Visit	Y		
Iron Therapy			Y
Blood Products	Y		Y
Exposure and Treatment Compliance			
Study Medication Overall Compliance	Y		Y
Extent of Exposure to Study Treatment	Y		Y

NOTES :

1. Subjects with protocol deviations leading to exclusions from Per Protocol population will be listed in Listing of Subjects Excluded from Any Populations
2. Listing of race will be generated, which includes both "Race and Racial Combinations" and "Race and Racial Combination Details"

6.2. Display Details

6.2.1. Subject Disposition

The number of subjects who completed the study for purpose of the disposition table will consist of all randomized subjects who, as documented in the eCRF, have completed all study visits, including the follow-up visit.

Reasons for withdrawal from study and study treatment will be summarized for each treatment group and overall. A by-subject listing of reasons for study withdrawal and a by-subject listing of reasons for study treatment discontinuation will be produced.

The number and percentage of subjects who failed screening and were therefore not entered into the study, overall and by reason, will be summarized. A listing of the screen failure record for all subjects who failed screening, including the reasons for screen failure will be produced.

The number and percentage of subjects at each visit will be summarized for each treatment group and overall.

A listing of subjects for whom the treatment blind was broken and a listing of randomized and actual treatment assignment will be produced.

6.2.2. Protocol Deviations

The number and percentage of subjects who had important/significant protocol deviations defined in Section 11.1.1 will be summarized overall and by treatment group. (Note: Given that different terminologies have been used by GSK and PPD, the terms "important protocol deviation" and "significant protocol deviation" will be used interchangeably throughout the RAP.)

Protocol deviations leading to exclusion from Per Protocol population will be summarized overall and by treatment group. (See Section 11.1.2 for protocol deviations, which may lead to the exclusion of a subject from the Per Protocol population)

A listing of important protocol deviations will be produced. Subjects excluded from Per Protocol can be found in the listing of subjects excluded from any populations (see below).

Inclusion and exclusion criteria deviations will be summarized and listed.

6.2.3. Populations Analyzed

The number of subjects who were randomized into the study, the number of subjects within each analysis population (ITT, Per Protocol, Completers, Safety and PK) will be summarized for each treatment group and overall. A by-subject listing showing inclusion within each study population and a listing of subjects excluded from any populations will be produced.

The number and percentage of subjects will be summarized by country and by center within each country for each treatment group and overall.

6.2.4. Demography

Demographic and baseline data will include age, gender, ethnicity, race, diabetes, baseline height, baseline weight, baseline body mass index (BMI), prior ESA dose (stratification factor, Low ESA dose: <100 IU/kg/week epoetin OR <0.5 µg/kg/week darbepoetin OR<0.6 µg/kg/week methoxy PEG-epoetin beta vs. High ESA dose: ≥100 IU/kg/week epoetin OR ≥0.5 µg/kg/week darbepoetin OR ≥0.6 µg/kg/week methoxy PEG-epoetin beta), type of ESA, standardized prior rhEPO Dose (IU/kg/Week, including epoetin, darbepoetin, and Mircera), baseline Hgb, baseline ferritin, baseline absolute reticulocyte count, baseline iron-based phosphate binder (ferric citrate and sucroferric oxyhydroxide), and baseline pre-dose plasma EPO. In addition, the following data will be categorized and summarized for each treatment group and overall:

- Age (<65, >=65 years)
- Baseline Hgb (< 10, >= 10 g/dL)
- Baseline Weight (<=Median, > Median kg)
- Baseline BMI (<27, >=27 kg/m^2)
- Race (White, African American, Asian, Other)
- Standardized Prior rhEPO (<=xx.xx, >xx.xx and < xx.xx, >=xx.xx) (Tertile)
- Diabetes (Yes, No)
- Iron-based Phosphate Binders (Yes, No)
- Baseline Absolute Reticulocyte Count (<= Median, >Median TI/L)

All the above demographic and baseline data will be summarized by treatment group and overall for the Safety, ITT and All Randomized populations.

A by-subject listing of demographic and baseline characteristics will also be produced.

Summaries of race and racial combinations and race and racial combination details will be produced for each treatment group and overall. A listing of race and racial combination details by subject will also be produced.

6.2.5. Medical Conditions and Concomitant Medications

The number and percentage of subjects with each past and current medical condition will be reported for each treatment group and overall. Past conditions are those reported as 'past' and current conditions are those reported as 'current' at screening. Past and current conditions will be reported separately. Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (current MedDRA version at the time of DBR) and reported by system organ class (SOC) and preferred term.

Summaries of family history of cardiovascular risk, and substance use history will be provided by treatment group and overall.

Furthermore, summaries of baseline hemodialysis (mode of dialysis) will be produced by treatment group and overall.

By-subject listings of data for past and current medical conditions, cardiovascular risk assessments, and history of substance use will be produced separately. In addition, a listing of hemodialysis will be provided.

For reporting purposes, medications will be classified as prior, concomitant, and/or post-treatment using the associated start and stop dates recorded in the eCRF and relative to the first and last dose dates of IP (see Section 11.4.2.3). Medications will be coded using the GSK Drug coding dictionary (current version at the time of DBR).

Concomitant medications will be summarised by GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1 (body system) and ingredient. Drugs that are composed of a combination of ingredients will be displayed according to the ATC classifications of the ingredients, not of the combination.

A summary of the number and percentage of subjects receiving concomitant medications will also be displayed using a method that presents multi-ingredient medications according to their combination ATC classification rather than the classifications of the ingredients. This display will also include single-ingredient medications. Multi-ingredient medications will be labelled according to the sum of their ingredients, e.g., "TYLENOL Cold and Flu" would appear as "CHLORPHENAMINE MALEATE + DEXTROMETHORPHAN HYDROBROMIDE + PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE" under the ATC headings for "Nervous System" and "Respiratory System" (the combination's ATC classifications). A multi-ingredient drug's component ingredients will not be summarized separately.

A listing of all medications taken by subjects, including any which are only prior or post-treatment, will be produced. The relationship between ATC level 1, ingredients and verbatim text for all medications in the study will be listed.

A summary of prior erythropoiesis-stimulating agents taken in the 12 weeks prior to randomization will be produced. In addition, if any subject takes erythropoiesis-stimulating agents during the 29-day treatment period of the study (prohibited medication for all subjects between Day 1 and Day 29) this will be tabulated by treatment group. A bar chart showing the proportions of subjects taking different prior erythropoiesis-stimulating agents will be provided. A histogram of prior standardized rhEPO dose will also be produced.

A listing of prior erythropoiesis-stimulating agents and a listing of all (prior, concomitant, and post-treatment) erythropoiesis-stimulating agents will be provided.

Pre-therapy and on-therapy average iron dose (separately for oral and IV) by treatment group will be summarized. In addition, a table showing the number of subjects (i) using IV iron at Study Treatment Start and Final visit, (ii) stopping IV iron on-therapy and (iii) starting IV iron after treatment start will be produced for the Safety and Completers population. All iron therapy data taken during the study will be listed.

A summary and a listing of any blood products or blood supportive care products taken during the study will be produced by treatment group.

6.2.6. Exposure and Treatment Compliance

The complete dosing experience will be listed for all subjects. The total duration of exposure (number of days on study drug), average three times a week dose and cumulative dose will be summarized by treatment group and Dapro total.

The average three times a week dose (the cumulative actual dose divided by the expected number of doses during the treatment period) is calculated for each subject first and the summary statistics for each treatment group and for Dapro Total are calculated based on the subject average TIW dose.

$$Cumulative\ actual\ dose = \sum_{bottle=1}^{3} \left(\begin{matrix} \text{No.of tablets taken from each bottle} * \\ tablet\ strength\ (mg/tablet) \end{matrix} \right)$$

Note: The tablet strengths are 5 mg or 25 mg for subjects randomized to dapro arms, and 0 mg for subjects randomized to placebo arm (unless the subject received daprodustat by mistake during the study).

For subjects who completed the 29-day treatment period, the expected number of doses during the treatment period is 13. For subjects who permanently discontinued the study treatment and/or withdrew from the study, the expected number of doses during the treatment period will be calculated in the same way as the calculation of the expected cumulative number of tablets for each bottle described below for compliance calculation.

For each subject "Days on study drug" will be calculated as Last Dose Date – First Dose Date +1.

A summary and a listing of study medication compliance will be produced by treatment group.

For each bottle, the compliance will be calculated for the whole study treatment period as the percentage of the cumulative number of tablets taken [100*(cumulative number of tablets taken) / (expected cumulative number of tablets for the subject's treatment duration)]. For subjects who completed the 29-day treatment period, the expected cumulative number of tablets should be 13. For subjects who were permanently discontinued study treatment or early withdrew from the study, following algorithm will be used to calculate the "expected cumulative number of tablets" taken from each bottle during the treatment period:

1. Determine the expected "dose day", where "dose day" is defined as days since the first dose date. (i.e. dosing date – first dose date +1)
    a. For a subject who receives dialysis 3-5 times per week and starts dosing on Monday or Tuesday, the expected dose days are: 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, and 29.
    b. For a subject who receives dialysis 3-5 times per week and starts dosing on Wednesday or Thursday, the expected dose days are: 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27, and 29.
    c. For a subject who receives dialysis 3-5 times per week and starts dosing on Friday or Saturday, the expected dose days are: 1, 4, 6, 8, 11, 13, 15, 18, 20, 22, 25, 27, and 29.
2. Determine the "expected cumulative number of tablets" by comparing the last dose day (last dose date – first dose date +1) with the expected dose days. For example, for a subject who received dialysis 3 times per week and started dosing on Wednesday, if the subject's last dose day is day 7, then the expected cumulative number of tablets taken from a bottle should be 3 (because the last dose was administered before the fourth dose day); if the subject's last dose day is day 8, then the expected cumulative number of tablets taken from a bottle should be 4 (because the last dose was administered on the fourth dose day).
3. For all other situations which is not covered in step "1" (i.e. a subject who does not receive dialysis 3-5 times per week and/or does not start dosing on Monday – Saturday), the following formula will be used to estimate the "expected cumulative number of tablets" taken from each bottle during the treatment period:

$$\text{Expected cumulative number of tablets} = round\left((t-1) * 3/7,1\right) + 1$$

Where "i" is the "last dose day".

Overall compliance for a subject is categorized as follows: >0% and <80% if compliance for at least one bottle is <80%, 80% to 120% if compliance for all three bottles is between 80% and 120%, and >120% otherwise.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the "Intent-To-Treat" population, unless otherwise specified.

Table 4 provides an overview of the planned Hgb efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 4 Overview of Planned Hgb Efficacy and Sensitivity Analyses based on Emax Model and Other Analyses of Hgb

Endpoint and Related Analyses	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Analyses of Hgb change from baseline at Day 29 based on Emax Model														
Posterior Estimates from the Bayesian 3 Parameter Emax Dose-Response Model for the Primary and Sensitivity Prior Analyses and the Estimates from the Frequentist 3 Parameter Emax Dose-Response Model								Y[1]	Y[1]	Y[1]				
Posterior Probability Distribution for Predicted Hemoglobin Change (g/dL) from Baseline at Day 29 Based on Primary Analysis									Y					
Density Plots Associated with Emax Model Parameter, E0									Y					
Density Plots Associated with Emax Model Parameter, Emax									Y					
Density Plots Associated with Emax Model Parameter, ED50									Y					
Density Plots Associated with Emax Model Parameter,									Y					

Endpoint and Related Analyses	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Variance														
Posterior Predictive Distribution for Hemoglobin (g/dL) Change from Baseline at Day 29 for a Future Subject based on Primary Analysis									Y					
Posterior Predictive Probability that Day 29 Hemoglobin (g/dL) Change for a Future Subject will be in the Range [−0.5, 0.5] g/dL by Daprodustat Dose									Y					
Other Summary and Analyses of Hgb														
Hgb Imputations				Y										
Dose-Response Linear Model for Change in Hemoglobin at Day 29								Y[2]						
Linear Model between the corresponding QD and TIW doses with the same Change in Hemoglobin at Day 29								Y						
Summary of Dose Ratio Between Three-Times Weekly Doses (Observed) and QD Doses	Y													
Summary of Dose Ratio Between Three-Times Weekly Doses and QD Doses at Selected Hgb Responses	Y													
Summary of Posterior Estimates from the Bayesian 3 Parameter Emax Dose-Response Model and the Estimates from the Frequentist 3 Parameter Emax Dose-Response Model for Change in Hemoglobin at Week 4 (Based on PHI113633								Y						

Endpoint and Related Analyses	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
data excluding Japan)														
Dose-Response Linear Model for Change in Hemoglobin at Week 4 (Based on PHI113633 data excluding Japan)								Y						
Scatter Plot of Hgb Response vs. TIW/QD Weekly Dose												Y		
TIW Doses vs. QD Doses Corresponding Selected Hgb Responses												Y		

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Primary analysis based on ITT population will be repeated for completer and per protocol populations.
[2] This linear regression analysis will be repeated for ITT, completer, and per protocol populations.

7.1.2. Planned Hgb Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Hgb change from baseline at Day 29

Model Specification

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

This model assumes the following form:

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

Where:

- ΔHgb is the change in Hgb from baseline at Day 29
- E0 is the placebo response
- Emax is the maximum response

Primary Statistical Analyses

- ED50 is the dose that attains the intermediate response, i.e. where (E0+Emax) / 2, is attained
- ε is a random error assumed to be normally distributed with mean zero and constant variance (σ^2)

The observed change in Hgb from baseline at Day 29 will be used as the response variable in the Emax model. Subjects who have a Day 15 Hgb measurement but a missing Day 29 Hgb measurement will be included with a Day 29 value imputed (see Section 11.7.2.1). Any subject who prematurely discontinues dosing prior to Day 15 will be non-evaluable for the dose-response analysis.

Prior Distribution

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

Prior Distributions of the Primary Model

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

Model Fitting in SAS

The model will be fitted in SAS using the MCMC procedure.

- **Blocking:** Sampling blocks of parameters instead of the parameters separately may speed up the convergence to the target distribution. Blocks are specified in the *PARMS* statement.
- **Seed:** The seed for reproducibility of results will be set to 123.

Starting Values

In order to check the validity of the Emax model fit, five separate Monte Carlo Markov Chain's chains will be fitted each with the following starting points:

- Chain 1) E0 = -1.2, Emax = 5.5, ED_{50} = 50, var = 1
- Chain 2) E0 = -0.75, Emax = 7, ED_{50} = 22.5, var = 2
- Chain 3) E0 = -1.65, Emax = 4, ED_{50} = 80, var = 0.5

Primary Statistical Analyses

- Chain 4) E0 = -1.65, Emax = 7, ED_{50} = 22.5, var = 1
- Chain 5) E0 = -0.75, Emax = 4, ED_{50} = 100, var = 2

When the starting values are taken in an area where the posterior probability is low, it may take a long time to escape from the starting positions and mixing could be low initially. In this case, other starting values could be tried.

Burn In

"Burn-in" is the portion of the chain where convergence has not yet been achieved. "Discarding burn-in" is the practice of discarding the initial portion of a Markov chain. This will be set to 5000 iterations.

Convergence Diagnostics

Convergence of the chains to the posterior distribution for each parameter will be assessed using:

- MCMC error of the model parameters
- Autocorrelation plot to assess the autocorrelation of each parameter
- Visual inspection of the trace plots for each parameter
- Gelman and Rubin Diagnostics

The following points will be reviewed and evaluated:

1. Monte Carlo Standard Error (MCSE) is the standard error of the posterior mean estimate and provides the measurement of the accuracy of the posterior estimates. All parameters MCSE/SD will be derived. All MCMC chains will be run until the posterior estimates of the variance, E0, the minimal effective dose (MED) and the target dose (TD) have MCSE/SD values of < 0.015 and Emax, ED50 and the doses of GSK1278863 that achieve a -0.25, 0.25, 0.5, 0.75 and 1 g/dL change over 29 days have MCSE/SD of < 0.05. Note the MCSE/SD criteria for all parameters must be met.

2. Autocorrelation measures dependency among Markov chain samples. When the autocorrelation takes many sample iterations to reduce, this indicates poor mixing of the Markov chain. When the autocorrelation reduces more quickly over time, this indicates good mixing. Autocorrelation plot will be generated for all chains for visual inspection.

3. A visual inspection of all parameters associated trace plots will be performed to assess the mixing of the 5 chains – to check if each chain is independently realizing values similar to the other chains. This is shown by the chain having a constant mean and variance, and by moving around the parameter space freely (i.e. the plot resembles random noise).

4. Gelman and Rubin diagnostics (Gelman and Rubin, 1992; Brooks and Gelman, 1997) are based on analysing multiple simulated MCMC chains by comparing the variances within each chain and the variance between chains. Large deviation between these two variances indicates non-convergence. A refined version of the

Primary Statistical Analyses

potential scale reduction factor (PSRF) as suggested by Brooks and Gelman, (1997) will be calculated for each parameter using the autocall macro %gelman in SAS. The significance level (alpha) of this test will be set to 0.002. A large PSRF indicates that the between-chain variance is substantially greater than the within-chain variance, so that longer simulation is needed. A PSRF < 1.05 suggests that each of the 5 chains has stabilized, and they are likely to have reached the target posterior distribution.

From the above review, if it is felt the burn-in is inadequate as evidenced by (3) and (4), then this will be increased in increments of 5000 iterations. After which, a sample size of 100,000 will be obtained from the estimated posterior from each of the 5 chains, for a total sample size of 500,000 iterations. If the chain appears to be mixing slowly as evidenced by (2) and (3), then re-allocation of parameters in the PARM statement or increasing the number of iterations in increments of 10,000 iterations will be investigated. By monitoring these diagnostics and making adjustments to the modelling code as stated above, it is anticipated that that the required parameter precision as stated in (1) will be achieved. If this is not the case, increases in the number of sample iterations and/or incorporation of thinning will be used to ensure the required level of precision is achieved.

Pairwise comparison plot (cross plot) of the posterior sample for all parameters will be created and inspected.

The Deviance Information Criteria (DIC) for the model will also be obtained for reference.

Posterior Estimates

Once the dose response model has been fitted satisfactorily, the posterior distribution of the model parameters (E0, Emax, ED50, and variance) will be summarized through means, standard deviation, median, MCSE/SD and equal-sided 95% credibility intervals. The predicted value of Hgb value change from baseline on day 29 at a series of doses (range of possible doses from 0 to 50 will be sectioned off into a sequence of 0.5 increments; i.e. dose levels of 0, 0.5, 1.0, 1.5, …, 25.0..., 50.) will also be monitored and the median and 95% credibility values will be obtained at each dose. The Hgb dose response curve will be plotted as a line through these medians and 95% credibility bands, and overlaid on a scatter plot of the observed data. This estimated dose response curve is a composite best fit at each dose and is not in itself an Emax curve.

The model will be used to make the following inferences to describe the dose response relationship:

- Estimation of the three-times weekly minimally effective dose (MED), defined as the smallest dose achieving a change of -0.5 g/dL over 29 days after being switched from ESA. To estimate this value a variable in the PROC MCMC code will be tracked with the MCMC algorithm and calculated as follows where ΔHgb = -0.5

Primary Statistical Analyses

$$MED = ED50\left(\frac{\Delta Hgb - E0}{E\max - \Delta Hgb}\right)$$

- Estimation of three-times weekly dose levels from the MED in +0.25 g/dL mean Hgb increments, including estimation of the target dose (TD), defined as the three-times weekly dose of GSK1278863 that achieves a 0 g/dL change over 29 days after being switched from ESA will be made. These variables will be calculated similar to the MED, as shown above, where ΔHgb equals -0.25, 0, 0.25, 0.5, 0.75 and 1.

As well as the dose-response Emax curve, the following figures will be produced:

- A posterior probability distribution of predicted Hgb (g/dL) change over 29 days for each treatment group. Seperate variables to estimate the predicted Hgb (g/dL) change at day 29 for doses 0, 10, 15, 25, and 30 will be derived and tracked within the MCMC algorithm. The mean and SD will be calculated for each variable. The dose, along with the mean and SD of its corresponding predicted Hgb change at day 29 will be output into a text file, then R or SAS will be used to produce the plot.

- A predictive posterior probability distribution of Hgb (g/dL) change over 29 days anticipated for a future subject, for each treatment group. The PREDDIST statement will be used in PROC MCMC to predict Hgb change from baseline in future subjects, for each of the studied doses.

- Density plots for each Emax parameter showing the prior and posterior distribution for the primary and sensitivity priors analyses overlaid (Sensitivity priors are described below in Section Sensitivity and Supportive Statistical Analyses.) The sample data generated from the MCMC method will be used to plot the posterior density. R or SAS will then be used to produce this plot for each Emax parameter.

- A predictive posterior probability plot over the dose range to describe the probability that dose will maintain Hgb within the range of [-0.5, 0.5] g/dL after 29 days for a future subject. This plot will be used to determine the probability of a future subject achieving Hgb in [-0.5, 0.5] range at each dose. By comparing across doses, evidence will be provided for the expected improvement of one dose over another, and may aid selection of titration doses in phase 3.

Additional Dose Response Modeling

A Frequentist 3-parameter Emax model in the model form defined as above will also be fitted to data. The derived data from this Emax model (estimates of E0, Emax, ED50 and Var along with their standard error, and 95% CI) will be tabulated and a dose-response curve (alongside the primary analysis curve and sensitivity prior analysis) will also be produced.

Primary Statistical Analyses

If problems are encountered fitting a three parameter Emax model, or if the Emax shape is a poor fit for the data, or a linear relationship looks plausible across the three-times weekly dose range, then a linear model will be considered of the form:

$$\Delta Hgb = E0 + \alpha Dose$$

Other appropriate models, such as quadratic model and log-transformed dose will also be explored if necessary.

Dose Response Exploration

- A scatter plot will be produced by study with total weekly doses as x-axis, and Hgb responses as y-axis including the combined QD (PHI113633 excluding Japan) and three-times weekly (204836) data. The pattern can be examined to explore whether or not the two regimens with the same weekly dose would have the same response.

Dose Ratio Estimation

Dose ratio between TIW and QD doses that produce the same Hgb response will be estimated by different approaches. The dose ratio that will be used to make an informative decision about conversion of QD initial and maintenance dose regimens to three-times weekly doses/regimens will be based on the totality of the data obtained from different approaches.

- The TIW dose response estimations will be obtained from the above fitted models. In addition, the QD dose response estimations will also be obtained by fitting the same models as described above (two Emax models and a linear model) using GSK study PHI113633 data excluding Japan. The prior information and the starting values for the QD Bayesian Emax model is shown below:

Five separate Monte Carlo Markov Chain's chains will be fitted each with the following starting points:

- Chain 1) E0 = -1.2, Emax = 5.5, ED_{50} = 16, var = 1
- Chain 2) E0 = -0.75, Emax = 7, ED_{50} = 22.5, var = 2
- Chain 3) E0 = -1.65, Emax = 4, ED_{50} = 9.5, var = 0.5
- Chain 4) E0 = -1.65, Emax = 7, ED_{50} = 22.5, var = 1
- Chain 5) E0 = -0.75, Emax = 4, ED_{50} = 9.5, var = 2

Prior Distributions for QD Bayesian Emax Model

Emax Model Parameters	Bayesian Priors
E0	~Normal (-1.2, $(0.45)^2$)
Emax	~Normal (5.5, $(1.5)^2$)
ED50	~Uniform (5, 50)
Tau ($1/\sigma^2$)	~Gamma (1,1)

Primary Statistical Analyses

- For each TIW dose (10mg, 15mg, 25mg, and 30mg), the observed mean Hgb response (Hgb change from baseline) at day 29 can be calculated. Using the observed mean Hgb response values as a bridge, the corresponding QD doses will be estimated using Emax models or a linear model. TIW dose divided by the corresponding QD dose will be used to estimate the dose ratio between them. The TIW doses, the observed mean Hgb responses, and the corresponding estimated QD doses, dose ratios, and the 95% CIs (bootstrap CIs or Bayesian credibility intervals) will be displayed in a table.

- Another way to estimate the dose ratios is to use a selected series of Hgb responses. For each Hgb response value (such as a change of 0.25 g/dL), the corresponding TIW dose and QD dose can be calculated using either an Emax model, or a linear model. The possible Hgb responses choices are: a change of -0.5, -0.25, 0, 0.25, 0.5, 0.75, 1 g/dL between baseline and day 29. The Hgb responses, and the corresponding TIW doses, QD doses, Dose ratios, and their 95% CIs (bootstrap CIs or Bayesian credibility intervals) will be presented in a table.

- In the above two methods, fairly similar dose ratios across the doses indicate the dose ratios is not dose-dependent. Under this assumption, the ratio between the estimated ED50s from the TIW Emax model (this study) and the QD Emax model (GSK study PHI113633) would be equivalent to the dose ratio, as well as the ratio between the estimated slopes from the QD linear model (GSK study PHI113633) and three-times weekly linear model (this study).

- An additional way to explore the dose ratio is to draw a TIW dose vs. QD dose plot using the pair of TIW doses and QD doses obtained from the above methods. The appropriate models to investigate the dose ratio will be fitted based on the plot. If the relationship between the TIW doses and the QD doses is linear, then a linear model $Dose_{TIW} = a + bDose_{QD}$ can be fitted. If the relationship between the TIW and QD doses is generally linear and the magnitude of a dose not deviate from zero in a clinically meaningful way, then it suggests that the dose ratio is not dose dependent. Otherwise if a shows a clinically meaningful difference from 0 or the relationship between the TIW and QD doses is not linear, then it suggests that the dose ratio may be dose dependent. Additional models may be used to further examine how the dose ratio changes when QD dose changes.

- Although the Emax models and the linear model will be explored to estimate the dose ratio between the TIW and the QD doses, the linear model will be more reliable if it is well-fitted across the TIW and the QD dose range. This is because the QD and TIW dose ranges are expected to only cover the beginning part of the Emax curves. Therefore if any doses lie outside the dose ranges (such as ED50), they will be poorly estimated.

- The 95% bootstrap CI of the estimated dose ratios can be constructed based on the 2.5 percentile and the 97.5 percentile of 1000 bootstrap simulations (Efron and

Primary Statistical Analyses
Tibshirani, 1993). • For Bayesian Emax models, the posterior distributions of the estimated doses will be obtained by the PROC MCMC procedure to estimate the dose ratios, of which the 95% Bayesian credibility intervals can be constructed based on the 2.5 percentile and the 97.5 percentile of the 500,000 estimations.
Model Checking & Diagnostics
• Refer to Convergence Diagnostics and Posterior Estimates
Model Results Presentation
• As described above with **Posterior Estimates**, model parameters estimated from the Bayesian Emax model will be summarized through means, SD, median, MCSE/SD and equal-sided 95% credibility intervals. • Median and 95% credibility intervals from Bayesian analyses and the model estimates and 95% CIs from frequentist analysis will be presented for MED, TD, and selected doses corresponding to the change of -0.25, 0.25, 0.5, 0.75 and 1 g/dL in Hgb from baseline. • The Hgb dose response curve will be plotted as a line through the medians (of the predicted values of Hgb change from baseline on day 29 at a series of doses) and 95% credibility bands, and overlaid on a scatter plot of the observed data. • A posterior probability distribution of predicted Hgb (g/dL) change over 29 days for each treatment group will be generated. • A predictive posterior probability distribution of Hgb (g/dL) change over 29 days anticipated for a future subject, for each treatment group will be plotted. • Density plots for each Emax parameter showing the prior and posterior distribution for the primary analysis overlaid with sensitivity priors analyses will be generated. • A predictive posterior probability plot over the dose range to describe the probability that dose will maintain Hgb within the range of [-0.5, 0.5] g/dL after 29 days for a future subject will be generated. • Dose ratios estimated by different approaches will be tabulated.
Additional Results Presentation
Listing of Hgb (and HemoCue Hgb data), Hgb change from baseline and Hgb derived parameters will be provided.
Analysis Datasets
• Unless otherwise specified, efficacy inference will be based on the ITT population using an observed case dataset, comprising of all non-missing data collected up to discontinuation of study drug and withdrawal from the trial. • For dose response analysis based on ITT population, the analysis dataset comprises (1) all observed non-missing Hgb data collected up to Day 29; and (2) imputed Hgb value at Day 29 for subjects who have a Day 15 Hgb measurement but a missing Day 29 Hgb measurement.

Sensitivity and Supportive Statistical Analyses

To assess the robustness of the primary efficacy conclusions the dose-response analysis will be repeated using the sensitivity approaches described below.

- The primary dose-response model will be fitted based on the completer population. A table summarizing the results of these dose response analyses along with the dose response curve (alongside the primary analysis curve) will be produced on this population.
- The primary dose-response analysis will be repeated using the PP population if it comprises ≤80% of the ITT population. A table summarizing the results of these dose response analyses along with the dose response curve (alongside the primary analysis curve) will be produced on this population.
- The dose-response Emax model will be fitted using alternative (weaker, less informative) prior distributions for the Emax model parameters. The results from this sensitivity prior analysis will be tabulated as previously described for the primary dose-response model.

Alternative Prior Distributions

Emax Model Parameters	Bayesian Priors
E0	~Normal (-1.2, $(1)^2$)
Emax	~Normal (5, $(3)^2$)
ED50	~Uniform (2, 200)
Tau ($1/\sigma^2$)	~Gamma (1,1)

- A 3-parameter frequentist Emax model will be fitted based on ITT population. It will be fitted using PROC NLMIXED or PROC NLIN, and will be presented as described above.

- A linear model will be fitted to the dose-response data based on ITT population, if a linear relationship looks plausible across the three-times weekly dose range and will be presented as described above. This analysis will be repeated in the Completers and Per Protocol populatipons.

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the Intent-To-Treat population, unless otherwise specified. All secondary Hgb summaries/analyses will use the ITT population with an observed case on-therapy dataset. If the Hgb concentration measurement from Quest is missing and a corresponding valid Hemocue Hgb concentration measurement is available, the Hemocue Hgb concentration measurement will be used for all summaries and analyses.

Table 5 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 5 Overview of Planned Efficacy Analyses

Endpoint	Absolute							Change or %Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Hemoglobin (Hgb)														
Summary of Treatment Difference for Hemoglobin (g/dL) Change from Baseline at Day 29 by Subgroups								Y	Y	Y				
Exploratory Summary of Repeated Measures Analysis for Hemoglobin (g/dL) Change from Baseline at Day 29								Y		Y				
Summary of Hemoglobin (g/dL) by Visit				Y	Y						Y	Y		
Summary of Hemoglobin (g/dL) Change from Baseline by Visit by Subgroups											Y			
Individual Subject Hemoglobin Change from Baseline at Day 29 with Means and 95% CIs												Y	Y	
Subjects Who Reach Pre-defined Hgb Stopping Criteria				Y			Y							Y

Endpoint	Absolute							Change or %Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Subjects Meeting Different Hemoglobin Criteria				Y							Y			
Subject Profiles of Hgb and Dose over Time						Y								
Hgb Assessments: Quest vs. HemoCue						Y								
Secondary Efficacy Endpoints														
Hepcidin				Y	Y						Y	Y		
CHr				Y	Y						Y	Y		
Hematocrit				Y	Y						Y	Y		
RBC Count				Y	Y						Y	Y		
Reticulocyte Count(%)				Y	Y						Y	Y		
Reticulocyte Count(Absolute)				Y	Y						Y	Y		
Plasma EPO				Y							Y			
VEGF				Y							Y			
Plasma EPO and Hepcidin						Y								
Individual Post-Dose EPO						Y								
Individual Post-Dose VEGF						Y								
Iron-related Parameters														
Ferritin				Y	Y						Y	Y		
Transferrin				Y	Y						Y	Y		
Transferrin Saturation				Y	Y						Y	Y		
Total Iron				Y	Y						Y	Y		
UIBC				Y							Y			
TIBC				Y	Y						Y	Y		
Iron-related Parameters (Ferritin, Transferrin, Total Iron, Hepcidin)						Y								

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses
Endpoint(s)
• Hgb change from baseline at Day 29
Model Specification
• Repeated Measures Analysis of Hgb Change from Baseline The observed change in Hgb from baseline to Day 29 will be analyzed by a repeated measures model using the PROC MIXED procedure. Hgb data will be used from Day 15 and Day 29 provided it is collected on-treatment; a subject must have a baseline value and at least one on-treatment Hgb assessment to be included in the analysis. Model effects will include baseline Hgb, treatment, time, and treatment-by-time interactions. The estimation method to use will be Restricted Maximum Likelihood (REML). The Kenward and Roger version of the F-test will be used. The variance-covariance structures for repeated measures within the same subject will be unstructured (UN). For Day 29, least squares mean differences will be calculated as estimates of the difference between the GSK1278863 groups and placebo, together with 95% CIs. These results will be tabulated. • Subgroup Analysis The observed change in Hgb from baseline to Day 29 by subgroups will be analyzed by a repeated measures model using the PROC MIXED procedure. The subgroups of interest are detailed in Section 11.10.1 In order to analyse a particular subgroup, at least 30% of total ITT subjects will be required in each subgroup (approximately 27 subjects per subgroup anticipated). Hgb data will be used from Day 15 and Day 29 provided it is collected on-treatment; a subject must have a baseline value and at least one on-treatment Hgb assessment to be included in the analysis. Model effects will include baseline Hgb, treatment, time, subgroup, treatment-by-time, treatment-by-subgroup, subgroup-by-time and treatment-by-time-by-subgroup interactions. The estimation method to use will be Restricted Maximum Likelihood (REML). The Kenward and Roger version of the F-test will be used. The variance-covariance structures for repeated measures within the same subject will be unstructured (UN). For Day 29, the least squares mean differences will be calculated as estimates of the difference between each GSK1278863 treatment group and placebo for each subgroup, together with 95% CIs. All comparisons will be presented, irrespective of the number of subjects per treatment arm within each subgroup. Note: if subgroup is baseline Hgb (<10 vs. >=10 g/dL), drop the continuous variable for baseline Hgb from the model.
Model Results Presentation
• For repeated measures analysis of Hgb change from baseline, model-adjusted change from baseline, SE, and 95% CI for dapro arms and placebo will be presented. Model-adjusted treatment difference and the associated 95% CI will also be presented in an analysis table. • For subgroup analyses, a forest plot will be produced showing the placebo-corrected Hgb change from baseline at Day 29 for each dose and subgroups. A table of these results will also be provided.

Summary of Other Endpoints
Endpoint(s)
• Hepcidin • CHr • Hematocrit • RBC Count • Reticulocyte Count(%) • Reticulocyte Count(Absolute) • Plasma EPO • VEGF • Ferritin • Transferrin • Transferrin Saturation • Total Iron • UIBC • TIBC
Summary Results Presentation
• Summaries over time and change or percent change from baseline will be produced by treatment group for parameters listed above. • For plasma erythropoietin and VEGF, summary statistics will be calculated and presented by visit and sample time within visit. In addition, maximum observed change / %change from baseline will also summarized for plasma erythropoietin and VEGF. • Line plots of mean/geometric mean with 95 CI will be produced by visit for parameters listed above (except that no line plots will be created for UIBC, Plasma EPO, and VEGF). • Line plots of mean change/%change with 95% CI will be produced by visit for parameters listed above (except that no line plots will be created for UIBC, Plasma EPO, and VEGF). • Graphs of individual post-dose EPO at Day 15 by actual time will be plotted with a loess curve fitted for each treatment group • Graphs of individual post-dose VEGF at Day 15 by actual time will be plotted with a loess curve fitted for each treatment group. • Graph of subject profiles of iron-related parameters with mean line by visit for each treatment group • Graph of subject profiles of plasma erythropoietin and hepcidin by visit for each treatment group

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population, unless otherwise specified.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 6 Overview of Planned Safety Analyses

Endpoint / Parameter/ Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events								
AE Overview	Y							
On-therapy/Post-therapy AEs by System Organ Class (SOC)	Y			Y				
On-therapy/Post-therapy AEs by Preferred Term (PT)	Y							
Subject Numbers for Individual AE				Y				
On-Therapy Common AEs by Overall Frequency	Y	Y						
On-Therapy Common Non-Serious Adverse Events by Overall Frequency	Y							
On-therapy Adverse Events by System Organ Class and Maximum Intensity	Y							
On-Therapy Treatment-Related AEs by SOC	Y			Y				
On-Therapy Treatment-Related AEs by PT	Y							
On-Therapy Serious AEs by SOC	Y							
On-Therapy Serious AEs by PT	Y							
Post-Therapy Serious AEs by PT	Y							

Endpoint / Parameter/ Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
On-Therapy Treatment-Related Serious AEs by SOC	Y							
On-Therapy Treatment-Related Serious AEs by PT	Y							
Drug-Related Serious AEs				Y				
On-Therapy AEs Leading to Withdrawal/ Permanent Discontinuation of Study Treatment by Overall Frequency (By System Organ Class)	Y			Y				
On-Therapy AEs Leading to Withdrawal/ Permanent Discontinuation of Study Treatment by Overall Frequency (By PTs)	Y							
Fatal AEs				Y				
Non-Fatal SAEs				Y				
Relationship of AE SOC, PT and Verbatim Text				Y				
Death				Y				
Reasons for Considering as a Serious AE				Y				
On-Therapy AEs of Special Interest	Y			Y				
Subjects and Number of Occurrences of Common Non-Serious AEs by SOC and PT	Y							
Subjects and Number of Occurrences of Serious, Treatment-Related Serious, Fatal, and Treatment-Related Fatal Serious AEs	Y							
Cancer Data				Y				
Patient Profile Listing of Arrhythmias				Y				
Patient Profile Listing				Y				

Endpoint / Parameter/ Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
of Congestive Heart Failure								
Patient Profile Listing of Cerebrovascular Events/Stroke/Transient Ischemic Attack				Y				
Patient Profile Listing of Deep Venous Thrombosis /Pulmonary Embolism				Y				
Patient Profile Listing of Myocardial Infarction/Unstable Angina				Y				
Patient Profile Listing of Peripheral Arterial Thrombosis Embolism				Y				
Patient Profile Listing of Pulmonary Hypertension				Y				
Patient Profile Listing of Revascularisation				Y				
Patient Profile Listing of Valvulopathy				Y				
Possible Suicidality-Related Adverse Event Data				Y				
Laboratory Values								
Clinical Chemistry by Visit	Y			Y	Y			
Hematology by Visit	Y			Y	Y			
Hematology Data Outside the Reference Range	Y							
Hematology and Chemistry Data of Potential Clinical Importance at Any Time On-Therapy	Y			Y				
Hematology and Chemistry Data of Potential Clinical Importance at Any Time Post-Therapy	Y			Y				
Chemistry Changes from Baseline Relative to the Reference Range (or with					Y			

Endpoint / Parameter/ Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Respect to the Normal Range)								
Hematology Changes from Baseline Relative to the Reference Range (or with Respect to the Normal Range)					Y			
ECG's								
ECG Findings	Y							
ECG Values					Y			
All ECG Values for Subjects with Any Value of Potential Clinical Importance				Y				
All ECG Findings for Subjects with an Abnormal Finding				Y				
Vital Signs								
Vital Sign Values by Visit	Y			Y	Y			
Vital Signs of Potential Clinical Importance at Any Time On-therapy	Y			Y				
Mean and 95% CI for Systolic and Diastolic Blood Pressure by Visit		Y						
Hepatobiliary (Liver)								
Liver Monitoring/ Stopping Event Reporting	Y							
Hepatobiliary Laboratory Abnormalities	Y							
Liver Function Tests by Visit		Y						
Matrix Display of Maximum Liver Function Test Values			Y					
Liver Function Test Values			Y					

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.2. Display Details

8.2.2.1. Adverse Event Safety Analyses

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

- Adverse events overview
- All on-therapy AEs by System Organ Class (Sorted by Dapro Total in descending order)
- All post-therapy AEs by System Organ Class (Sorted by Dapro Total in descending order)
- All on-therapy AEs by Preferred Term (Sorted by Dapro Total in descending order)
- All post-therapy AEs by Preferred Term (Sorted by Dapro Total in descending order)
- On-therapy common adverse events by overall frequency (Common adverse event is defined as an AE with >= 2 subjects in any treatment group or >=2% in Dapro Total)
- On-therapy common non-serious adverse events by overall frequency (Common adverse event is defined as an AE with >= 2 subjects in any treatment group or >=2% in Dapro Total)
- On-therapy AEs by System Organ Class and maximum intensity
- On-therapy treatment-related AEs by System Organ Class
- On-therapy treatment-related AEs by Preferred Term
- On-therapy serious AEs by System Organ Class
- On-therapy serious AEs by Preferred Term
- Post-therapy serious AEs by Preferred Term
- On-therapy treatment-related serious AEs by Preferred Term
- On-therapy treatment-related serious AEs by System Organ Class
- On-therapy AEs leading to withdrawal from study/permanent discontinuation of study treatment by System Organ Class
- On-therapy AEs leading to study withdrawal from study/permanent discontinuation of study treatment by preferred term
- Subjects and number of occurrences of common on-therapy non-serious AEs by System Organ Class and Preferred Term with occurrences >= 5%
- Subjects and number of occurrences of on-therapy serious, treatment-related serious, fatal serious, and treatment-related fatal serious adverse events by System Organ Class and Preferred Term
- AEs of special interest assessed by the SRT prior to study end as:

- Death, MI, stroke, congestive heart failure, venous thromboembolism, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)
- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Cardiomyopathy
- Pulmonary artery hypertension
- Cancer-related mortality and tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

For reporting purposes, the AEs of special interest will be displayed as:

- Fatal, CV and thrombotic events
- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Cardiomyopathy
- Pulmonary artery hypertension
- Cancer
- Esophageal and gastric erosions
- Retinal and choroidal neovascularization
- Exacerbation of rheumatoid arthritis

For AEs reported more than once by a subject, the most severe intensity will be included in summaries where applicable.

Listings will be produced for:

- All Adverse Events
- On-Therapy Treatment-Related Adverse Events
- Fatal Adverse Events
- Non-Fatal Serious Adverse Events
- Post-Randomization Treatment-Related Serious Adverse Events
- Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Study Treatment
- A listing showing the relationship of AE System Organ Class, Preferred Terms, and Verbatim Text
- A listing of Reasons for Considering as a Serious Adverse Event

Additionally, a listing of subject numbers for the individual AEs will be presented. Any possible suicidality-related AE will be listed separately.

A plot (sorted by Dapro Total) showing the proportion of the most frequent AEs (defined as at least 2 subjects in any treatment group) for each treatment group and Dapro Total will be presented.

The following listings of safety data will also be produced:

- Listing of Deaths
- Listing of AE of Special Interest
- Listing of MACE Data
- Listing of Cancer Data
- Patient Profile Listing of Arrhythmias
- Patient Profile Listing of Congestive Heart Failure
- Patient Profile Listing of Cerebrovascular Events/Stroke/Transient Ischemic Attack
- Patient Profile Listing of Deep Venous Thrombosis /Pulmonary Embolism
- Patient Profile Listing of Myocardial Infarction/Unstable Angina
- Patient Profile Listing of Peripheral Arterial Thrombosis Embolism
- Patient Profile Listing of Pulmonary Hypertension
- Patient Profile Listing of Revascularisation
- Patient Profile Listing of Valvulopathy

8.2.2.2. Clinical Laboratory Safety Analyses

Hematology, clinical chemistry and additional parameters collected in this study are listed in Table 7 below:

Table 7 Protocol Required Safety Laboratory Assessments

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

[1]As needed in women of non-child bearing potential only

Any parameters already evaluated in the efficacy section will not be reported again within the clinical laboratory evaluations (Note: Efficacy lab parameters will be listed in the clinical chemistry and hematology listings.). Efficacy lab parameters include: Hemoglobin, Hepcidin, Ferritin, Transferrin, Transferrin Saturation, Total Iron, Unsaturated (i.e. Unbound) Iron Binding Capacity, Total Iron Binding Capacity (Note: derived by Q2/Quest), Reticulocyte Hemoglobin (CHr), Hematocrit (in both SI (Fraction of 1), and conventional (%) unit), RBC count, Reticulocyte Count, Absolute Reticulocyte Count, Plasma Erythropoietin, VEGF.

Laboratory data will be reported out in SI units as listed in the CONV dataset; any required conversions will be carried out programmatically. Conventional units will also be reported for phosphate, albumin, and calcium corrected.

Folate and B_{12} are measured only at week -4 and will be summarized in the clinical chemistry by-visit table.

Laboratory values and change from baseline for hematology and clinical chemistry parameters will be summarized by visit and by treatment group and Dapro Total in the following order:

Clinical Chemistry: Sodium, Potassium, Glucose, Albumin (both units), Protein, Calcium Corrected (both units), Phosphate (both units), ALT, AST, Bilirubin, Direct Bilirubin, Indirect Bilirubin, Alkaline Phosphatase, Folate, and B_{12}.

Hematology: MCH (Mean Corpuscular Hgb), MCHC (Mean Corpuscular Hgb Concentration), MCV (Mean Corpuscular Volume), RDW (Erythrocytes Distribution Width), Leukocytes, Neutrophils, Basophils, Eosinophils, Lymphocytes, Monocytes, Platelets.

In addition, the number and percentage of subjects with values outside the normal range at each visit will be reported for hematology parameters. The number and percentage of subjects with values outside the potential clinical importance range at any time on-therapy and anytime post-therapy will be summarized (potential clinical importance criteria is specified in Section 11.8).

Chemistry and hematology changes from baseline relative to the reference range will be summarized by visit, including "Any time on-therapy".

Chemistry data and hematology data for all subjects and for subjects with abnormalities of potential clinical importance will be listed.

8.2.2.3. Other Safety Analyses

8.2.2.3.1. Electrocardiograms

A summary of the number and percentage of subjects who had normal, abnormal and/or clinically significant ECG findings will be displayed by treatment group and Dapro Total. For all ECG parameters, change from baseline in ECG values will be summarized by visit and displayed by treatment group and Dapro Total.

A listing of ECG values for subjects with any value of potential clinical importance and a listing of all ECG findings for subjects with an abnormal finding will also be produced.

8.2.2.3.2. Vital Signs

Each vital sign parameter and change from baseline for each vital sign parameters will be summarized by visit for both pre-dialysis and post-dialysis measurements. Vital sign parameters will also summarized with respect to whether the observed values are of potential clinical importance at any time on-therapy.

A plot of mean and 95% CI for systolic and diastolic blood pressure by visit will be created for both pre-dialysis and post-dialysis measurements.

A by-subject listing of vital signs for all subjects and a listing of all vital signs for subjects with any value of potential clinical importance will be produced.

8.2.2.3.3. Hepatobiliary (Liver)

Liver monitoring/stopping event reporting will be summarized by treatment group and Dapro Total. A summary of hepatobiliary laboratory abnormalities will be displayed.

The following graphical displays will be created for liver function tests (LFT):

- box plots over time,
- matrix display of maximum LFT values
- LFT subject profiles. (Note: include subjects who have normal baseline, but have any LFT outside normal range any time post-baseline. LFT subject profiles will include a separate line for dose.)

In addition, the following listings will be created:

- Listing of Liver Event Results and Time of Events Relative to Treatment
- Listing of Past and Current Liver Disease Medical Conditions
- Listing of Alcohol Intake at Time of Liver Event
- Listing of Laboratory Data from Liver Event Follow-Up

8.3. Pharmacokinetic Analyses

8.3.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic population, unless otherwise specified.

Table 8 provides an overview of the planned analyses, with full details being presented in Appendix 14: List of Data Displays.

Table 8 Overview of Planned Pharmacokinetic Analyses

Endpoint / Parameter/ Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
GSK1278863 and Metabolites														
GSK1278863 and Metabolites Plasma Pharmacokinetic Concentration Time Data (ng/ml)				Y	Y[1]							Y[1]		
Individual GSK1278863 and Metabolites Plasma Concentration-Actual Time Plot by Treatment						Y							Y	
GSK1278863 and Metabolites Plasma Pharmacokinetic Parameter Data	Y			Y			Y	Y			Y			Y

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Mean and Median Plots will be generated.

8.3.2. Drug Concentration Measures

Daprodustat (GSK1278863) and metabolites [GSK2391220 (M2), GSK2499166 (M4), GSK2531403 (M3), GSK2531400 (M13), GSK2531399 (M5), and GSK2531398 (M6)] plasma pharmacokinetic concentration will be summarized by visit and planned collection time point for each dose level of daprodustat, and will be listed. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum). The merge of PK concentration data, randomization and CRF data will be performed by statistical programmers.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. Figures for individual plasma concentrations will be presented

on both a linear and semilog scale daprodustat, and its six predominant metabolites. Linear and semi-log figures for mean and median plasma concentrations versus time for each treatment regimen will also be generated.

Overlaid individual plasma concentration-actual time profiles and median/mean plasma concentration-planned time profiles by dose level at visit will be plotted. All plots will include PK data from all visits on the same plot. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot).

8.3.3. Pharmacokinetic Parameters

Plasma concentration-time data for daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) will be analyzed by non-compartmental methods with Phoenix® WinNonlin 6.3 or higher (Pharsight Corporation, St. Louis, MO). The data from each PK sampling day will be combined to generate a single profile, i.e., PK concentration data from Days 1, 15 and 29 (taken at non-overlapping time points on these days) will be combined with the actual times, normalized to a 24 hour period to create a "Day 1" profile for non-compartmental analysis (NCA). The exposure estimates obtained from such an analysis will be a close approximation as compared to sampling a subject over a single 24 hour period with minimal patient inconvenience.

Pharmacokinetic parameters described in Table 9 will be determined from the plasma concentration-time data for daprodustat and its six predominant metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)), as data permits.

Table 9 Derived Pharmacokinetic Parameters

Please refer to GSK "SOP_00000314000 - 1.0, Non-Compartmental Analysis of Clinical Pharmacokinetic Data, CPMS Global" for calculating PK parameters.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**

NOTES:

- Lambda_z is the terminal phase rate constant.

All pharmacokinetic endpoints will be summarized in tabular form. Descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum) will be calculated for all pharmacokinetic endpoints by regimen. In addition, for AUC, C_{max}, $t_{1/2}$, geometric means and geometric CVs (CVb(%)) will be calculated for each regimen. Geometric mean and geometric CV% will not be calculated for t_{max}. A subject listing of individual PK parameters for each treatment group will be provided. Pharmacokinetic parameters will be summarized by treatment group using descriptive statistics.

8.4. Pharmacokinetic / Pharmacodynamic Analyses

The relationship between plasma concentrations of daprodustat and selected endpoints may be explored using appropriate pharmacokinetic/pharmacodynamic models. Exploratory modeling of the plasma EPO, VEGF and/or hepcidin concentrations also may be conducted, as a function of daprodustat dose or PK, and may be used to further characterize the effect of daprodustat. Other PD data such as iron parameters and RBC indices may also be included if relevant to characterize the PD response. Relevant measures of the secondary and exploratory endpoints (if meaningful) will be initially explored graphically and where appropriate modeling approaches will be used. Pharmacokinetic/Pharmacodynamic exploratory analysis will be the responsibility of CPMS. If additional details are needed, they will be included in a separate PK/PD RAP. The results of the PK/PD analyses may be reported in separate PK/PD report(s).

9. OTHER STATISTICAL ANALYSES

No other statistical analyses are planned.

10. REFERENCES

Besarab A, Reyes CM, and Hornberger J. Meta-Analysis of Subcutaneous Versus Intravenous Epoetin in Maintenance Treatment of Anemia in Hemodialysis Patients. *American Journal of Kidney Diseases.* 2002; 40 (No. 3): 439-446.

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Efron, B., & Tibshirani, R. J. (1993). An introduction to the bootstrap. New York: Chapman & Hall.

Gelman A, and Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. *Statistical Science.* 1992; 7: 457–472.

GlaxoSmithKline Document Number 2015N241222_01 Study ID 204836. A 29-day, randomized, double-blinded, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of GSK1278863 in hemodialysis-dependent subjects with anemia associated with chronic kidney disease who are switched from a stable dose of an erythropoiesis-stimulating agent. 2016.

11. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Time and Events
Section 11.3	Appendix 3: Assessment Windows
Section 11.4	Appendix 4: Treatment States & Study Phases
Section 11.5	Appendix 5: Data Display Standards & Handling Conventions
Section 11.6	Appendix 6: Derived and Transformed Data
Section 11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
Section 11.8	Appendix 8: Values of Potential Clinical Importance
Section 11.9	Appendix 9: Multicentre Studies
Section 11.10	Appendix 10: Examination of Covariates and Subgroups
Section 11.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 11.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 11.13	Appendix 13: Abbreviations & Trade Marks
Section 11.14	Appendix 14: List of Data Displays
Section 11.15	Appendix 15: Example Mock Shells for Data Displays

11.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

11.1.1. Important Protocol Deviation

All deviations are to be tracked in PPD CTMS. PPD is responsible for collating all identified deviations and, after internal review, for sending this list to GSK on monthly basis. Protocol deviations will be reviewed by PPD and GSK study team and important/significant protocol deviations will be identified according to PPD's Study Deviation Rules Document. (Note: Given that different terminologies have been used by GSK and PPD, the terms "important protocol deviation" and "significant protocol deviation" will be used interchangeably throughout the RAP.)

11.1.2. Exclusions from Per Protocol Population

The following criteria define the protocol deviations, which may lead to the exclusion of a subject from the per protocol (PP) population (refer to Section 4 for population definitions). These are the deviations that are considered to affect interpretation of the primary endpoint (Hgb change from baseline at Day 29). Protocol deviations will be recorded and documented in the PPD's protocol deviation capturing tool. Potential protocol deviations listed below will be reviewed by the clinical team to establish whether subjects meeting these criteria should be excluded from the PP population. This review will occur before the clinical database has been locked for the final analysis.

Number	Exclusion Description
01	Inclusion/Exclusion criteria not met. • Subjects who deviate from any inclusion or exclusion criteria, as recorded in the eCRF)
02	Not withdrawn after meeting the following stopping criteria prior to Day 29 • receiving blood transfusion • receiving kidney transplant • having active GI bleed • liver stopping criteria • patient not discontinued from the study treatment despite having missed two or more consecutive dialysis sessions • diagnosis of cancer, with the exception of squamous cell and basal cell carcinoma • pregnancy
03	Prohibited medication taken during study treatment phase, prior to Day 29 • Subject taking single dose of long-acting darbepoetin or Mircera during the study (Day 1 – Day 29) • Subject taking more than one dose of Epoetin, or more than 2 non-consecutive Epoetin administrations

Number	Exclusion Description
	• Subject taking the prohibited medications (inhibitor or inducer of CYP2C8: gemfibrozil and rifampin/rifampicin) during the 29-day study treatment phase and 7 days after last dose of study treatment).
04	Incorrect study treatment or Non- compliance • Dispensed incorrect study treatment at Day1 • Incorrect bottle used for administration to the patient • Expired study drug administered to the patient • Administration of study drug that was incorrectly stored and was not approved by GSK for use (Study drug stored incorrectly/ temperature monitoring not documented/ storage temperature excursion) • Non-compliance for IP (defined as < 80% or > 120%; refer to RAP Section 6.2.6 for treatment compliance definition) for any single bottle of study treatment between Day 1 and Day 29. Note: <80% is equal to 3 or more doses over 29 days • Two or more consecutive missed doses, or 3 or more non-consecutive missed doses • Patient takes more than the scheduled number of tablets or doses of Study treatment, e.g. more than 3 tablets per dose or more than 3 doses per week. • Patient did not receive one tablet from each of 3 bottles (e.g., took 3 tablets from single bottle).
05	Error in Randomization procedure • Subject randomized in error. (This should capture any protocol deviation which is not covered by another protocol deviation category such as deviation to eligibility criteria.) (Note: Randomization to incorrect stratum will not lead to the exclusion of a subject from the per protocol (PP) population.)
06	Other (lack of PI oversight) • Exclude subject(s) if failed audit/compliance
07	If Day15 visit or Day 29 visit is done on first dialysis session of the week (we would check each patient's estimated dry weight (EDW) to see if there is a greater than 4% difference in EDW between the first dialysis session of the week and the dialysis session at mid or end of the week).
08	Informed Consent • Patient not consented prior to screening procedure • ICF not properly completed (Consideration should be given to whether the ICF was later completed properly, and whether a valid consent was in place.) • Patient not consented with a current ICF version (e.g. inappropriate re-consenting

Number	Exclusion Description
	process). (Consideration should be given to what new information is contained in the revised ICF, and whether any procedures/assessments were performed to which the subject had not given consent, as a result of not using a current ICF version.)
09	Dialysis modality changed from hemodialysis (HD, hemofiltration or hemodiafiltration) to peritoneal dialysis during the study

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

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

[1] All assessments should be done pre-dialysis except as noted.
[2] Allowable time window of ± 2 days for all study visits, except the follow-up visit for which it is ± 3 days.
[3] As detailed in Inclusion Criteria in study protocol Section 5.2
[4] Weight measured post-dialysis only & height measured at screening only.
[5] Obtain samples as per the Day 29 visit in Table 2 of the study protocol. If subject does not receive a dose of study medication at this early withdrawal visit, no post-dose PK/PD samples should be obtained.
[6] Subjects who withdraw early from treatment should attend a follow-up visit 14 days ± 3 days after the last dose of study treatment.
[7] Serious adverse events are assessed from the time of consent as stated in study protocol Section 7.4.1.1

Pharmacokinetic/Pharmacodynamic Time and Events Table

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

[1] Subject to take their dose of study medication at home and arrive for clinic visit approx 6-10 h post-dose. Subjects may take their Day15 dose the evening prior to the Week 2 study visit to accommodate the 6-10 h PK/PD sampling window

[2] Sample to be collected within 30 minutes of planned collection time

[3] Sample can be pre- or post-GSK1278863 administration

11.3. Appendix 3: Assessment Windows

11.3.1. Assessment Windows Assignment

For efficacy data, laboratory data, vital signs, and ECG measurements to be summarized or analyzed by visit, unscheduled and early withdrawal (EW) data measurements will be assigned to one of the protocol specified visits using the following algorithm:

1. Determine Study Day of assessment (refer to Section 11.6.1)

2. Based on the Study Day, assessment will be assigned as shown in Table 10 below

Table 10 Assessment Windows

Study Day of Assessment	Assessment Window	Target Study Day of Window
1	Day 1	1
2 to 22	Day 15	15
23 to 36	Day 29	29
This will not be slotted	Day 43 (Follow-up)	

Note: If an unscheduled value is recorded prior to Day 1 then this will be slotted as follows (Table 11; Refer to Section 11.5.2 for the derivation of Baseline):

Table 11 Assessment Windows for Screening

Study Day of Assessment	Assessment Window
<= -22	Week -4
-21 to -1	Week -2

As specified in the protocol, if a subject does not receive a dose of study medication at the early withdrawal visit, no post-dose PK/PD samples should be obtained. Hence if we do have EW EPO, hepcidin and VEGF values, it will be slotted to the appropriate visit as specified in Table 10 and summarized. These parameters are collected at scheduled time points (e.g. 6 to10 hrs post-dose) within a visit and so this data will be reported as pre-specified for the tables and by actual time for graphics.

Local laboratory assessments (efficacy or safety) will not be slotted and will not be summarized. Only central lab assessments will be summarized. For parameters which are not scheduled to be assessed at particular visits, the all-inclusive windows defined in Table 10 and Table 11 above will still be used. However, if a value is slotted to a visit unscheduled for a parameter, it will not be summarized but will be included in data listings. Assessments at unscheduled visits will be included for ‘any time on-treatment’ time points and “any time post-treatment”, and in data listings, as well any algorithms that make use of additional data.

11.3.2. Multiple Assessments

For assessments on or after Day 1, if after window assignment there are multiple valid assessments of a parameter from the central lab within the same window (nominal and slotted visit data), then the scheduled assessment at a nominal visit takes precedence over any unscheduled assessments and will be reported for summary statistics/analyses. If the scheduled assessment is missing for the target visit within the same window, then the last on-treatment value in the window will be reported for on-treatment summary statistics/analyses, and the last post-treatment value in the window will be reported for post-treatment summary statistics/analyses.

For assessments during the screening period prior to Day1, if after window assignment there are multiple valid assessments of a parameter from the central lab within the same window (nominal and slotted visit data), then the last/most recent values will be reported for summary statistics/analyses.

For the primary endpoint, Hemoglobin (Hgb), if the scheduled Hgb concentration measurement during the study (including screening, treatment, and follow-up period) from the central lab is missing and a corresponding valid HemoCue Hgb concentration measurement is available, then the HemoCue Hgb concentration measurement takes precedence over unscheduled Hgb concentration measurements within the same window and will be used for all summaries and analyses.

ECG values and vital signs measured at the local sites will be slotted and selected following the same algorithm applied to the central lab assessments described above and will be reported for summary statistics/analyses, unless otherwise specified.

All assessments, including local lab assessments, will still appear in the associated listings.

11.4. Appendix 4: Treatment States and Study Phases

11.4.1. Study Phases

- Screening Period: Day -28 to Day -1
- Treatment Period: Day 1 to Day 29/study treatment stop date
- Follow-up period: Study treatment stop date + 1 to follow-up visit date (study treatment stop date + 14 if follow-up visit date is missing)

11.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment as either pre-treatment, on-treatment, or post-treatment.

11.4.2.1. Treatment States for Laboratory Data, Vital Signs, ECG Data

For laboratory data, pre-dialysis vital signs, and ECGs, treatment state will be defined as:

Treatment State	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 1
Post-Treatment	Date > Study Treatment Stop Date +1

NOTES:

- If the study treatment stop date is missing then any assessment after study treatment Start Date will be considered to be On-Treatment.
- Post-dialysis vital signs measured on the "Study Treatment Start Date" will be considered to be On-Treatment.

11.4.2.2. Treatment States for AE Data

For adverse events (AEs), treatment state will be defined as:

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date +1. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1
Post-Treatment	If AE onset date is after the treatment stop date + 1. AE Start Date > Study Treatment Stop Date + 1
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Onset Time Since Last Dose (Days)	If Treatment Stop Date + 1 ≤ AE onset date: AE onset date – treatment stop date + 1 If Treatment Stop Date + 1 > AE onset date: AE onset date – treatment stop date Missing otherwise.
Duration (Days)	AE Resolution Date/AE End Date – AE Onset Date + 1

NOTES:

- If the study treatment stop date is missing then any AEs with a start date on or after study treatment start date will be considered to be On-Treatment.
- In the case of a completely missing AE start date, the event will be considered to have started on-treatment unless an end date for the AE is provided which is before start of investigational product; in such a case the AE is assigned as pre-treatment.

11.4.2.3. Classification of Prior, concomitant, an Post-Therapy Medications

Prior medications are those taken (i.e., started) before the start date of study treatment. Concomitant medications are those taken (i.e., started or continued) at any time between the start date and stop date of study treatment, inclusive. Prior medications that were continued during the study treatment period are also considered as concomitant medications. Post-treatment medications are those started after the stop date of study treatment. Concomitant medications that were continued after the stop date of the study treatment are also considered as post-treatment medications.

It will be assumed that medication has been taken on the date in which it is reported as started or stopped. Also, for any medication starting on the same date as study treatment, it will be assumed that the medication was taken after the subject started taking the study treatment.

Table 12 below illustrates how a medication is classified as prior, concomitant, or post-treatment.

Table 12 Prior, Concomitant, and Post-treatment Classification of Medications

	Pre-treatment	On-treatment			Post-treatment		Prior	Concomitant	Post
		Study Treatment Start Date		Study Treatment Stop Date	Study Treatment Stop Date+1				
(a)	x————x						Y	N	N
(b)	x————		————x				Y	Y	N
(c)	x————		————			————x	Y	Y	Y
(d)			x————x				N	Y	N
(e)			x————			————x	N	Y	Y
(f)						x————x	N	N	Y
(g)	?————x						Y	N	N
(h)	?————		————x				Y*	Y	N
(i)	?————		————			————x	Y*	Y*	Y
(j)	x————		————			————?	Y	Y**	Y**
(k)			x————			————?	N	Y	Y**
(l)						x————?	N	N	Y
(m)	?————		————			————?	Y***	Y***	Y***
(n)	x————	x					Y	Y	N
(o)	?————	x					Y*	Y	N
(p)		x	————x				N	Y	N
(q)		x	————	x			N	Y	N
(r)				x	—	————x	N	Y	Y
(s)				x	—	————?	N	Y	Y**
(t)					x	————x	N	N	Y
(u)					x	————?	N	N	Y
(v)			x————	—	x		N	Y	Y

1. x = start/stop date of medication
2. ? = missing start/stop date of medication
3. * If a medication is stopped On-treatment or Post-treatment and no start date is recorded it will be assumed that the medication was ongoing from the Pre-treatment phase
4. ** If a medication is started Pre-treatment or On-treatment and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study
5. *** If a medication has no start and stop date it will be assumed that the medication was ongoing from the Pre-treatment phase to the Post-treatment phase

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
PPD Randomization System		Data Displays for Reporting[3][4]	
Code	Description	Description	Order [1]
1	10 mg GSK1278863 three-times weekly	Dapro 10 mg[2]	2
2	15 mg GSK1278863 three-times weekly	Dapro 15 mg[2]	3
3	25 mg GSK1278863 three-times weekly	Dapro 25 mg[2]	4
4	30 mg GSK1278863 three-times weekly	Dapro 30 mg[2]	5
5	Placebo three-times weekly	Placebo	1

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.
2. When display space is limited, 10 mg, 15 mg, 25 mg, and 30 mg can used as the description under an overall column/row title, “Dapro”.
3. “Dapro Total” will be used as the description when the four Daprodustat groups are pooled.
4. “Total” will be used as the description when the five treatment groups are pooled.

11.5.2. Baseline Definition & Derivations

11.5.2.1. Baseline Definitions

For Hgb the average of Hgb measured by the central lab, Quest, at Week -2 and Day 1 visits will serve as the baseline value. If an unscheduled Hgb value is taken pre-treatment then this will be slotted following the algorithm in Section 11.3.1 and Section 11.3.2.

Vital signs will be measured both pre-dialysis and post-dialysis. The baseline values for vital signs will be defined as:

Pre-dialysis baseline = vital sign value obtained pre-dialysis on Day 1

Post-dialysis baseline = vital sign value obtained post-dialysis at Week -2

Weight baseline= post-dialysis weight measured at Week -2.

Unless stated otherwise, the baseline value for all other lab parameters and ECG are defined as the last pre-treatment value observed. This is generally expected to be from the Day 1 visit (except for Folate, B12 and ECG, which are only measured at Week -4), although such values may be missing or unscheduled assessments may be performed before treatment start.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Week -4	Week -2	Day 1 (Pre-Dose)	
Safety				
Vital Signs		X	X	See description above [1]
ECG	X			Week -4
Laboratory (clinical chemistry and hematology)		X	X	Day 1
Folate, Vitamin B12	X			Week -4
Ferritin, Transferrin, Total Iron, UIBC	X		X	Day 1
Efficacy				
Hgb		X	X	Mean (Quest) See description above
PK/PD				
PK Plasma, EPO & VEGF, Hepcidin			X	Day 1

NOTES:

1. Three measurements of SBP, DBP and HR will be recorded at each study-specified visit and the mean of the replicate assessments will be used as the baseline value.

11.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Baseline Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given post-baseline timepoint and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- For this study %Change from Baseline (without log transformation) will be calculated only for "Absolute Reticulocyte Count."

Some lab parameters will be log-transformed and percent change from baseline will be reported for these parameters: Hepcidin, Transferring Saturation, and VEGF.
To calculate a geometric mean for baseline measurement or at a specified timepoint, the following steps are used:

1. Log-transform the data points

2. Calculate the mean and standard error (SE) of the log-transformed data
3. Exponentiate the mean, (if required, the mean – SE, mean + SE) and the endpoints of the confidence interval back to the original scale in order to obtain the geometric mean, (the geometric mean – SE, the geometric mean + SE) and the confidence interval for the geometric mean.
4. Coefficient of variation will be calculated as

$$CV = \sqrt{\exp(Var_{\log scale}) - 1} \times 100\%$$

To calculate a geometric mean for the ratio of a specific timepoint to baseline (expressed as a percent change from baseline), the following steps are used:

1. Log-transform the data at both the baseline and the specified timepoint
2. For each subject, calculate a change from baseline using the log-transformed data
3. Calculate the mean and standard error (SE) of the log-transformed data
4. Exponentiate the mean, (if required, the mean – SE, the mean + SE) and the endpoints of the confidence interval, back to the original scale and then subtract 1, then multiply everything by 100% in order to express the geometric mean, (the geometric mean – SE, the geometric mean + SE) and the confidence interval (CI) as the percent change from baseline.

So, geometric mean for percent change from baseline =

[Exp(∑ {log(value at specified time point_i) – log(baseline value_i) }/n) – 1] x 100,

Where i = subject, n= total number of subjects, and ∑ represents the sum over all subjects.

To calculate the minimum, median and maximum for the ratio of a specific timepoint to baseline (expressed as a percent change from baseline), the following steps are used:

1. Log-transform the data at both the baseline and the specified timepoint
2. For each subject, calculate a change from baseline using the log-transformed data
3. Calculate the minimum (median and maximum) of change from baseline using the log transformed data.
4. Exponentiate the minimum (median and maximum), back to the original scale and then subtract 1, then multiply everything by 100% in order to express the minimum (median and maximum) as the percent change from baseline.

So, minimum percent change from baseline =

[Exp(min {log(value at specified time point_i) – log(baseline value_i) }) – 1] x 100,

Where i = subject.

11.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software, version 9.3. or higher will be used for all analyses unless otherwise specified. Additionally, R version 3.1.1 or higher may be used, if necessary, for analysis and the production of graphics.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /arenv/arprod/gsk1278863/mid204836/final/
QC Spreadsheet	: /arenv/arprod/gsk1278863/mid204836/final/qc/
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & ADaM IG Version 1.1.	
Generation of RTF Files	
• RTF files will be generated.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings.
Unscheduled Visits
• Unscheduled visits (including early withdrawal visit) will be included in summary tables after

Reporting Standards	
they are slotted to the planned visits, as described in Section 11.3.1. • Assessments at unscheduled visits will be included for 'any time on-treatment' time points and any time post-treatment, and in data listings, as well any algorithms that make use of additional data, as described in Section 11.3.1. • Unscheduled visits will be included in figures after they are slotted to the planned visits, as described in Section 11.3.1. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13. • Y-axis breaks will be implemented in order to best show the distribution of values in the y-dimension. GSK Study PHI113747 figures will provide examples of the y-axis break levels, and clinical scientist review feedback will be provided on proposed y-axis breaks positions at the Dry Run Review. • SAS goptions will be set to provide hardware fonts wherever possible. • A color scheme will be established that is similar to that used for GSK Study PHI113747 (e.g., Orange for daprodustat, Blue for Placebo). • GSK Programming will work with PPD programming to establish default SAS goptions.	

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Time Point
• Three pre-dialysis measurements and three post-dialysis measurements of SBP, DBP and HR will be recorded at each study-specified visit. Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • After window assignment, if there are two or more values within a time window, the algorithm described in Section 11.3.2 will be followed. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from randomisation date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

Randomization Date
• Date subject was randomized
Treatment Start Date
• The date of first dose of study treatment
Treatment Stop Date
• Calculated as the date of final dose of study treatment received. If treatment stop date is missing, then, for purposes of calculating exposure, it will be imputed using the date of last visit or the recorded date of withdrawal/completion, whichever is earlier. Note that the follow-up visit date must not be used as the date of last visit or recorded date of withdrawal/completion because this date will be off-treatment.
Study Completion/Withdrawal Date
• Date of withdrawal for subjects withdrawing (i.e., subjects who actively withdraw or are deemed lost to follow-up) from study or date of completion of study for subjects who complete the study, as documented in the eCRF.   • Note: Subjects who die while on study are considered as having completed the study
Time Definitions (per GSK standard principles)
• 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days

11.6.2. Study Population

Demographics

Age

- GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  - Missing date and month will be imputed as '30th June'.
- Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)

- Calculated as **Weight (kg) / [Height (m)^2**

Standardized rhEPO

For this study, ESA dose can be administered in five different ways: epoetin IV (Intravenous), epoetin SC (Subcutaneous), darbepoetin IV, darbepoetin SC or Mircera IV. The dose of ESA will be standardized to obtain a continuous single unit of prior ESA dose in terms of **epoetin IV IU/kg/week**. The standardization will be carried out using the formula:

- Weekly darbepoetin IV or SC dose (mcg) = Weekly epoetin IV dose (IU)/200
- 113 epoetin IV = 161 epoetin SC [Besarab et al]

1. For subjects taking epoetin IV no adjustment is needed.

Standardized rhEPO IV dose (IU/kg/week) = epoetin IV dose (IU) / (frequency*weight (kg))

2. For subjects taking darbepoeitin (IV or SC), their dose will be converted as follows:

Standardized rhEPO IV dose (IU/kg/week) = (darbepoeitin dose (mcg) * 200) / (frequency* weight (kg))

3. For subjects taking epoetin SC, their dose will be converted as follows:

Standardized rhEPO IV dose (IU/kg/week) = 161/113 * (epoetin SC dose (units)) / (frequency* weight (kg))

4. For subjects taking Mircera (IV), their dose will be converted as follows:

Standardized rhEPO IV dose (IU/kg/week) = (Mircera dose (mcg)) / (1.2*frequency* weight (kg))

Where frequency = 4 if the subject takes the Mircera dose once every 4 weeks (Note: Once a month (QM) will be handled same as once every 4 weeks.), 2 if the subject takes the darbepoeitin or Mircera dose once every 2 weeks, 1 if the subject takes the darbepoeitin dose once a week, 0.5 if the subject takes the epoetin dose 2 times a week, 0.333 if the

Demographics

subject takes the epoetin dose 3 times a week etc. (For dose frequency = ONCE, please see the algorithm described later in this section.) Note, weight is the weight recorded at screening Week -2. If the screening weight is missing, the baseline weight will be used.

If a subject has multiple doses of prior ESA during the 12 weeks prior to randomization, the weighted mean would be calculated to obtain the standardized rhEPO.

In order to account for changes in ESA dose and pauses in ESA dose, the following algorithm will be used to determine the average weekly dose per subject over the 12-week period prior to randomization:

1. Derive the standardized weekly dose in terms of Epoetin IV (IU/kg/week) for each dose recorded in the eCRF during the 12-week period of interest, as detailed above. (Note, where the first dose started after the cutoff date for the 12-week period, defined by "randomization date – 12 weeks", the dose prior to the first dose start date will be assumed to be 0. When the first dose started before the cutoff date defined by "randomization date – 12 weeks", first day of the period (i.e. Randomization date – 12 weeks) is defaulted as the start date of that dose.)

2. Convert dose into units of dose per day (IU/kg/day) by dividing the weekly dose from step 1 by 7.
   Standardized rhEPO IV Daily Dose (IU/kg/day) = Standardized rhEPO IV weekly dose IU/kg/week) / 7

3. Identify whether a pause in dosing has occurred, i.e. a period of time deemed to be a break from the planned treatment regimen, for each dose recorded. A pause in dosing will be identified as follows. In the table below, Dose 1 refers to the dose received before the pause (if one exists), and Dose 2 to the dose received after the pause (if one exists).

Dosing Regimen	Definition of a pause in dosing	Criteria for dosing pause	Gap factor (days) (to be added to stop date if dose pause exists)
3 times per week	3 or more days where no dose is administered	(Start Date Dose 2) – (Stop Date Dose 1) > 3	2
2 times per week	5 or more days where no dose is administered	(Start Date Dose 2) – (Stop Date Dose 1) > 5	4
1 times per week	8 or more days where no dose is	(Start Date Dose 2) – (Stop Date Dose 1) > 8	7

Demographics

	administered		
0.5 times per week	15 or more days where no dose is administered	(Start Date Dose 2) – (Stop Date Dose 1) > 15	14
0.33 times per week	22 or more days where no dose is administered	(Start Date Dose 2) – (Stop Date Dose 1) > 22	21
0.25 times per week	29 or more days where no dose is administered	(Start Date Dose 2) – (Stop Date Dose 1) > 29	28

4. Calculate the duration of dose for each dose received. (Note that the duration of a dose will be capped at the start date of a new dose (Start Date Dose 2) or at randomization date.)

If a pause was identified between doses, the duration of dosing will be defined as follows:

(Duration of Dose 1) = (Stop Date Dose 1) + (Gap Factor) – (Start Date Dose 1) + 1
= Min(Randomization Date, Start Date Dose 2, Stop Date Dose 1+ Gap Factor + 1) – Start Date Dose 1

If no pause was identified between doses, the duration of dosing will be defined as follows:

(Duration of Dose 1) = (Stop Date Dose 1+ Gap factor) – (Start Date Dose 1) + 1

= Min(Randomization Date, Start Date Dose 2, Stop Date Dose 1 + Gap Factor +1) – (Start Date Dose 1)

5. Calculate the actual dose received for each dose, by multiplying the daily dose from step 2 by the duration of dose derived in step 4:

   Actual Dose (IU/kg) = Daily Dose (IU/kg/day) x Duration of Dose (days)

6. Calculate the total cumulative dose received over the subject's 12-week period prior to randomization:

   Cumulative Dose (IU/kg) = Sum of all Actual Doses from step 5 (IU/kg)

7. Calculate the average weekly dose over the 12-week period prior to randomization, by dividing the cumulative dose from step 6 by the duration of the 12-week period

Demographics

Average Dose (IU/kg/week) = Cumulative Dose (IU/kg)/12

For the special situation of dose frequency = "ONCE", the following algorithm will be followed: (Note: Only for dosing within the 12-week period prior to randomization (i.e. randomization date – 12 weeks)).

1. Calculate the standardized rhEPO IV dose (IU/kg) for this specific prior ESA use
    1) For subjects taking epoetin IV no adjustment is needed.

Standardized rhEPO IV dose (IU/kg) = epoetin IV dose (IU) / (weight (kg))

    2) For subjects taking darbepoetin (IV or SC), their dose will be converted as follows:

Standardized rhEPO IV dose (IU/kg) = (darbepoetin dose (mcg) * 200) / (weight (kg))

    3) For subjects taking epoetin SC, their dose will be converted as follows:

Standardized rhEPO IV dose (IU/kg) = 161/113 * (epoetin SC dose (units)) / (weight (kg))

    4) For subjects taking Mircera (IV), their dose will be converted as follows:

Standardized rhEPO IV dose (IU/kg) = (Mircera dose (mcg)) / (1.2*weight (kg))

2. If all the records of prior ESA use during the 12-week period prior to randomization have dose frequency = "ONCE", then:

Standardized rhEPO IV dose (IU/kg/week) = Sum of Standardized rhEPO IV dose (s) (IU/kg) calculated from Step 1 / 12

Note: This includes the situations when either a subject has only one prior ESA use record with dose frequency = "ONCE" or a subject has more than one prior ESA use records and all of them have dose frequency = "ONCE".

3. If, in addition to the prior ESA use record(s) with dose frequency = "ONCE", a subject has other ESA use record(s) with different dose frequency during the 12-week period prior to randomization, then the Standardized rhEPO IV doses calculated from Step 1 in terms of epoetin IV (IU/kg) will contribute directly (without considering "Gap Factor") to the total Cumulative Dose derived in Step 6 of calculation of average weekly dose.

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – Treatment Start Date + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum (Each dose taken recorded in the eCRF, including the dose taken on or prior to PK day Day 15 study visit)**

11.6.3. Safety

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '≤x' or '≥x' is present, then the corresponding numeric value will be set equal to x.
• The following will be used to convert laboratory values from SI units to conventional unit: • Phosphate: Divide the mmol/L value by 0.32290 to get the mg/dL value • Albumin: Divide the g/L value by 10 to get the g/dL value • Calcium corrected: Divide the mmol/L value by 0.2495 to get the mg/dL value • Hematocrit: Divid the Fraction of 1 by 0.01 to get the %

11.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (as specified in the protocol Section 5.8) was defined as completing all phases of the study including the follow-up visit, with the following exception: subjects who die while on study are also considered as having completed the study.The number of subjects who completed the study for purpose of the disposition table will consist of all randomized subjects who, as documented in the eCRF, have completed all study visits, including the follow-up visit. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing Hgb and Other Data

Element	Reporting Detail
Hgb	• The Hgb concentration analyzed by Quest Diagnostics is referred to as Hgb throughout this document. These data will be summarized and analyzed. If the Hgb concentration measurement is missing and a corresponding valid HemoCue Hgb concentration measurement is available, the Hemocue Hgb concentration measurement will be used for all summaries and analyses. • The dose response dataset will be based on the ITT population using an observed case dataset, comprising all non-missing data collected up to Day 29. For subjects who have a Day 15 Hgb measurement but a missing Day 29 Hgb measurement, a change from baseline at Day 29 value will be imputed using 2 * (Day 15 Hgb – Baseline Hgb). The assumption is deemed appropriate based on phase 2a data indicating linear response over time. Any subject who prematurely

Element	Reporting Detail
	discontinues dosing prior to Day 15 will be non-evaluable for the dose-response analysis. In general, the imputed data for the dose response analysis will not be used in summaries and figures, except for those generated specifically for dose response results. However, for descriptive summaries of Hgb over time, raw Day 29 Hgb will be summarised as well as Day 29 Hgb including imputations. The number of imputed Day 29 Hgb values will be summarized by treatment group. • All other efficacy inference will be based on the ITT population using an observed case dataset.
Other Data	• For laboratory data no imputation for missing data or premature discontinuation will be performed and the observed values will be used. The same approach applies to other assessments such as vital signs and electrocardiograms (ECGs) examination data.

11.7.2.2. Handling of Missing/Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day and Non-missing End Date: If the day in a start date is missing, e.g. - -JUN2006, and the month is the one in which treatment started, assign the day to the day treatment started (i.e. the event is considered on-treatment as per Appendix 4, Section 11.4.2.2) if treatment start date <= AE end date). Otherwise, set to the first of the month, 01JUN2006. ○ Missing Stop Day and Non-missing Start Date: Last day of the month (28th, 29th, 30th, or 31st as appropriate for the month and year) will be used. If the last day of the month is after the stop date of study treatment in the same month and treatment stop date >= AE start date, then study treatment stop date will be used. ○ Missing Start Day and Missing End Day: If both the day in a start date and the day in an end date are missing, set them to the first day of the month and the last day of the month, respectively. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • The recorded partial date will be displayed in listings
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the missing/unknown day and 'Jan' will be used for the missing/unknown month. ○ If the partial date is a stop date, last day of the month (28, 29, 30, 31, dependent on the month and year) will be used for the missing/unknown day and 'Dec' will be used for the missing/unknown month. • The recorded partial date will be displayed in listings.

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

Haematology		
Laboratory Test	**Unit**	**PCI Value**
White Blood Cell Count	GI/L	>1 x GI/L below the lower limit of reference range (LLRR) or >5 x GI/L above the upper limit of reference range (ULRR)
Total Neutrophils	GI/L	<0.5x LLRR
Lymphocytes	GI/L	<0.5x LLRR
Platelet Count	GI/L	<80 or >500 x GI/L
Clinical Chemistry		
Laboratory Test	**Unit**	**PCI Value**
Total Bilirubin	umol/L	≥2x ULRR
Total Protein	g/L	>15 g/L above or below the RR
Albumin	g/L	>5 g/L above or below the RR
Aspartate Aminotransferase	IU/L	≥3x ULRR
Alanine Aminotransferase	IU/L	≥3x ULRR
Alkaline Phosphatase	IU/L	≥3x ULRR
Sodium	mmol/L	>5 mmol/L above ULRR or below LLRR
Potassium	mmol/L	>0.5 mmol/L below the LLRR or >1.0 mmol/L above the ULRR
Glucose	mmol/L	<3.9 or >22 mmol/L
Phosphorus (phosphate)	mmol/L	>0.323 mmol/L above ULRR or below LLRR
Calcium (Albumin adjusted)	mmol/L	<1.8 or >3.0 mmol/L
PD Markers		
Laboratory Test	**Unit**	**PCI Value**
Ferritin	ng/mL	<100 or > 800 ng/mL
Transferrin Saturation	%	< 20% or >40%

11.8.2. Vital Signs

Vital Sign	PCI Range	Unit
Systolic Blood Pressure	< 85 or > 170	mmHg
Diastolic Blood Pressure	< 45 or > 100	mmHg
Heart Rate	< 40 or > 110	bpm

11.8.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Change from Baseline			
Increase from Baseline QTc	msec	> 60	

11.9. Appendix 9: Multicenter Studies

11.9.1. Methods for Handling Centres

This study will be conducted in Germany, Russia, Spain, Canada and the US. There will be a large number of centres and a relatively small number of subjects per centre, hence data will be summarized for all centres combined. Statistical analyses will not be adjusted for centre. A summary of the number of subjects by centre will be produced.

11.10. Appendix 10: Examination of Covariates and Subgroups

11.10.1. Handling of Covariates and Subgroups

- The following is a non-exhaustive list of covariates that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses (See Section 8.1.1 and Section 8.1.2 for further details).
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.

Category	Covariates and / or Subgroups
Baseline Hgb	<10, >=10 g/dL
Weight	<=Median, >Median kg
Body Mass Index (BMI)	<27, 27 to <30, >=30 kg/m^2
Type of Prior ESA	Epoetin IV, Darbepoetin, Mircera
Standardized Prior rhEPO dose	standardized dose by tertile (<=xx.xx, >xx.xx and < xx.xx, >=xx.xx)
Prior ESA dose (stratification factor)	Low ESA dose: <100 IU/kg/week epoetin OR <0.5 µg/kg/week darbepoetin OR<0.6 µg/kg/week methoxy PEG-epoetin beta High ESA dose: ≥100 IU/kg/week epoetin OR ≥0.5 µg/kg/week darbepoetin OR≥0.6 µg/kg/week methoxy PEG-epoetin beta
Ethnicity	Not Hispanic or Latino, Hispanic or Latino
Race	White, African American, Asian, Other
Gender	Male, Female
Age	<65, >=65 to < 75, >=75 years
Region	North America, Europe
Diabetes	Yes, No
Phosphate Binders	Yes, No
Baseline Absolute Reticulocyte Count	<= Median, >Median TI/L

NOTES :

- Subgroup summaries will only be produced if there are at least 30% of total ITT subjects in each subgroup.

11.11. Appendix 11: Multiple Comparisons & Multiplicity

11.11.1. Handling of Multiple Comparisons & Multiplicity

No adjustment for multiplicity will be made because (1) all statistical analyses are estimation based, and (2) the focus of this study is on characterizing the Hgb-three-times weekly dose-response relationship and using the results to estimate the dose ratio between three-times weekly and QD doses that produce the same Hgb response, not on formal testing of hypotheses.

11.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

Refer to Section 7.1.2 for “Convergence Diagnostics” and “Posterior Estimates”.

11.13. Appendix 13 – Abbreviations & Trade Marks

11.13.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical classification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CHr	reticuloctye Hgb
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CRO	Contract Research Organization
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DBR	Database Release
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EPO	Erythropoietin
ESA	Erythropoiesis-Stimulating Agent
EW	Early Withdrawal
FSH	follicle stimulating hormone
GSK	GlaxoSmithKline
HD	Hemodialysis
Hgb	Hemoglobin
HR	Heart Rate
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
ICF	Informed Consent Form
IP	Investigational Product
ITT	Intent-To-Treat
IU	International Unit
IV	Intravenous
IVWRS	Interactive Voice/Web Response System
LFT	Liver Function Test
MCV	Mean Corpuscular Volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Potential Clinical Importance

Abbreviation	Description
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
QD	Once daily
QTc	QT Interval Corrected for Heart Rate
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RBC	Red Blood Cell
RDW	Red cell distribution width
rhEPO	Recombinant Human Erythropoietin
SAC	Statistical Analysis Complete
SBP	Systolic Blood Pressure
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
TFL	Tables, Figures & Listings
TIBC	Total iron-binding capacity
TIW	Three-times weekly
UIBC	unsaturated iron-binding capacity
Var	Variance
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell

11.13.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
HemoCue
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11.14. Appendix 14: List of Data Displays

11.14.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Section	**Listings**	
ICH Listings	1 to 50	
Other Listings	51 to 81	

11.14.2. Mock Example Shell Referencing

IDSL and Non-IDSL shells will be referred by either the IDSL example shell name (e.g. ES6) or a TFL number (e.g. Table 6.03) from study PHI113633, to which the result of a similar, corresponding TFL created for this study will be compared. Example TFL shells will be provided in Appendix 15.

11.14.3. Data Display Convention

The table, figure and listing shells are for *guidance only* and programming notes have been included to indicate how these outputs will look for this study.

Treatment Labels
The approved generic name for GSK1278863 is daprodustat, and its abbreviation, dapro, will be used in the displays. The five treatment groups in this study with the *Total* and *Dapro Total* will be displayed as shown below. Some of the templates/shells provided show less treatment groups, this is for guidance purposes and the tables should show the treatment groups shown below.

a) For Study population

			Dapro			
Placebo	Total	Dapro Total	10 mg	15 mg	25 mg	30 mg
(N=39)	(N=216)	(N=177)	(N=39)	(N=40)	(N=39)	(N=40)

b) For Safety and Efficacy

		Dapro			
Placebo	Dapro Total	10 mg	15 mg	25 mg	30 mg
(N=39)	(N=177)	(N=39)	(N=40)	(N=39)	(N=40)

Note: When possible, display all treatment columns on the same page regardless of how they are shown on the templates.

Note: To be consistent with CDISC, USUBJID will be used for all listings even when SUBJID or SUBJ etc are shown in the listing shells.

11.14.4. Study Population Tables

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Subject Disposition				
1.1.	All Randomized	Table 6.03	Summary of Subject Disposition	
1.2.	All Screened	ES6	Summary of Reasons for Screen Failure	
1.3.	Safety	Table 6.04	Summary of Study Treatment Discontinuation	Use the primary reasons and the subreasons for IP discontinuation collected from the eCRF. The ones on the shell are for guidance purposes only.
1.4.	All Randomized	Table 6.05	Summary of Subjects at Each Visit	
Protocol Deviations				
1.5.	All Randomized	DV1A	Summary of Important Protocol Deviations	See RAP Section 11.1.1 for categories of important protocol deviations
1.6.	ITT	SA2	Summary of Deviations Leading to Exclusions from Per Protocol Population	See RAP Section 11.1.2 for categories of protocol deviations leading to exclusions from PP population
1.7.	All Randomized	Table 6.12	Summary of Inclusion/Exclusion Criteria Deviation	See eCRF and study protocol Section 5.2 and Section 5.3 for inclusion and exclusion criteria
Populations Analyzed				
1.8.	All Randomized	Table 6.01	Summary of Study Populations	
1.9.	All Randomized	Table 6.02	Summary of Number of Subjects by Center	Countries will be ordered in descending order of the Dapro Total column. Centres will be ordered within each country by descending order of Dapro Total

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
				column.
Demography				
1.10.	Safety	DM1	Summary of Demographic and Other Baseline Characteristics	Age, Gender, Ethnicity, Race, Diabetes, Weight, Height, BMI, Prior ESA Dose (Low ESA dose: <100 IU/kg/week epoetin OR <0.5 µg/kg/week darbepoetin OR <0.6 µg/kg/week methoxy PEG-epoetin beta vs. High ESA dose: ≥100 IU/kg/week epoetin OR ≥0.5 µg/kg/week darbepoetin OR ≥ 0.6 µg/kg/week methoxy PEG-epoetin beta), Type of ESA, Standardized Prior rhEPO Dose, Baseline Hgb, Baseline Ferritin, Baseline Absolute Reticulocyte count, Baseline Pre-dose Plasma EPO, Baseline iron-based phosphate binder (ferric citrate and sucroferric oxyhydroxide) For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.1 Summary of Demographic Characteristics
1.11.	ITT	DM1	Summary of Demographic and Other Baseline Characteristics	Age, Gender, Ethnicity, Race, Diabetes, Weight, Height, BMI, Prior ESA Dose (Low ESA dose: <100 IU/kg/week epoetin OR <0.5 µg/kg/week darbepoetin OR <0.6 µg/kg/week methoxy PEG-epoetin beta vs. High ESA dose: ≥100 IU/kg/week epoetin OR ≥0.5 µg/kg/week darbepoetin OR ≥ 0.6 µg/kg/week methoxy PEG-epoetin beta), Type of ESA,

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
				Standardized Prior rhEPO Dose, Baseline Hgb, Baseline Ferritin, Baseline Absolute Reticulocyte count, Baseline Pre-dose Plasma EPO, Baseline iron-based phosphate binder (ferric citrate and sucroferric oxyhydroxide) For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.1 Summary of Demographic Characteristics

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
1.12.	All Randomized	DM1	Summary of Demographic and Other Baseline Characteristics	Age, Gender, Ethnicity, Race, Diabetes, Weight, Height, BMI, Prior ESA Dose (Low ESA dose: <100 IU/kg/week epoetin OR <0.5 µg/kg/week darbepoetin OR <0.6 µg/kg/week methoxy PEG-epoetin beta vs. High ESA dose: ≥100 IU/kg/week epoetin OR ≥0.5 µg/kg/week darbepoetin OR ≥0.6 µg/kg/week methoxy PEG-epoetin beta), Type of ESA, Standardized Prior rhEPO Dose, Baseline Hgb, Baseline Ferritin, Baseline Absolute Reticulocyte count, Baseline Pre-dose Plasma EPO, Baseline iron-based phosphate binder (ferric citrate and sucroferric oxyhydroxide) For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.1 Summary of Demographic Characteristics
1.13.	ITT	Table 6.10	Summary of Race & Racial Combinations	For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.2 Summary of Race and Racial Combinations
1.14.	ITT	Table 6.11	Summary of Race and Racial Combination Details	For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.2.1 Summary of Race and Racial Combination Details
1.15.	All Randomized	Table 6.11	Summary of Race and Racial Combination Details	For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.2.1 Summary of Race and Racial

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
				Combination Details
Medical Condition & Concomitant Medications				
1.16.	Safety	Table 6.14	Summary of Past Medical Conditions	Categories of medical conditions will be sorted in descending order of "Total" incidence, and medical conditions within each category will be sorted in descending order of "Total" incidence. If the "Total" incidence for any two or more medical conditions is equal, then they will be presented in alphabetical order.
1.17.	Safety	Table 6.15	Summary of Current Medical Conditions	Categories of medical conditions will be sorted in descending order of "Total" incidence, and medical conditions within each category will be sorted in descending order of "Total" incidence. If the "Total" incidence for any two or more medical conditions is equal, then they will be presented in alphabetical order.
1.18.	Safety	Table 6.21	Summary Concomitant Medication ATC Level 1 by Ingredient	Medications will be sorted in descending order of total incidence of "Dapro Total" for the ATC level 1 and in descending order of total incidence for the ingredient within each ATC level. If the total incidence of "Dapro Total" for any two or more ingredients is equal, the events will be presented in alphabetical order. See GSK IDSL "CONCOMITANT MEDICATIONS STATISTICAL DISPLAY STANDARDS" (Version 12), Section 1.1.1

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
1.19.	Safety	Table 6.21	Summary Concomitant Medication ATC Level 1 by Ingredient and Ingredient Combinations	Medications will be sorted in descending order of total incidence of "Dapro Total" for the ATC level 1 and in descending order of total incidence for the ingredient within each ATC level. If the total incidence of "Dapro Total" for any two or more ingredients is equal, the events will be presented in alphabetical order. See GSK IDSL "CONCOMITANT MEDICATIONS STATISTICAL DISPLAY STANDARDS" (Version 12), Section 1.1.2
1.20.	Safety	Table 6.16	Summary of Family History of Cardiovascular Risk	The frequency count (%) for "First degree relatives" are the number (%) of subjects with any first degree relatives (biologic father, mother, brother, and sister) who have cardiovascular risk factors. It should be derived from the four categories of first degree relatives captured on the eCRF.
1.21.	Safety	Table 6.17	Summary of Substance Use History	.
1.22.	Safety	Table 6.18	Summary of Baseline Hemodialysis	
1.23.	Safety	Table 6.23	Summary of Prior Erythropoiesis-Stimulating Agents	
1.24.	Safety	Table 6.24	Summary of Concomitant Erythropoiesis-Stimulating Agents	
1.25.	Safety	Table 6.26	Summary of On-Therapy Average Iron Dose	IV: weekly average Oral: daily average
1.26.	Safety	Table 6.26	Summary of Pre-therapy Average Iron Dose	IV: weekly average

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
				Oral: daily average "Pre-therapy" include 4-week screening period and 4-week period prior to the screening period.
1.27.	Safety	Table 6.29	Summary of Subjects Using IV Iron Dose Between Study Treatment Start and Final Visit	First row title: "Using iron at Treatment Start and Day 29" 1. The subjects who used IV iron between Study Treatment Start and final on-treatment visit must fall into one and only one of the 3 categories in this table (i.e. they capture all types of IV iron users): a. Using Iron at Treatment Start and Day 29 (completers) or Using Iron at Treatment Start and Last Available Visit (Safety pop) (Note: Day 29 or Last Available Visit must be on-treatment visit. These are the subjects who were on IV iron at treatment start AND at the last on-treatment visit). b. Stopping iron on-therapy. (Note: These are the subjects who were on IV iron at treatment start but stopped before the last on-treatment visit c. Starting iron after treatment start. (Note: These are the subjects who were not on IV iron at treatment start, but started taking iron after treatment start.)

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
				2. The study subjects can be categorized using an algorithm that is similar to the one shown below: a. (1) Using iron at treatment start: "Any IV Iron Therapy -Iron Start Date" <= "Treatment Start Date" and ("Any IV Iron Therapy -Iron End Date" >= "Treatment Start Date" or ongoing). (2) Using iron at Day 29 or Last Available On-treatment Visit: "Any IV Iron Therapy -Iron End Date" >= "Last on-treatment visit date" (Note: The IV iron used at treatment start does not have to be the same IV iron used at Day 29 or the Last Available On-treatment Visit) b. Stopping iron on-therapy: "Any IV Iron Therapy - Iron Start Date" <= "Treatment Start Date" and Any IV Iron Therapy - "Iron End Date" >= "Treatment Start Date" and "All IV Iron Therapy-Iron End Date" < "Last on-treatment visit date"" (Note: The IV iron used at treatment start does not have to be the same IV iron that stopped prior to the last on-treatment visit date (i.e. We are

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
				flagging the subjects and not the Iron therapy.)) c. Starting iron after treatment start: "Iron Start Date" > "Treatment Start Date" with no other IV Iron therapy at treatment start.
1.28.	Completer	Table 6.29	Summary of Subjects Using IV Iron Dose Between Study Treatment Start and Final Visit	First row title: "Using iron at Treatment Start and Day 29" Also see the programming notes above for the previous table
1.29.	Safety	Table 6.32	Summary of Blood Products	
Exposure and Treatment Compliance				
1.30.	Safety	Table 6.33	Summary of Study Medication Overall Compliance	
1.31.	Safety	Table 8.01	Summary of Extent of Exposure to Study Treatment	

11.14.5. Study Population Figures

Study Population Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
1.1.	Safety	Figure 6.05	Bar Chart of Prior Erythropoiesis Stimulating Agents	
1.2.	Safety	Figure 6.06	Histogram of Standardized Prior Recombinant Human Erythropoietin Dose	

11.14.6. Efficacy Tables

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Summary and Analysis of Hemoglobin				
2.1.	ITT	Table 7.001	Summary of Hemoglobin (g/dL) by Visit	Show Week-2, Day 1, Baseline, Day 15, Day 29, Day 29 Including Imputed, Day 43 Follow-up Only on-treatment Hgb will be summarized for Day 15 and Day 29 visits.
2.2.	ITT	Table 7.002	Summary of Hemoglobin (g/dL) Change from Baseline by Visit	Baseline is the average of Hgb values measured by Quest at Week -2 and Day 1 visits Show Baseline, Change from baseline at Day 15, Day 29, Day 29 Including Imputed, Day 43 Follow-up Only on-treatment Hgb will be summarized for Day 15 and Day 29 visits.
2.3.	ITT	Table 7.004	Summary of Hemoglobin (g/dL) Change from Baseline by Visit by Subgroups	Baseline is the average of Hgb values measured by Quest at Week -2 and Day 1 visits Use the subgroups defined in RAP Section 11.10.1 Show Baseline, Change from baseline at Day 15, Day 29, Day 43 Follow-up Only on-treatment Hgb will be summarized for Day 15 and Day 29 visits.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.4.	ITT	Table 7.005	Summary of Treatment Difference for Hemoglobin (g/dL) Change from Baseline at Day 29 by Subgroups	Baseline is the average of Hgb values measured by Quest at Week -2 and Day 1 visits Only on-treatment Hgb will be included in this analysis Use the subgroups defined in RAP Section 11.10.1
2.5.	ITT	Table 7.010	Summary of Posterior Estimates from the Bayesian 3 Parameter Emax Dose-Response Model for Change in Hemoglobin at Day 29 for the Primary and Sensitivity Prior Analyses and the Estimates from the Frequentist 3 Parameter Emax Dose-Response Model	There are 3 analyses (1) based on the prior defined for the primary analysis (2) weak priors (3) frequentist analysis Based on both observed on-treatment Hgb and imputed Hgb at Day 29 visit. If Day 29 Hgb is imputed using Day 15 Hgb, Day 15 Hgb must be measured on-treatment. Will be performed by GSK
2.6.	Completers	Table 7.011	Sensitivity Summary of Posterior Estimates from the Bayesian 3 Parameter Emax Dose-Response Model for Change in Hemoglobin at Day 29	Same as template 7.010, just based on different pop Will be performed by GSK

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.7.	Per-Protocol	Table 7.012	Sensitivity Summary of Posterior Estimates from the Bayesian 3 Parameter Emax Dose-Response Model for Change in Hemoglobin at Day 29	Same as template 7.010, just based on different pop Based on both observed on-treatment Hgb and imputed Hgb at Day 29 visit. If Day 29 Hgb is imputed using Day 15 Hgb, Day 15 Hgb must be measured on-treatment. Will be performed by GSK
2.8.	ITT	Linear_DR	Dose-Response Linear Model for Change in Hemoglobin at Day 29	Based on both observed on-treatment Hgb and imputed Hgb at Day 29 visit. If Day 29 Hgb is imputed using Day 15 Hgb, Day 15 Hgb must be measured on-treatment. Will be performed by GSK
2.9.	Completers	Linear_DR	Dose-Response Linear Model for Change in Hemoglobin at Day 29	Based on observed on-treatment Hgb at Day 29 visit. Will be performed by GSK
2.10.	Per Protocol	Linear_DR	Dose-Response Linear Model for Change in Hemoglobin at Day 29	Based on both observed on-treatment Hgb and imputed Hgb at Day 29 visit. If Day 29 Hgb is imputed using Day 15 Hgb, Day 15 Hgb must be measured on-treatment. Will be performed by GSK
2.11.	ITT	Dose_Ratio_1	Summary of Dose Ratio Between Three-Times Weekly Doses (Observed) and QD Doses (Estimated by Bayesian Emax Model)	Will be performed by GSK when the dose-response model is appropriate

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.12.	ITT	Dose_Ratio_1	Summary of Dose Ratio Between Three-Times Weekly Doses (Observed) and QD Doses (Estimated by Frequentist Emax Model)	Will be performed by GSK when the dose-response model is appropriate
2.13.	ITT	Dose_Ratio_1	Summary of Dose Ratio Between Three-Times Weekly Doses (Observed) and QD Doses (Estimated by Linear Model)	Will be performed by GSK when the dose-response model is appropriate
2.14.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated by Bayesian Emax Model) and QD Doses (Estimated by Bayesian Emax Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.15.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated by Bayesian Emax Model) and QD Doses (Estimated by Frequentist Emax Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.16.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated by Bayesian Emax Model) and QD Doses (Estimated by Linear Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.17.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated by Frequentist Emax Model) and QD Doses (Estimated by Bayesian Emax Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.18.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated Frequentist Emax Model) and QD Doses (Estimated by Frequentist Emax Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.19.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated by Frequentist Emax Model) and QD Doses (Estimated by Linear Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.20.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated by Linear Model) and QD Doses (Estimated by Bayesian Emax Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.21.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated by Linear Model) and QD Doses (Estimated by Frequentist Emax Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.22.	ITT	Dose_Ratio_2	Summary of Dose Ratio Between Three-Times Weekly Doses (Estimated Linear Model) and QD Doses (Estimated by Linear Model) at Selected Hgb Responses	Will be performed by GSK when the dose-response models are appropriate
2.23.	ITT	Model_ratio	Summary of Dose Ratio between Three-Times Weekly Dose and QD Dose Estimated by Emax Model and Linear Model	Will be performed by GSK
2.24.	ITT	Linear_TQ	Linear Model between the corresponding QD and TIW doses with the same Change in Hemoglobin at Day 29	Will be performed by GSK
2.25.	ITT (PHI113633)	Emax633	Summary of Posterior Estimates from the Bayesian 3 Parameter Emax Dose-Response Model and the Estimates from the Frequentist 3 Parameter Emax Dose-Response Model for Change in Hemoglobin at Week 4 (Based on PHI113633 data excluding Japan)	Will be performed by GSK
2.26.	ITT (PHI113633)	Linear633	Dose-Response Linear Model for Change in Hemoglobin at Week 4 (Based on PHI113633 data excluding Japan)	Will be performed by GSK
2.27.	ITT	Table 7.013	Summary of Hemoglobin Imputations	"n(%)"s in this table reflect the number(%) of subjects who are included in the primary efficacy analyses. Therefore the post-baseline "n(%)"s should be the number(%) of subjects who are on-treatment at Day 15 visit and/or at Day 29 visit.
2.28.	ITT	PHI116581 Table 7.23	Summary of Subjects who Reach Pre-defined Hemoglobin Stopping Criteria	Based on Hgb measured by Quest "≥2.0 decrease" and "≥1.0 increase" refer to change over 2 weeks. See protocol Section 5.6.2.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.29.	ITT	Table 7.054	Exploratory Summary of Repeated Measures Analysis for Hemoglobin (g/dL) Change from Baseline at Day 29	
2.30.	ITT	Ac hoc Table 67.01601	Summary of Subjects Meeting Different Hemoglobin Criteria	Based on on-treatment Hgb
Summary and Analyses of Other Efficacy Parameters				
2.31.	ITT	Table 7.021	Summary of Hepcidin (ug/L) by Visit	Show summary stat at Day1, Day 15, and Day 29 Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.32.	ITT	Table 7.022	Summary of Hepcidin (ug/L) Percent Change from Baseline by Visit	Show Baseline, % Change from baseline at Day 15, and Day 29 Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.33.	ITT	Table 7.023	Summary of Ferritin (ug/L) by Visit	Show summary stat at Week -4, Day1, Day 29,and Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.34.	ITT	Table 7.024	Summary of Ferritin (ug/L) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 29, Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.35.	ITT	Table 7.023	Summary of Transferrin (g/L) by Visit	Show summary stat at Week -4, Day1, Day 29,and Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.36.	ITT	Table 7.024	Summary of Transferrin (g/L) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 29, Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.37.	ITT	Table 7.021	Summary of Transferrin Saturation (%) by Visit	Show summary stat at Week -4, Day1, Day 29,and Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.38.	ITT	Table 7.022	Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit	Show Baseline, % Change from baseline at Day 29, Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.39.	ITT	Table 7.023	Summary of Total Iron (umol/L) by Visit	Show summary stat at Week -4, Day1, Day 29,and Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.40.	ITT	Table 7.024	Summary of Total Iron (umol/L) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 29, Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.41.	ITT	Table 7.023	Summary of Unsaturated Iron Binding Capacity (umol/L) by Visit	Show summary stat at Week -4, Day1, Day 29,and Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.42.	ITT	Table 7.024	Summary of Unsaturated Iron Binding Capacity (umol/L) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 29, Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.43.	ITT	Table 7.023	Summary of Total Iron Binding Capacity (umol/L) by Visit	Show summary stat at Week -4, Day1, Day 29,and Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.44.	ITT	Table 7.024	Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 29, Day 43 Follow-up Only on-treatment assessment will be summarized for Day 29 visit.
2.45.	ITT	Table 7.023	Summary of Reticulocyte Hemoglobin (CHr) (pg) by Visit	Show summary stat at Week -2, Day1, Day 15, Day 29,and Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.46.	ITT	Table 7.024	Summary of Reticulocyte Hemoglobin (CHr) (pg) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 15, Day 29, Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.47.	ITT	Table 7.023	Summary of Hematocrit (Fraction of 1) by Visit	Show summary stat at Week -2, Day1, Day 15, Day 29,and Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.48.	ITT	Table 7.024	Summary of Hematocrit (Fraction of 1) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 15, Day 29, Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.49.	ITT	Table 7.023	Summary of Hematocrit (%) by Visit	Show summary stat at Week -2, Day1, Day 15, Day 29,and Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.50.	ITT	Table 7.024	Summary of Hematocrit (%) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 15, Day 29, Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.51.	ITT	Table 7.023	Summary of Red Blood Cell Count (10^12/L) by Visit	Show summary stat at Week -2, Day1, Day 15, Day 29,and Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.52.	ITT	Table 7.024	Summary of Red Blood Cell Count (10^12/L) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 15, Day 29, Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.53.	ITT	Table 7.023	Summary of Reticulocyte Count (%) by Visit	Show summary stat at Week -2, Day1, Day 15, Day 29,and Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.54.	ITT	Table 7.024	Summary of Reticulocyte Count (%) Change from Baseline by Visit	Show Baseline, Change from baseline at Day 15, Day 29, Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.55.	ITT	Table 7.023	Summary of Absolute Reticulocyte Count (10^12/L) by Visit	Show summary stat at Week -2, Day1, Day 15, Day 29,and Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.56.	ITT	Table 7.024	Summary of Absolute Reticulocyte Count (10^12/L) Percent Change from Baseline by Visit	Show Baseline, Percent Change from baseline at Day 15, Day 29, Day 43 Follow-up Only on-treatment assessments will be summarized for Day 15 and Day 29 visits. %Change = 100 x [(Post-Baseline Visit Value – Baseline) / Baseline]
2.57.	ITT	Table 7.047	Summary of Plasma Erythropoietin (IU/L) by Visit and Sample Time	Show summary stat at scheduled visit and sample time specified in Protocol Section 7 Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.

Efficacy: Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.58.	ITT	Table 7.048	Summary of Plasma Erythropoietin (IU/L) Change from Baseline by Visit and Sample Time	Show Baseline and Change from baseline at scheduled visit and sample time specified in Protocol Section 7 Only on-treatment assessments will be summarized for Day 15 and Day 29 visits.
2.59.	ITT	Table 7.049	Summary of Plasma Erythropoietin (IU/L) Maximum Observed Change from Baseline	Only on-treatment assessments will be summarized
2.60.	ITT	Table 7.050	Summary of VEGF (ng/L) by Visit and Sample Time	Show summary stat at scheduled visit and sample time specified in Protocol Section 7
2.61.	ITT	Table 7.051	Summary of VEGF (ng/L) Percent Change from Baseline by Visit and Sample Time	Show Baseline and %Change from baseline at scheduled visit and sample time specified in Protocol Section 7
2.62.	ITT	Table 7.052	Summary of VEGF (ng/L) Maximum Observed Percent Change from Baseline	Only on-treatment assessments will be summarized

11.14.7. Efficacy Figures

Programming notes:

- If the horizontal x axis label in the figure template is “Visit (weeks)” (copied from study PHI113633), replace it with “Visit (days)”, and make the corresponding changes on the tick mark values.
- If the horizontal x axis label in the figure template is “Dose (mg)” (copied from study PHI113633), replace it with “Three-Times Weekly Dose (mg)”.

Efficacy: Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Hemoglobin				
2.1.	ITT	Figure 7.002	Mean and 95% CI for Hemoglobin by Visit	Show pre-baseline data, baseline data, “on-treatment” data for on-treatment visits (Day 15 and Day 29), and data at day 43 follow-up
2.2.	ITT	Figure 7.004	Mean and 95% CI for Hemoglobin Change from Baseline by Visit	Show on-treatment data for on-treatment visits (Day 15 and Day 29) and data at day 43 follow-up
2.3.	ITT	Figure 7.007	Subject Profiles of Hemoglobin and Exposure over Time	Remove the right Y-axis from the shell. Show Hgb profile, but do not show “Dose”. Instead, add a horizontal line to show exposure time. Including baseline, on-treatment, and post-treatment data
2.4.	ITT	Figure 7.012	Scatter plot of Hemoglobin Assessments: Quest vs. HemoCue	Use different symbols and show 5 regression lines for the 5 different countries. In the footnote, show the fitted overall regression model. Based on all data collected at any time in the study
2.5.	ITT	Figure 7.013	Posterior Emax Dose−Response Curve for Hemoglobin (g/dL) Change from Baseline at Day 29	Replace “Note: Bayesian 4−parameter Emax model is presented.” with “Note: Bayesian 3−parameter Emax model is presented.” X axis: 0 to 50 Create it in house at GSK

Efficacy: Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.6.	Completer	Figure 7.015	Posterior Emax Dose−Response Curve for Hemoglobin (g/dL) Change from Baseline at Day 29 for Primary Analysis and Completers Sensitivity Analysis	Replace “Note: Bayesian 4−parameter Emax model is presented.” with “Note: Bayesian 3−parameter Emax model is presented.” Replace “Note: Solid grey lines: 95% credible bands associated with Week 4 Completers Analysis.” with” Note: Solid grey lines: 95% credible bands associated with Completers Analysis.” X axis: 0 to 50 Create it in house at GSK
2.7.	ITT	Figure 7.016	Posterior Emax Dose−Response Curve for Hemoglobin (g/dL) Change from Baseline at Day 29 for Primary Analysis and Sensitivity Priors and Frequentist Sensitivity Analyses	Replace “Note: Bayesian 4−parameter Emax, model for Primary ITT [Sensitivity Prior] analyses and Frequentist 3−parameter Emax model are presented.” with “Note: Bayesian 3−parameter Emax, model for Primary ITT [Sensitivity Prior] analyses and Frequentist 3−parameter Emax model are presented.” X axis: 0 to 50 Create it in house at GSK

Efficacy: Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.8.	Per Protocol	Figure 7.017	Posterior Emax Dose−response Curve for Hemoglobin Change at Day 29 for Primary Analysis and Per Protocol Sensitivity Analysis	Replace “Note: Bayesian 4−parameter Emax model is presented.” with “Note: Bayesian 3−parameter Emax model is presented.” X axis: 0 to 50 Create it in house at GSK
2.9.	ITT	Figure 7.018	Posterior Probability Distribution for Predicted Hemoglobin Change (g/dL) from Baseline at Day 29 Based on Primary Analysis	Replace “Note: Posterior probability distributions reflect Hemoglobin change from baseline over 4 weeks, on average, and do not reflect probability for any single patient” with “Note: Posterior probability distributions reflect Hemoglobin change from baseline over 29 days, on average, and do not reflect probability for any single patient” Create it in house at GSK
2.10.	ITT	Figure 7.019	Density Plots Associated with Emax Model Parameter, E0	Create it in house at GSK
2.11.	ITT	Figure 7.020	Density Plots Associated with Emax Model Parameter, Emax	Create it in house at GSK
2.12.	ITT	Figure 7.021	Density Plots Associated with Emax Model Parameter, ED50	Create it in house at GSK
2.13.	ITT	Figure 7.024	Density Plots Associated with Emax Model Parameter, Variance	Create it in house at GSK

Efficacy: Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.14.	ITT	Figure 7.026	Posterior Predictive Distribution for Hemoglobin (g/dL) Change from Baseline at Day 29 for a Future Subject based on Primary Analysis	Replace "Note: Posterior predictive probability distributions reflect the Hemoglobin change from baseline at week 4 for a future subject." with "Note: Posterior predictive probability distributions reflect the Hemoglobin change from baseline at Day 29 for a future subject." Create it in house at GSK
2.15.	ITT	Figure 7.027	Posterior Predictive Probability that Day 29 Hemoglobin (g/dL) Change for a Future Subject will be in the Range [−0.5, 0.5] g/dL by Daprodustat Dose	Replace "Note: The probability describes the likelihood that a future subject will be maintained within the range +/− 0.5 g/dL from Baseline over 4 Weeks, by dose" with "Note: The probability describes the likelihood that a future subject will be maintained within the range +/− 0.5 g/dL from Baseline over 29 days, by dose" Create it in house at GSK
2.16.	ITT	Figure 7.028	Individual Subject Hemoglobin Change from Baseline at Day 29 with Means and 95% CIs	Don't distinguish Japan from Non-Japan. Show data from different countries by different symbols On-treatment Hgb only Create it in house at GSK
2.17.	ITT	Hgb_Scatter	Scatter Plot of Hgb Responses vs. Three-Times Weekly Doses and QD Weekly Doses	Add jittering to the plot if there are too many dots at a specific dose level Create it in house at GSK

Efficacy: Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.18.	ITT	TIW_QD	Three-Times Weely Doses vs. QD Doses Corresponding to Selected Hgb Responses	Create it in house at GSK
2.19.	ITT	Figure 7.031	Forest plot of Model−Adjusted Treatment Difference for Hemoglobin at Day 29	Delete "Note: results for race group=Other are provided in Table 7.005" Based the corresponding repeated measures analysis sas output
Other Efficacy Parameters				
2.20.	ITT	Figure 7.036	Geometric Mean and 95% CI for Hepcidin by Visit	See programming notes for the corresponding summary table
2.21.	ITT	Figure 7.037	Mean and 95% CI for Hepcidin Percent Change from Baseline by Visit	See programming notes for the corresponding summary table
2.22.	ITT	Figure 7.039	Mean and 95% CI for Ferritin by Visit	See programming notes for the corresponding summary table
2.23.	ITT	Figure 7.040	Mean and 95% CI for Ferritin Change from Baseline by Visit	See programming notes for the corresponding summary table
2.24.	ITT	Figure 7.041	Mean and 95% CI for Transferrin by Visit	See programming notes for the corresponding summary table
2.25.	ITT	Figure 7.042	Mean and 95% CI for Transferrin Change from Baseline by Visit	See programming notes for the corresponding summary table
2.26.	ITT	Figure 7.043	Geometric Mean and 95% CI for Transferrin Saturation by Visit	See programming notes for the corresponding summary table
2.27.	ITT	Figure 7.044	Mean and 95% CI for Transferrin Saturation Percent Change from Baseline by Visit	See programming notes for the corresponding summary table

Efficacy: Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.28.	ITT	Figure 7.045	Mean and 95% CI for Total Iron by Visit	See programming notes for the corresponding summary table
2.29.	ITT	Figure 7.046	Mean and 95% CI for Total Iron Change from Baseline by Visit	See programming notes for the corresponding summary table
2.30.	ITT	Figure 7.049	Mean and 95% CI for Total Iron Binding Capacity by Visit	See programming notes for the corresponding summary table
2.31.	ITT	Figure 7.050	Mean and 95% CI for Total Iron Binding Capacity Change from Baseline by Visit	See programming notes for the corresponding summary table
2.32.	ITT	Figure 7.051	Mean and 95% CI for Reticulocyte Hemoglobin Content by Visit	See programming notes for the corresponding summary table
2.33.	ITT	Figure 7.052	Mean and 95% CI for Reticulocyte Hemoglobin Content Change from Baseline by Visit	See programming notes for the corresponding summary table
2.34.	ITT	Figure 7.053	Mean and 95% CI for Hematocrit by Visit	See programming notes for the corresponding summary table
2.35.	ITT	Figure 7.054	Mean and 95% CI for Hematocrit Change from Baseline by Visit	See programming notes for the corresponding summary table
2.36.	ITT	Figure 7.055	Mean and 95% CI for Red Blood Cell Count by Visit	See programming notes for the corresponding summary table
2.37.	ITT	Figure 7.056	Mean and 95% CI for Red Blood Cell Count Change from Baseline by Visit	See programming notes for the corresponding summary table
2.38.	ITT	Figure 7.057	Mean and 95% CI for Reticulocyte Count (%) by Visit	See programming notes for the corresponding summary table
2.39.	ITT	Figure 7.058	Mean and 95% CI for Reticulocyte Count (%) Change from Baseline by Visit	See programming notes for the corresponding summary table

Efficacy: Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
2.40.	ITT	Figure 7.059	Mean and 95% CI for Reticulocyte Count (Absolute) by Visit	See programming notes for the corresponding summary table
2.41.	ITT	Figure 7.060	Mean and 95% CI for Reticulocyte Count (Absolute) Percent Change from Baseline by Visit	See programming notes for the corresponding summary table
2.42.	ITT	Figure 7.067	Subject Profiles of Iron−related Parameters with Mean Line by Visit	Replace the horizontal x axis label “Weeks Since First Dose” with “Days Since First Dose”
2.43.	ITT	Figure 7.068	Subject Profiles of Plasma Erythropoietin and Hepcidin by Visit	Delete “with Mean Line” from shell title.
2.44.	ITT	Figure 7.069	Individual Post−Dose Plasma Erythropoietin at Day 15	Plotted with a loess curve fitted for each treatment group based on Day 15 data.
2.45.	ITT	Figure 7.070	Individual Post−Dose VEGF at Day 15	Plotted with a loess curve fitted for each treatment group based on Day 15 data

11.14.8. Safety Tables

Safety : Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Adverse Events				
3.1.	Safety	EXAMPLE AE13	Adverse Event Overview	

Safety : Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
3.2.	Safety	Table 8.07	Summary of On-Therapy Adverse Events by System Organ Class	For details on how to sort the AEs in AE summary tables, please see GSK IDSL "Adverse Event Statistical Display Standards". For this study, AEs will be sorted by the incidence of "Dapro Total" (unrounded), instead of "total incidence (i.e., summed across all treatment groups)", in descending order. Re-confirm the MedDRA version number (19.0) in the footnote
3.3.	Safety	Table 8.07	Summary of Post-Therapy Adverse Events by System Organ Class	Sorted by Dapro Total (unrounded) in descending order
3.4.	Safety	Table 8.05	Summary of On-therapy Adverse Events by Preferred Term	Sorted by Dapro Total (unrounded) in descending order Re-confirm the MedDRA version number (19.0) in the footnote
3.5.	Safety	Table 8.05	Summary of Post-therapy Adverse Events by Preferred Term	Sorted by Dapro Total (unrounded) in descending order
3.6.	Safety	Table 8.05	Summary of On-Therapy Common Adverse Events by Overall Frequency	Common AE is defined as an AE with >=2 subjects in any treatment group or >=2% (based on unrounded value) in the Dapro Total group.
3.7.	Safety	Table 8.07	Summary of On-Therapy Common Non-Serious Adverse Events by Overall Frequency	Common AE is defined as an AE with >=2 subjects in any treatment group or >=2% (based on unrounded value) in the Dapro Total group.
3.8.	Safety	Table 8.10	Summary of On-therapy Adverse Events by System Organ Class and Maximum Intensity	
3.9.	Safety	Table 8.07	Summary of On-Therapy Treatment-Related Adverse Events by System Organ Class	

Safety : Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
3.10.	Safety	Table 8.05	Summary of On-Therapy Treatment-Related Adverse Events by Preferred Term	
3.11.	Safety	Table 8.07	Summary of On-Therapy Serious Adverse Events by System Organ Class	
3.12.	Safety	Table 8.05	Summary of On-therapy Serious Adverse Events by Preferred Term	
3.13.	Safety	Table 8.05	Summary of Post-therapy Serious Adverse Events by Preferred Term	
3.14.	Safety	Table 8.05	Summary of On-Therapy Treatment-Related Serious Adverse Events by Preferred Term	
3.15.	Safety	Table 8.07	Summary of On-Therapy Treatment-Related Serious Adverse Events by System Organ Class	
3.16.	Safety	Table 8.07	Summary of On-Therapy Adverse Events Leading to Withdrawal/Permanent Discontinuation of Study Treatment by Overall Frequency (By System Organ Class)	
3.17.	Safety	Table 8.05	Summary of On-Therapy Adverse Events Leading to Withdrawal/Permanent Discontinuation of Study Treatment by Overall Frequency (By Preferred Term)	
3.18.	Safety	Table 8.18	Summary of On-Therapy Adverse Events of Special Interest	AESI: Defined in PSAP Section 8.6.1.1. The identification of AESI will be based on SRT in-stream, blinded review of AEs Footnotes of the shell need to be modified according to the AESI identified for this study. See RAP Section 8.2.2.1.

Safety : Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
3.19.	Safety	EudraCTNon-serious	Summary of Subjects and Number of Occurrences of Common On-therapy Non-Serious Adverse Events by System Organ Class and Preferred Term (with Occurrences >=5%)	Total number of subjects having any non-serious AE at or above >=5% within any treatment group
3.20.	Safety	EudraCTSAE	Summary of Subjects and Number of Occurrences of On-therapy Serious, Treatment-related Serious, Fatal Serious, and Treatment-related Fatal Serious Adverse Events by System Organ Class and Preferred Term	
Laboratory Parameters				
3.21.	Safety	Table 8.20	Summary of Chemistry by Visit	
3.22.	Safety	LB1	Summary of Chemistry Change from Baseline by Visit	Includes Baseline values
3.23.	Safety	Table 8.21	Summary of Hematology by Visit	
3.24.	Safety	LB1	Summary of Hematology Change from Baseline by Visit	Includes Baseline values
3.25.	Safety	Table 8.22	Summary of Hematology Data Outside the Reference Range	
3.26.	Safety	Table 8.23	Summary of Hematology and Chemistry Data of Potential Clinical Importance at Any Time On-Therapy	
3.27.	Safety	Table 8.23	Summary of Hematology and Chemistry Data of Potential Clinical Importance at Any Time Post-Therapy	.

Safety : Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
3.28.	Safety	LB3	Summary of Chemistry Changes from Baseline Relative to the Reference Range (or with Respect to the Normal Range)	Use normal ranges provided by Quest/Q2 as the reference ranges. On-treatment assessment only Generate one table for each scheduled visit, and one for “any time on-therapy” See GSK IDSL Laboratory Statistical Display Standards, Section 1.2.1 for additional details.
3.29.	Safety	LB3	Summary of Hematology Changes from Baseline Relative to the Reference Range (or with Respect to the Normal Range)	Use normal ranges provided by Quest/Q2 as the reference ranges. On-treatment assessment only Generate one table for each scheduled visit and one for “any time on-therapy”. See GSK IDSL Laboratory Statistical Display Standards, Section 1.2.1 for additional details.
ECGs				
3.30.	Safety	EG1	Summary of ECG Findings by Visit	
3.31.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	Include all ECG parameters collected.

Safety : Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Vital Signs				
3.32.	Safety	Table 8.25	Summary of Vital Signs by Visit	Summarize both pre and post-dialysis vital signs in separate tables SBP, DBP, Heart Rate, and Weight (Weight is measured post-dialysis only)
3.33.	Safety	Table 8.26	Summary of Change from Baseline in Vital Signs by Visit	Summarize both pre and post-dialysis vital signs in separate tables SBP, DBP, Heart Rate, and Weight (Weight is measured post-dialysis only)
3.34.	Safety	Table 8.27	Summary of Vital Signs of Potential Clinical Importance at Any Time On-therapy	Summarize both pre and post-dialysis vital signs in separate tables. SBP, DBP, and Heart Rate
Hepatobiliary (Liver)				
3.35.	Safety	Example LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	
3.36.	Safety	Example: LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	Follow the following treatment order: Placebo, Dapro Total, 10 mg, 15 mg, 25 mg and 30 mg

11.14.9. Safety Figures

Safety : Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
[Insert Endpoint Category]				
3.1.	Safety	F8.02	Most Frequent Adverse Events Sorted by Total Daprodustat Proportion	Remove the RR section in the template. For the "Proportion" section, add each Dapro arm in addition to Dapro Total and placebo.
3.2.	Safety	F8.23	Boxplot of Liver Function Tests by Visit	
3.3.	Safety	F8.24	Matrix Display of Maximum Liver Function Test Values	Y-axis Scale of liver function tests set to a common value across pages selected to show the data in the range of the clinical concern levels. Outliers beyond the y-axis are described in a footnote.
3.4.	Safety	F8.25	Subject Profiles: Liver Function Test Values	Include subjects who have normal baseline, but have any LFT outside normal range any time post-baseline. Add "dose" in the plot.
3.5.	Safety	F8.27	Mean and 95% CI for Systolic and Diastolic Blood Pressure by Visit	Placebo vs. Dapro Total Display pre- and post-dialysis BP in separate plots with the same figure number

11.14.10. Pharmacokinetic Tables

Pharmacokinetic : Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
4.1.	Pharmacokinetic	Table 14.01	Summary of GSK1278863 and Metabolites Plasma Pharmacokinetic Concentration Time Data (ng/ml)	
4.2.	Pharmacokinetic	PK Table 4.2	Summarized Daprodustat Plasma Concentrations (ng/mL) by Scheduled Time for Each Treatment Group	
4.3.	Pharmacokinetic	PK Table 4.3	Summarized Daprodustat Plasma Pharmacokinetic Parameters for Each Treatment Group	

11.14.11. Pharmacokinetic Figures

Pharmacokinetic : Figures				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
4.1.	Pharmacokinetic	Figure 14.02	Individual GSK1278863 and Metabolites Plasma Concentration-Actual Time Plot by Treatment	
4.2.	Pharmacokinetic	Figure 14.03	Mean GSK1278863 and Metabolites Plasma Concentration-Planned Time Plot (Linear and Semi-Log)	
4.3.	Pharmacokinetic	Figure 14.04	Median GSK1278863 and Metabolites Plasma Concentration-Planned Time Plot (Linear and Semi-Log)	

11.14.12. ICH Listings

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Subject Disposition				
1.	All Screened	ES7	Listing of Reasons for Screen Failure	For "Did not meet inclusion/exclusion criteria", the corresponding inclusion/exclusion criteria should also be reported. For "Investigator discretion" and "Withdrew consent", the free-text captured in eCRF should also be reported with "Investigator discretion" and "Withdrew consent"
2.	All Randomized	ES2	Listing of Reasons for Study Withdrawal	See PHI113633 Listing 6.01 about "Subreason". For "Withdrew consent" and "Investigator discretion", use free-text as the subreason. Otherwise, repeat the primary reason as the subreason.
3.	All Randomized	Listing 6.02	Listing of Reasons for Study Treatment Discontinuation	Subreason should be displayed with the primary reason when it is captured in the eCRF. For example, when the primary reason is "Adverse Event" and "GI Bleeding" or "Cancer Event" is selected as the subreason, then it should be displayed under "Subreason"
4.	All Randomized	BL1	Listing of Subjects for Whom the Treatment Blind Was Broken	"Remove "Time Blind Broken" from shell if not collected.
5.	All Randomized	Listing 6.10	Listing of Randomized and Actual Treatment Assignment	
Protocol Deviations				
6.	All Randomized	Example DV2	Listing of Important Protocol Deviations	

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
7.	All Randomized	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	
Populations Analyzed				
8.	All Randomized	SA3a	Listing of Subjects Excluded from Any Populations	Including those excluded from Safety, ITT, Completer, PP and PK population
Demography				
9.	All Randomized	DM2	Listing of Demographic and Baseline Characteristics	The following demographic and baseline characteristics will be included in this listing: Year of birth, age, age category, sex, ethnicity, Geographic Ancestry, Rescreened, Child bearing potential, Diabetes,, Weight, Baseline Weight Category, Height, BMI,Type of ESA, Standardized Prior ESA dose, Standardized Prior ESA Category(actual eCRF value), Prior ESA (stratification factor from IVRS), Baseline Heart Rate, Baseline Diastolic Blood Pressure, Baseline Systolic Blood Pressure, Baseline Hgb, Baseline Hgb Category, Baseline Ferritin, Baseline Absolute Reticulocyte Count, Baseline Pre-dose Plasma Erythropoietin, Baseline iron-based phosphate binder (ferric citrate and sucroferric oxyhydroxide), Country.
10.	All Randomized	Listing 6.08	Listing of Race	Please make sure that the details shown on the template will be included in this listing.

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Medical Condition & Concomitant Medications				
11.	All Randomized	Listing 6.17	Listing of Concomitant Medications	This listing displays all data captured in the concomitant medications dataset, including medications used prior to screening and post-treatment.
Exposure				
12.	Safety	EX3	Listing of Exposure Data	
Efficacy				
13.	ITT	Listing 7.01	Listing of Hemoglobin Data	Hemocue Hgb is not used for calculation of "Change from Baseline". When scheduled Quest Hgb at Day 29 visit is missing, "Change from Baseline" can be calculated using imputed Hgb. Slotted post-treatment Hgb cannot be used for calculation of "Change from Baseline"
14.	ITT	Listing 7.01	Listing of Hemoglobin Data for Subjects Who Reach Pre-defined Hemoglobin Stopping Criteria	Based on the HemoCue Hgb stopping criteria described in study protocol Section 5.6.2 Hemoglobin Stopping Criteria. For programming purpose (1) compare Hemocue Hgb at a scheduled visit to Hemocue Hgb at previous scheduled visit (i.e. compare Day 15 back to Day 1, and Day 29 back to Day 15); (2) compare Hemocue Hgb at an unscheduled visit to that measured at previous scheduled/unscheduled visit within 2 weeks. Remove the following columns from the template: (1) Imputed Day 29 Hgb (2) Change From Baseline

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
15.	ITT	Listing 7.03	Listing of Markers of Iron Metabolism and Utilization	ferritin, hepcidin, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), total iron, reticulocyte Hgb (CHr),transferrin, transferrin saturation. "Visit" shown in the listing should be corresponding to those in the RAP Section 11.2.1 Protocol Defined Time & Events Table
16.	ITT	Listing 7.04	Listing of Indices of Hematopoiesis	hematocrit, RBC (erythrocyte) count and reticulocyte count. "Visit" shown in the listing should be corresponding to those in the RAP Section 11.2.1 Protocol Defined Time & Events Table
17.	ITT	Listing 7.05	Listing of Plasma Erythropoietin and VEGF Data	See protocol Section 7.1 Table 2 for visit and planned timepoint "Visit" shown in the listing should be corresponding to those in the RAP Section 11.2.1 Protocol Defined Time & Events Table and PK/PD Time and Events Table
Adverse Events				
18.	Safety	AE8	Listing of All Adverse Events	Modification to AE8:Added another line to All "AE8" listings to show "Treatment State" (whether a AE is on-treatment or post-treatment)
19.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	
20.	Safety	AE8	Listing of On-therapy Treatment-Related Adverse Events	

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
21.	Safety	AE8	Listing of Fatal Adverse Events	
22.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	
23.	Safety	AE8	Listing of Post-Randomization Treatment-Related Serious Adverse Events	
24.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Study Treatment	
25.	Safety	AE2	Listing of Relationship of Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	
26.	Safety	SAE	Listing of Reasons for Considering as a Serious Adverse Event	
27.	Safety	Listing 8.20	Listing of Deaths	
28.		AE8	Listing of AE of Special Interest	In AE8 template, replace “Preferred Term/VERBATIM TEXT” with “AESI Category/Preferred Term”
29.	Safety	Listing 8.10	Listing of MACE Data	MACE data is not collected in a specific eCRF form MACE will be collected as AEs, and will be part of AESI. AESI will be identified and documented by SRT.
30.	Safety	Listing 8.21	Listing of Cancer Data	
31.	Safety	Listing 8.11	Patient Profile Listing of Arrhythmias	
32.	Safety	Listing 8.12	Patient Profile Listing of Congestive Heart Failure	
33.	Safety	Listing 8.13	Patient Profile Listing of Cerebrovascular Events/Stroke/Transient Ischemic Attack	
34.	Safety	Listing 8.14	Patient Profile Listing of Deep Venous Thrombosis /Pulmonary Embolism	

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
35.	Safety	Listing 8.15	Patient Profile Listing of Myocardial Infarction/Unstable Angina	
36.	Safety	Listing 8.16	Patient Profile Listing of Peripheral Arterial Thrombosis Embolism	
37.	Safety	Listing 8.17	Patient Profile Listing of Pulmonary Hypertension	
38.	Safety	Listing 8.18	Patient Profile Listing of Revascularisation	
39.	Safety	Listing 8.19	Patient Profile Listing of Valvulopathy	
Laboratory				
40.	Safety	LB5	Listing of Chemistry Data for Subjects with Abnormalities of Potential Clinical Importance	
41.	Safety	LB5	Listing of Hematology Data for Subjects with Abnormalities of Potential Clinical Importance	
ECGs				
42.	Safety	CP_EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	See Section 11.8.3 for ECG value of potential clinical importance: Increase from baseline QTc > 60 msec
43.	Safety	CP_EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding	
Vital Signs				
44.	Safety	CP_VS4	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance	
Hepatobiliary (Liver)				
45.	Safety	Example LIVER5	Listing of Liver Event Results and Time of Events Relative to Treatment	

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
46.	Safety	MH2	Listing of Past and Current Liver Disease Medical Conditions	Data from Liver Form: 1. Medical Conditions at Onset of Liver Event. 2. Other Medical Conditions. 3. Other Liver Disease Conditions - Liver Event.
47.	Safety	L8.43 SU2	Listing of Alcohol Intake at Time of Liver Event	
48.	Safety	Listing 8.44	Listing of Laboratory Data from Liver Event Follow-Up	
Pharmacokinetics				
49.	Pharmacokinetic	Listing 14.01	Listing of GSK1278863 and Metabolites Pharmacokinetic Plasma Concentration-Time Data	
50.	Pharmacokinetic	PK Parameter Listing	Daprodustat Plasma Pharmacokinetic Parameters for Each Treatment Group	

11.14.13. Non-ICH Listings

Non-ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Additional listings in 204836				
51.	All Randomized	Listing 6.09	Listing of Study Populations	Include All Randomized, ITT, PP, Completers, Safety, and PK populations
52.	All Randomized	Listing 6.07	Listing of Prior Erythropoiesis Stimulating Agents Medications	
53.	All Randomized	Listing 6.11	Listing of Current and Past Medical History	
54.	All Randomized	Listing 6.12	Listing of Cardiovascular Risk Assessment	
55.	All Randomized	Listing 6.13	Listing of Hemodialysis	Display hemodialysis data captured on “Haemodialysis History form (on Day 1) and Haemodialysis on Study form at each visit.
56.	All Randomized	Listing 6.16	Listing of Substance Use History	We collect smoking data, but do not collect alcohol drink data
57.	All Randomized	Listing 6.18	Listing of Relationship Between ATC Level 1, Ingredients And Verbatim Text	
58.	All Randomized	Listing 6.19	Listing of Erythropoiesis Stimulating Agents Medications	Including prior, concomitant and post-treatment ESA
59.	All Randomized	Listing 6.20	Listing of Iron Therapy	
60.	All Randomized	Listing 6.22	Listing of Blood Product	
61.	All Randomized	Listing 6.23	Listing of Study Medication Compliance	

Non-ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
62.	ITT		Listing of SAS Output from the Bayesian 3 Parameter Emax Dose-Response Model for Hemoglobin Change at Day 29	Will be generated by GSK
63.	Completers		Listing of SAS Output from the Bayesian 3 Parameter Emax Dose-Response Model for Hemoglobin Change at Day 29	Will be generated by GSK
64.	ITT		Listing of SAS Output from the Bayesian 3 Parameter Emax Dose-Response Model for Hemoglobin Change at Day 29 (Sensitivity Priors)	Will be generated by GSK
65.	ITT		Listing of SAS Output from the Frequentist 3 Parameter Emax Dose-Response Model for Hemoglobin Change at Day 29	Will be generated by GSK
66.	Per Protocol		Listing of SAS Output from the Bayesian 3 Parameter Emax Dose-Response Model for Hemoglobin Change at Day 29	Will be generated by GSK
67.	ITT		Listing of SAS Output from the Dose-Response Linear Model for Change in Hemoglobin at Day 29	Will be generated by GSK
68.	Completers		Listing of SAS Output from the Dose-Response Linear Model for Change in Hemoglobin at Day 29	Will be generated by GSK
69.	Per Protocol		Listing of SAS Output from the Dose-Response Linear Model for Change in Hemoglobin at Day 29	Will be generated by GSK
70.	ITT		Listing of SAS Output from the Linear Regression Analysis: Hgb response vs. TIW/QD Weekly Dose	Will be generated by GSK
71.	ITT (PHI113633)		Listing of SAS Output from the Bayesian 3 Parameter Emax Dose-Response Model for Change in Hemoglobin at Week 4 (Based on PHI113633 data excluding Japan)	Will be generated by GSK
72.	ITT (PHI113633)		Listing of SAS Output from the Frequentist 3 Parameter Emax Dose-Response Model for Change in Hemoglobin at Week 4 (Based on PHI113633 data excluding Japan)	Will be generated by GSK
73.	ITT (PHI113633)		Listing of SAS Output from Dose-Response Linear Model for Change in Hemoglobin at Week 4 (Based on PHI113633 data excluding Japan)	Will be generated by GSK

Non-ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
74.	ITT		Listing of SAS Output for Treatment Difference for Hemoglobin (g/dL) Change from Baseline at Day 29	
75.	Safety	PSRAE1	Listing of Possible Suicidality-Related Adverse Event Data : Event and Description (Section 1-Section 2)	
76.	Safety	PSRAE3	Listing of Possible Suicidality-Related Adverse Event Data : Possible Cause(s) (Section 3)	
77.	Safety	PSRAE4	Listing of Possible Suicidality-Related Adverse Event Data (Section 4)	
78.	Safety	PSRAE5	Listing of Possible Suicidality-Related Adverse Event Data (Section 5-Section 8)	
79.	Safety	Listing 8.29	Listing of Chemistry Data	All lab parameters "Visit" shown in the listing should be corresponding to those in the RAP Section 11.2.1 Protocol Defined Time & Events Table
80.	Safety	Listing 8.30	Listing of Hematology Data	All lab parameters "Visit" shown in the listing should be corresponding to those in the RAP Section 11.2.1 Protocol Defined Time & Events Table
81.	Safety	Listing 8.32	Listing of Vital Signs	Include both pre- and post-dialysis vital signs. "Visit" shown in the listing should be corresponding to those in the RAP Section 11.2.1 Protocol Defined Time & Events Table