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

| | | |
|---|---|---|
| **Title** | : | Reporting and Analysis Plan for 201754<br>A 52-week, Phase III, double-blind, active-controlled, parallel-group, multi-center study to evaluate efficacy and safety of daprodustat compared to darbepoetin alfa in Japanese hemodialysis-dependent subjects with anemia associated with chronic kidney disease who are currently ESA users |
| **Compound Number** | : | GSK1278863 |
| **Effective Date** | : | 06-AUG-2018 |

**Description:**

- This RAP is an amendment version 1.
- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201754.
- This RAP is intended to describe the final analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

**RAP Author(s):**

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## TABLE OF CONTENTS

**PAGE**

# 1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 2015N266251_02:

| Revision Chronology: | | |
|---|---|---|
| Final_V1 | 28-Feb-2018 | Original |
| Amendment_Final_V1 | 06-Aug-2018 | Amendment 1 |

# 2. SUMMARY OF KEY PROTOCOL INFORMATION

## 2.1. Changes to the Protocol Defined Statistical Analysis Plan

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** |
| 9.3.3 Adjustment for Multiplicity<br><br>Adjustment for multiplicity will be applied to maintain an overall type I error rate of 5%. After a preliminary assessment, the primary endpoint will be evaluated to demonstrate the non-inferiority at a one-sided significance level of 2.5% (i.e. two-sided significance level of 5%). | 5.5 Multiple Comparisons and Multiplicity<br><br>Adjustment for multiplicity will be applied to maintain an overall type I error rate of **2.5% (one-sided)**. After a preliminary assessment, the primary endpoint will be evaluated to demonstrate the non-inferiority at a one-sided significance level of 2.5%. | An overall type I error rate ($\alpha$) of 2.5% is a one-sided nature of the non-inferiority test, which is the primary analysis for this study. This can be applicable to the following superiority test to maintain $\alpha$=2.5%. This is equivalent to two-sided significance level of 5%. |

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

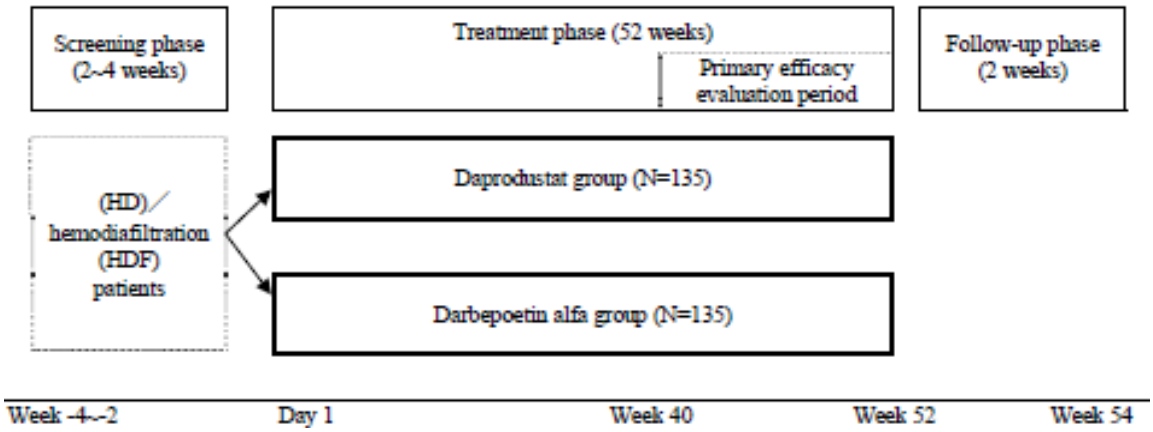
| Objectives | Endpoints |
|---|---|
| **Primary Objectives** | **Primary Endpoints** |
| • To demonstrate non-inferiority of daprodustat to darbepoetin alfa based on hemoglobin (Hgb) | • Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52) |
| **Principal Secondary Objectives** | **Principal Secondary Endpoints** |
| • To demonstrate superiority of daprodustat to darbepoetin alfa in terms of achievement/maintenance of target Hgb | • Number (%) of subjects with mean Hgb in the target range (10.0-12.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52) |
| **Secondary Objectives** | **Secondary Endpoints** |
| • To evaluate the appropriateness of the starting dose of daprodustat | • Change from baseline on Hgb at Week 4 (Hgb increase rate) |

| Objectives | Endpoints |
|---|---|
| | • Number (%) of subjects by Hgb change from baseline category at Week 4 |
| • To evaluate dose adjustment scheme of daprodustat | • Distribution of the dose level<br>• Duration of treatment interruption due to Hgb >13 g/dL<br>• Frequency of dose adjustments |
| • To evaluate the overall Hgb control of daprodustat using darbepoetin alfa as control | • Hgb and change from baseline at each assessment<br>• Number (%) of subjects who have an Hgb level within the target range (10.0–12.0 g/dL) at each assessment visit<br>• Time (%) in Hgb target range (10.0–12.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)<br>• Number (%) of subjects who have an Hgb level of less than 7.5 g/dL<br>• Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks<br>• Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes |
| • To evaluate the PK of daprodustat | • AUC and Cmax of plasma daprodustat |
| **Exploratory Objectives** | **Exploratory Endpoints** |
| • To evaluate the effect in iron use of daprodustat using darbepoetin alfa as control | • Dose of IV iron during the study period and the primary efficacy evaluation period (Weeks 40 to 52)<br>• Number (%) of subjects who use IV iron during the study period and primary efficacy evaluation period (Weeks 40 to 52) |
| • To evaluate the effect on iron metabolism of daprodustat using darbepoetin alfa as control | • Change from baseline in ferritin<br>• Change from baseline in transferrin saturation (TSAT) from baseline<br>• Change from baseline in hepcidin<br>• Change from baseline in serum iron<br>• Change from baseline in total iron binding capacity (TIBC) |
| **Patient Reported Outcome** | **Patient Reported Outcome Endpoints** |
| • To evaluate the effect on health-related QoL (HR-QoL) of daprodustat using darbepoetin alfa as control | SF-36<br>• Changes from baseline in SF-36 HR-QoL scores [Physical Component Summary (PCS), Mental Component Summary (MCS), and 8 subscales] at Week 12, 28, and 52<br>EuroQol Health Utility Index (EQ-5D-5L / EQ-VAS)<br>• Change from baseline in EQ-5D-5L score at Week 12, 28, and 52 |

| Objectives | Endpoints |
|---|---|
| | • Change from baseline in EQ-5D-5L Visual Analog Scale (VAS) at Week 12, 28, and 52 |
| **Safety Objectives** | **Safety Endpoints** |
| • To evaluate the safety and tolerability of daprodustat using darbepoetin alfa as control | • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including AEs of special interest (AESIs)<br>• Reasons for discontinuation of study medication<br>• Laboratory tests, electrocardiogram (ECG), vital signs, and ophthalmology assessments |

## 2.3. Study Design

**Overview of Study Design and Key Features**




| | |
|---|---|
| **Design Features** | • This is a Phase III, double-blind (double-dummy), active-controlled, parallel-group, multi-center study designed to evaluate the efficacy (non-inferiority) and safety of daprodustat, when administered for 52 weeks, compared to darbepoetin alfa in approximately 270 Japanese hemodialysis-dependent (HD) subjects with anemia associated with chronic kidney disease who are currently ESA users.<br>• This study consists of a 2~4-week screening phase, a 52-week treatment phase [including the primary efficacy evaluation period (Weeks 40 to 52)], and a 2-week follow-up phase following the treatment phase. |
| **Dosing** | Daprodustat<br>• HD subjects randomized to the daprodustat group will start oral treatment with daprodustat at the starting dose of 4 mg once daily (from Day 1) and remain on the same regimen until the day of Week 4.<br>• From Weeks 4 to 52, interruption of treatment or dose adjustments will be made within the maintenance dose range of 1 – 24 mg according to the dose adjustment algorithm to achieve and/or maintain Hgb within the target range (10.0 – 12.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks.<br>• HD subjects randomized to the darbepoetin alfa group will receive oral daprodustat matching placebo in the same manner.<br>Darbepoetin alfa<br>• HD subjects randomized to the darbepoetin alfa group will start intravenous treatment with darbepoetin alfa at the starting dose according to the dose convention which replaces prior ESA with darbepoetin alfa at the corresponding dose once weekly (from Day 1) as described in the protocol.<br>• From Week 2 to 52, dose interruptions or adjustments will be performed within the maintenance dose range of 10 – 60 μg according to the dose adjustment algorithm so |

| Overview of Study Design and Key Features | |
|---|---|
| | that the HemoCue value measured every other week will achieve or remain within the target range (10.0 – 12.0 g/dL). Dose adjustments will be made once every 2 weeks.<br>• HD subjects randomized to the daprodustat group will receive intravenous darbepoetin alfa matching placebo in the same manner. |
| **Time & Events** | • Refer to Appendix 2: Schedule of Activities |
| **Treatment Assignment** | • The randomization schedule will be generated by GlaxoSmithKline (GSK) using the randomization system (Randall NG).<br>• Subjects will be randomized centrally in a 1:1 ratio to one of the two groups, daprodustat group or darbepoetin alfa group, according to the randomization schedule. |
| **Interim Analysis** | • No interim analysis is planned. |

## 2.4. Statistical Hypotheses / Statistical Analyses

The primary objective of the study is to demonstrate the non-inferiority of daprodustat to darbepoetin alfa based on mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52) in HD subjects.

As a preliminary assessment, it will be confirmed whether the mean Hgb during the primary efficacy evaluation period in daprodustat group would be in target range (10.0-12.0 g/dL) at first. And then the following non-inferiority statistical hypotheses are to be tested at a one-sided significance level of 2.5%:

- $H_0$: Treatment difference in mean Hgb during the primary efficacy evaluation period, between treatment arms (daprodustat – darbepoetin alfa), is -1.0 g/dL or less.

- $H_1$: Treatment difference in mean Hgb during the primary efficacy evaluation period, between treatment arms (daprodustat – darbepoetin alfa), is greater than -1.0 g/dL.

Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority according to the step-down procedure. More specifically, the superiority of daprodustat to darbepoetin alfa in terms of target Hgb control in HD subjects is to be demonstrated at a one-sided significance level of 2.5% by testing the following statistical hypotheses:

- $H_0$: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (10.0-12.0 g/dL) is equal between the treatment groups.

- $H_1$: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (10.0-12.0 g/dL) is different between the treatment groups.

# 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. The study has completed with the last subject's last study visit.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures. Container number lists have been distributed by a CD-ROM from the external vendor (who is the owner for creating the original container number lists) just after unblinding.

# 4. ANALYSIS POPULATIONS

| Population | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| All Screening | • Consists of all subjects who are given subject number and are collected data at screening | • Study Population |
| Enrolled | • Consists of subjects in 'All Screening' except for screen failures (who never passed screening even if rescreened) | • Study Population (some displays for EudraCT) |
| Randomized | • Consists of all subjects who are given randomization number regardless of whether they actually receive study treatment | • Study Population |
| Safety | • Consists of all subjects who receive at least one dose of study treatment.<br>• Subjects will be analyzed according to the treatment received [1]<br>• This population will be used for safety analyses. | • Study Population<br>• Safety |
| Intent-To-Treat (ITT) | • Consists of all Randomized subjects who have a baseline and at least one post baseline schedule Hgb assessment [2]<br>• Subjects will be analyzed according to randomized treatment.<br>• This population will be the primary population for an assessment of non-inferiority. | • Study Population<br>• Efficacy |
| modified ITT (mITT) | • Consists of all ITT subjects who have at least one Hgb measurement during the evaluation period.<br>• Subjects will be analyzed according to randomized treatment.<br>• This population will be the primary population for an assessment of superiority. | • Study Population<br>• Efficacy |
| Per-Protocol (PP) | • Consists of all mITT subjects who are not major protocol violators.<br>• This population will be used for efficacy sensitivity analyses.<br>• 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 Definitions for Per Protocol Population). | • Efficacy |
| Pharmacokinetic (PK) | • Consists of all daprodustat -treated subjects from whom PK samples are collected and analyzed. | • PK |

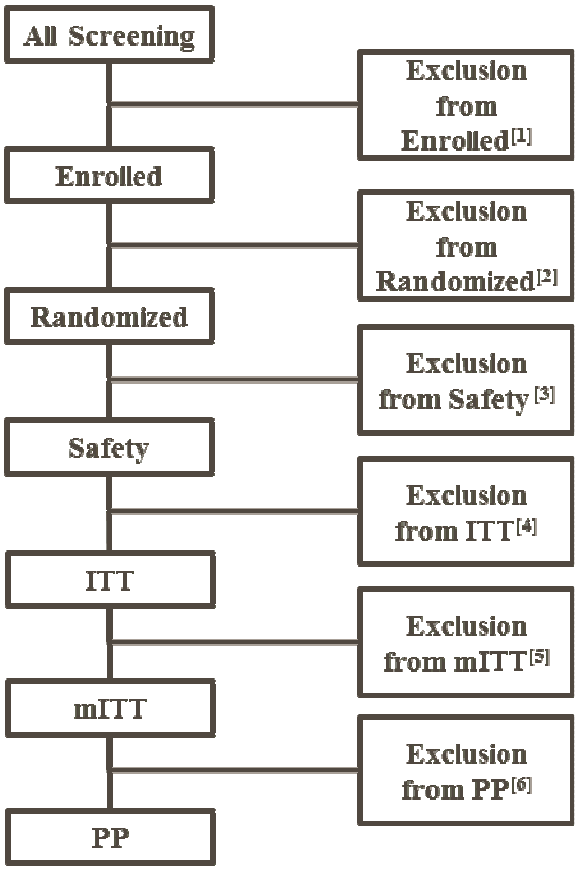
**NOTES:**

- Basically, enrolled population will be the same as randomized population because a subject is going to be given randomized number as soon as passed screening.
- Refer to Appendix 10: List of Data Displays which details the population used for each display

[1]: Only subjects receiving incorrect randomized treatment for the duration of their study participation will be analyzed according to the treatment received. Otherwise, subjects will be analyzed according to the treatment to which they were randomized. Refer to Appendix 10: List of Data Displays which details the population used for each display.

[2] See Appendix 3 for the Hgb assessment to be used for analyses

**Figure 1 Analysis Populations**




**NOTES:**
[1]: Subjects who never passed screening even if rescreened
[2]: Subjects who are not given randomization number
[3]: Subjects who never receive study treatment
[4]: Subjects who do not have Hgb measurement at both baseline and at least one scheduled visits following the baseline
[5]: Subjects who have no Hgb measurement during the efficacy evaluation period
[6]: Subjects who are major protocol violators (See Section 4.1 and Appendix 1)

## 4.1. Protocol Deviations

Important protocol deviations (including deviations related to study the inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized and listed.

Important deviations which resulted in exclusion from the analysis population will also be summarized and listed (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP).

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorized 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

## 5.1. Study Treatment & Sub-group Display Descriptors

| Treatment Group Descriptions | | | |
|---|---|---|---|
| RandAll NG | | Data Displays for Reporting | |
| Code | Description | Description | Order in TLF |
| D1 | Daprodustat | Daprodustat | 1 |
| D2 | Darbepoetin alfa | Darbepoetin alfa | 2 |

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. Daprodustat vs Darbepoetin Alfa

## 5.2. Baseline Definitions

The baseline Hgb value will be the value from the Day 1 visit. If missing at Day 1 visit, the baseline will be set to missing.

For all other endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value. This is generally expected to be the pre-dose value from the Day 1 visit, except for ECG. For ECG, screening assessment will be used as a baseline. The baseline value of vital signs at pre- and post-dialysis will be defined separately. If missing at Day 1 visit, screening assessment or other pre-dose assessment may be used as baseline. If baseline data is missing (i.e. Day 1, screening, and pre-dose assessment is all missing), no derivation will be performed and baseline will be set to missing.

| Definition | Reporting Details |
|---|---|
| Change from Baseline | = Post-Dose Visit Value – Baseline |
| Change from Baseline For Vital Signs | • Pre-dialysis: = Post-Dose Visit Value from Pre-Dialysis Assessment – Baseline from Pre-Dialysis Assessment<br>• Post-dialysis: = Post-Dose Visit Value from Post-Dialysis Assessment – Baseline from Post-Dialysis Assessment |
| % Change from Baseline | 1. Log-transform the data at both the baseline and the specified |

| Definition | Reporting Details |
|---|---|
| For TSAT, Hepcidin, and Lipid Parameters | timepoint<br>2. Calculate a change from baseline using the log-transformed data for each subject<br>3. Calculate the mean, and 95% CI and standard error (SE) of the log-transformed data<br>4. Exponentially back-transform to the original scale<br>5. Subtract 1, then multiply everything by 100%<br><br>So, geometric mean for percent change from baseline<br>= {exp(Mean [ln(Post-Dose Visit Value) – ln(Baseline)]) – 1 }x 100<br><br>Coefficient of variation will be calculated as<br>CV% = [exp(Var in loge scale)-1 ]$^{1/2}$ x 100<br>where 'Var in loge scale' represents variance of percent change from baseline in loge scale. |

## 5.3. Multicenter Studies

It is anticipated that subject accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative. Therefore, data from all participating centers will be just pooled for analysis.

## 5.4. Examination of Covariates, Other Strata and Subgroups

### 5.4.1. Covariates and Other Strata

The list of covariates will be used in statistical analyses. Additional covariates and other strata of clinical interest may also be considered.

| Category | Details |
|---|---|
| Strata | Not applicable |
| Covariates | For primary efficacy analyses:<br>• Mixed model for repeated measurements (MMRM) including covariates of treatment group, baseline Hgb, visit, treatment-by-visit interaction, and baseline Hgb-by-visit interaction will be used.<br>For principal secondary efficacy analyses:<br>• Logistic regression model including treatment group and baseline Hgb as covariates will be used. |

### 5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

| Subgroup | Categories |
|---|---|
| Age (year) | < 65, >=65 |
| Sex | Female, Male |
| Prior ESA dose (IU/week) [1][2] | <4,500, >=4,500 and <6,000, >=6,000 |
| Prior ESA type | Epoetin, Epoetin beta pegol, Darbepoetin alfa |
| ERI (IU/kg/week/g/dL) [2][3] | By tertile |
| Period of Time on Dialysis (year) | < 5, >= 5 and < 10, >= 10 |
| Baseline Iron Use [4] | Yes, No |
| Baseline Weight (kg) | < 55, >=55 |
| Baseline BMI (kg/m$^2$) | <20, >=20 |
| History of Diabetes [5] | Yes, No |

**NOTES:**

- BMI = Body Mass Index
- See Section 15.6.1 for the subgroup derivations

[1] Standardized dose on epoetin IV (IU/week) will be used.
[2] Additional thresholds might be added in order to divide the population equally as appropriate.
[3] See Section 15.6.2 for definition
[4] Subjects who used ferric citrate (trade name: Riona) will also be included in Baseline Iron Use group. This category will be used only for iron analyses. See Section 15.6.6.
[5] Past or current history of diabetes

## 5.5. Multiple Comparisons and Multiplicity

Adjustment for multiplicity will be applied to maintain an overall type I error rate of 2.5% (one-sided). After a preliminary assessment, the primary endpoint will be evaluated to demonstrate the non-inferiority at a one-sided significance level of 2.5%. Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority. Since the process will follow step-down manner, a multiplicity adjustment for one-sided significance level of 2.5% will not be needed according to a closed test procedure.

## 5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

| Section | Component |
|---|---|
| 15.3 | Appendix 3: Assessment Windows |
| 15.4 | Appendix 4: Study Phases and Treatment Emergent Adverse Events |
| 15.5 | Appendix 5: Data Display Standards & Handling Conventions |
| 15.6 | Appendix 6: Derived and Transformed Data |
| 15.7 | Appendix 7: Reporting Standards for Missing Data |
| 15.8 | Appendix 8: Values of Potential Clinical Importance |

# 6. STUDY POPULATION ANALYSES

## 6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the specified population.

Study population analyses including analyses of subject's disposition, protocol deviations, population analyzed, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Analyses of dialysis will also be included. Details of the planned displays are presented in Appendix 10: List of Data Displays.

| Endpoint / Parameter / Display Type | Population | Data Displays Generated | | |
|---|---|---|---|---|
| | | Table | Figure | Listing |
| **Subject's Disposition** | | | | |
| Subject Status and Reason for Study Withdrawal | Randomized | Y | | |
| Reasons for Study Withdrawal | Randomized | | | Y |
| Treatment Status and Reasons for Discontinuation of Study Treatment | Safety | Y | | Y |
| Screening Status and Reasons for Screen Failure | All Screening | Y | | Y |
| Subjects Enrolled by Country and Site ID | Enrolled | Y | | |
| Subjects for Whom the Treatment Blind was Broken | Randomized | | | Y |
| Planned and Actual Treatments | Safety | | | Y |
| **Protocol Deviations** | | | | |
| Important Protocol Deviations | Randomized | Y | | Y |
| Subjects with Inclusion/Exclusion Criteria Deviations | Randomized | Y | | Y |
| **Populations Analyzed** | | | | |
| Study Populations | Randomized | Y | | |
| Exclusion from the Per Protocol Population | mITT | Y | | Y |
| Subjects Excluded from Any Population | Randomized | | | Y |
| **Demographic and Baseline Characteristics** | | | | |
| Demographic Characteristics | ITT/Safety | Y | | Y |
| Other Baseline Characteristics [1] | Safety | | | Y |
| Prior ESA | ITT/Safety | Y | | Y |
| Age Ranges | Enrolled | Y | | |
| Race and Racial Combinations | Safety | Y | | Y [2] |
| Family History for CV Risk Factors | Safety | Y | | Y |
| Substance Use (History of Tobacco Use, Alcohol Intake) | Safety | Y | | Y |
| **Dialysis** | | | | |
| Baseline Mode of Dialysis | Safety | Y | | Y |
| Subjects with Change in Hemodialysis | Safety | | | Y |
| Baseline Mode of Vascular Access | Safety | Y | | Y |
| Subjects with Vascular Therapeutic Procedures during the study period | Safety | | | Y |
| Subjects with Vascular Access Intervention / Revision | Safety | | | Y |

| Endpoint / Parameter / Display Type | Population | Data Displays Generated | | |
|---|---|---|---|---|
| | | Table | Figure | Listing |
| **Medical Conditions and Concomitant Medications** | | | | |
| Current/Past Medical Conditions | Safety | Y | | Y |
| Concomitant Medications [3] | Safety | Y | | Y |
| Other Concomitant Medications (ESA, Iron, and Anti-Hypertensive Medications) | Safety | Y [4] | | Y |
| Blood Products and Blood Supportive Care Products | Safety | Y | | Y |
| **Exposure and Treatment Compliance** | | | | |
| Exposure to Study Treatment | Safety | Y | | Y |
| Treatment Compliance | Safety | Y | | Y |

**NOTES :**

- Y = Yes display generated.

[1] As a separate listing, include prior ESA type, standardized prior ESA dose, ERI, period of time on dialysis, iron use, and diabetes.
[2] Listing of race.
[3] Concomitant medications in pre-therapy, on-therapy, and post-therapy period will be summarized separately.
[4] On-therapy ESA, on-therapy iron, and on-therapy anti-hypertensive medications will be provided.

## 6.2. Planned Summary Display Details

Subjects who have multiple subject numbers (i.e. rescreened subjects) will be analyzed as unique subjects based on the latest screening results (see Section 15.6.1 and Section 15.6.2).

The definition of subgroup is described in Section 5.4.2.

- **Subject Disposition**

*Subject Status and Reason for Study Withdrawal*

The number and percentage of subjects completing the study (see Appendix 7) or withdrawing early from the study will be summarized overall and by reason for withdrawal by treatment group and total. Reasons for withdrawal of subjects will be listed.

*Treatment Status and Reasons for Discontinuation of Study Treatment*

The number and percentage of subjects completing the treatment or discontinuing the treatment during the study will be summarized overall and by reason (and subreason) by treatment group and total.

*Screening Status and Reasons for Screen Failure*

The number and percentage of subjects who passed screening (i.e. enrolled) and who failed screening and were therefore not entered into the study will be summarized regardless of treatment group. Note that the reasons for rescreen subjects who initially failed but subsequently enrolled are not included in the display (see Section 15.6.2).

*Subjects Enrolled by Country and Site ID*

The number and percentage of subjects by Country, Site ID and Investigator name will be summarized by treatment group and total.

- **Protocol Deviations**

*Important Protocol Deviations*

The number and percentage of subjects who had important protocol deviations defined in PDMP will be summarized by treatment group and total.

*Subjects with Inclusion/Exclusion Criteria Deviations*

The number and percentage of subjects, who were randomized into the trial, but deviated from the inclusion or exclusion criteria, will be summarized, further classifying inclusion/exclusion deviations by treatment group and total.

- **Population Analyzed**

*Study Populations*

The number and percentage of subjects in each analysis population (defined in Section 4) will be summarized by treatment group and total.

*Exclusion from Per Protocol Population*

The number of the exclusions from the PP population and the exclusion categories (See Appendix 1) will be summarized by treatment group and total.

- **Demographic and Baseline Characteristics**

*Demographic Characteristics*

The number and percentage of subjects or summary statistics will be provided by treatment group and total for the demographic and baseline characteristics: Sex, Age (years), Age Group (years), Ethnicity, Race detail, Height, Weight, and Body Mass Index. Age Group (years) will be categorized into 3 ('≤18', '19-64', '≥65'). Separate summaries for ITT and Safety population will be produced.

*Prior ESA*

For overall prior ESA, the weekly dose (standardized by IU/week), erythropoietin resistance index (ERI), and the number and percentage of subjects' dosing route (intravenous or subcutaneous) will be summarized by treatment group and total. These will be produced by type of prior ESA dose (epoetin, epoetin beta pegol, and darbepoetin

alfa). See Section 15.6.2 for standardized weekly dose and ERI. Separate summaries for ITT and Safety population will be produced.

*Age Ranges*

The number and percentage of subjects within each age range category will be provided by treatment group and total. Age range will be categorized into: 18-64 years, ≥65-84 years, ≥85 years.

*Race and Racial Combinations*

Summaries of race and racial combinations will be provided by treatment group and total.

*Family History for CV Risk Factors*

A summary of family (first degree relatives) history for CV risk factors will be provided by treatment group and total.

*Substance Use (History of Tobacco Use, Alcohol Intake)*

A summary of substance use will be provided by treatment group and total.

- **Medical Conditions and Concomitant Medications**

*Current/Past Medical Conditions*

The number and percentage of subjects with current and past medical conditions recorded in eCRF will be provided by treatment group and total.

*Concomitant Medications*

The number and percentage of subjects reporting the use of each concomitant medication will be summarized by treatment group and total by anatomical therapeutic chemical (ATC) Level 1, and Ingredient. Summaries for pre-therapy, on-therapy, and post-therapy medication will be provided separately. See Section 15.4.1.2 for the study phases.

*Other Concomitant Medications (On-Therapy ESA, Iron, and Anti-Hypertensive Medications)*

The similar summary as above will be provided by treatment group and total focusing on on-therapy ESA, on-therapy iron medication, and on-therapy anti-hypertensive medications. See Section 15.4.1.2 for the study phases.

*Blood Products and Blood Supportive Care Products (On-Therapy)*

The number and percentage of subjects who use blood products and/or blood supportive care products will be provided by treatment group and total. The details for the use will also be summarized.

- **Dialysis**

*Baseline Mode of Dialysis*

The number and percentage of subjects with each baseline mode of dialysis (i.e. haemodialysis, haemofiltration, or haemodiafiltration) will be provided by treatment group and total. The period of time on dialysis (years) will be summarized using mean, standard deviation, median, minimum, and maximum.

*Baseline Mode of Vascular Access*

The number and percentage of subjects with each baseline mode of vascular access will be provided by treatment group and total. Previous vascular access will be summarized in the same manner.

- **Exposure and Treatment Compliance**

*Exposure to Study Treatment*

Full details of exposure definition are presented in Section 15.6.2.

Time on study treatment (days), subject daily dose (for daprodustat) or weekly dose (for darbepoetin alfa), and cumulative dose will be summarized using the number of subjects exposed, mean, standard deviation, median, minimum, and maximum. Time on study treatment will be categorized in different time periods (< 3 months, 3 months to 6 months, >6 months to 12 months, >12 months; 1 month = 30.4375 days) and the number and percentage of subjects exposed will be displayed for each category.

*Treatment Compliance*

Full details of treatment compliance definition are presented in Section 15.6.2.

The number and percentage of subjects within each category will be summarized by treatment and total for up to Week 4, Week 40 to 52, and overall. The categories will be classified into under compliant, compliant, over compliant. Note that this is a double-dummy study but a summary will be made for the active treatment and a listing will contain both active and placebo compliance.

# 7. EFFICACY ANALYSES

## 7.1. Primary Efficacy Analyses

### 7.1.1. Endpoint / Variables

| Endpoint / Parameter/ Display Type | Population | Absolute | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Stats Analysis | | | Summary | | Individual | |
| | | T | F | L | T | F | F | L |
| **Mean Hgb Based on Observed Hgb During the Primary Efficacy Evaluation Period (i.e. Individual Mean of Hgb at Week 40, 44, 48, and 52)** | | | | | | | | |
| (Preliminary assessment) Observed Case mITT population | mITT | | | | Y | | | |
| **Model based Mean Hgb During the Primary Efficacy Evaluation Period** | | | | | | | | |
| (Primary) MMRM | ITT | Y | Y | | | | | |
| MMRM | mITT/PP | Y | Y | | | | | |
| MMRM By Subgroup | ITT | Y | Y[1] | | | | | |
| MMRM Evaluable Hgb | ITT | Y | Y | | | | | |
| Analysis of Covariance (ANCOVA) | mITT/PP | Y | | | | | | |
| ANCOVA By Subgroup | mITT | Y | Y[1] | | | | | |
| Tipping Point Analysis | ITT/mITT/ PP | Y | 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] Forest Plots

### 7.1.2. Summary Measure

*Mean Hgb based on observed Hgb during the primary efficacy evaluation period*

The values will be summarized using mean, standard deviation, 95% CI, minimum, P25, median, P75, and maximum by treatment group.

*Analysis of mean Hgb during the primary efficacy evaluation period*

For ITT population, model-based mean Hgb will be estimated using a statistical model (Section 7.1.5). The point estimates of model-based mean Hgb for each treatment will be presented with standard error and 95% CI. For non-inferiority assessment at a one-sided significance level of 2.5%, the estimate of treatment difference, its 95% CI, and a non-inferiority p-value will be provided. Analysis will be repeated by the mITT and PP

populations in the same manner. The subgroup analysis based on the ITT population will also be produced using tables and a forest plot. (See Section 7.1.5 for the detail)

*Sensitivity/Supplementary analysis for mean Hgb during the primary efficacy evaluation period*

- Evaluable Hgb (Section 7.1.6.1 for the statistical analysis specifications)

  Supplementary analysis using evaluable Hgb (See Section 15.6.3) based on the ITT population will be performed in the same manner as primary efficacy analysis using a mixed model for repeated measures.

- ANCOVA (Section 7.1.6.2 for the statistical analysis specifications)

  Supplementary analysis using ANCOVA based on the mITT population will be summarized in the same manner as the primary efficacy analysis with the use of a mixed model for repeated measures. Analysis will be repeated for the PP population. The subgroup analysis based on the mITT population will also be produced using tables and a forest plot.

- Tipping Point Analysis (Section 7.1.6.3 for the statistical analysis specifications)

  Tipping point sensitivity analysis based on the ITT population will be summarized using combined treatment differences, the associated 95% CIs and non-inferiority p-values by delta adjustments. Graphical display will be provided as a heatmap that represents non-inferiority p-values obtained from the test conducted for each delta adjustment. The horizontal and vertical axes indicate values of delta for daprodustat and darbepoetin alfa respectively. The color grids which highlight non-inferiority success or not will also be displayed.

### 7.1.3. Population of Interest

The primary efficacy analyses will be based on the ITT population, unless otherwise specified.

### 7.1.4. Strategy for Intercurrent (Post-Randomization) Events

| **Intercurrent events** | **Strategy** |
|---|---|
| Study withdrawal | The following hypothetical scenario is considered; what would have happened if the event did not occur. The primary analyses using MMRM assume missing at random mechanism, that is the observations of missing depend on just observed values, not on unobserved values. |

| Intercurrent events | Strategy |
|---|---|
| Prohibited medications (except for commercial ESA medications) | Basically, the occurrence of the event is taken to be irrelevant. Subjects with long-term use of prohibited medications will be excluded from the PP population. |
| Blood transfusion and/or commercial ESA medication | In primary analyses, the occurrence of the event is taken to be irrelevant. |
| Intermittent missing | The following hypothetical scenario is considered to assess what would have happened if the event did not occur. The hypothesis is that an intermittent missing would occur at at-random manner, that is the observations of the missing depend on just observed values, not on unobserved values. |

### 7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.1.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

As a preliminary assessment, it will be confirmed whether the mean Hgb during the primary efficacy evaluation period in the daprodustat group would be in the target range (10.0-12.0 g/dL) at first. This confirmation will be established if the lower and upper limit of 95% CI for the mean Hgb based on observed Hgb during the primary efficacy evaluation period in daprodustat group would lie fully within the target range. After the stated confirmation, non-inferiority will be assessed at a one-sided significance level of 2.5%.

#### 7.1.5.1. Statistical Methodology Specification

| **Endpoint / Variables** |
|---|
| • Mean Hgb during the primary efficacy evaluation period (Week 40 to 52) |
| **Model Specification** |
| • Analyses will be conducted by MMRM as follows:<br><br>$Hgb_{ik} = \beta_0 + \beta_{baseline} * Baseline_i + \beta_j + \beta_k + \beta_{jk} + \beta_{baseline*j} * Baseline_i + \varepsilon_{ik}$<br><br>$Hgb_{i, week}$: Hgb measurement for subject i at visit k<br>$\beta_0$: Intercept |

$\beta_{baseline}$: baseline Hgb effect
$Baseline_i$: Hgb measurement for subject i
$\beta_j$: treatment effect (j= daprodustat, darbepoetin alfa)
$\beta_k$: visit effect (k = Week 4, Week 8, …, Week 52)
$\beta_{jk}$: treatment-by-visit interaction
$\beta_{baseline*j}$: baseline-by-visit interaction
$\varepsilon_{ik}$: random error for subject i at visit k
i: subject (i = 1, 2, …, N)
N: number of subjects included in the analysis

- The model parameters will be estimated using Restricted Maximum Likelihood (method=REML) with the Newton-Raphson algorithm.
- The Kenward-Roger method for calculating the denominator degrees of freedom will be used.
- The variance-covariance structures for repeated measures within the individual subject will be unstructured (type=UN).
- LS means for treatment j at visit k will be calculated as follows.

$$\mu_{jk} = \beta_0 + \beta_{baseline} * \mu_{baseline} + \beta_j + \beta_k + \beta_{jk} + \beta_{baseline*k} * \mu_{baseline}$$

$\mu_{jk}$: LS mean for treatment j at visit k
$\mu_{baseline}$: mean for baseline Hgb

- Model based mean Hgb during the primary efficacy evaluation period for treatment j will be calculated as follows

$$\mu_{j*evaluation} = (\mu_{j*Week\ 40} + \mu_{j*Week\ 44} + \mu_{j*Week\ 48} + \mu_{j*Week\ 52})/4$$
$$= \beta_0 + \beta_{baseline} * \mu_{baseline} + \beta_j + (\beta_{Week\ 40} + \beta_{Week\ 44} + \beta_{Week\ 48} + \beta_{Week\ 52})/4 + (\beta_{j*Week\ 40} + \beta_{j*Week\ 44} + \beta_{j*Week\ 48} + \beta_{j*Week\ 52})/4 + (\beta_{baseline*Week\ 40} + \beta_{baseline*Week\ 44} + \beta_{baseline*Week\ 48} + \beta_{baseline*Week\ 52}) * \mu_{baseline}/4$$

- The treatment difference for model based mean Hgb during the primary efficacy evaluation period will be calculated as follows

$$\mu_{daprodustat*evaluation} - \mu_{darbepoetin\ alfa*evaluation} = \beta_{daprodustat} - \beta_{darbepoetin\ alfa} + (\beta_{daprodustat*Week\ 40} + \beta_{daprodustat*Week\ 44} + \beta_{daprodustat*Week\ 48} + \beta_{daprodustat*Week\ 52})/4 - (\beta_{darbepoetin\ alfa*Week\ 40} + \beta_{darbepoetin\ alfa\ *Week\ 44} + \beta_{darbepoetin\ alfa\ *Week\ 48} + \beta_{darbepoetin\ alfa\ *Week\ 52})/4$$

- P-value for non-inferiority test will be based on the following *t* test statistic (Mascha, 2011):

$$t = (\mu_{daprodustat*evaluation} - \mu_{darbepoetin\ alfa*evaluation} - \delta)/s$$

$\delta$: non-inferiority margin (= -1.0 g/dL)

s: standard error of treatment difference

The non-inferiority p-value is the probability of observing a larger value of *t* in a *t* distribution with degrees of freedom of the estimate of treatment difference based on the Kenward-Roger method.

**Model Checking & Diagnostics**

- In case there is a problem with convergence of the unstructured (type=UN) variance-covariance, the following strategy will be examined.
    1. Use Fisher's scoring algorithm for the estimation method.

| |
|---|
| 2. Set Heterogeneous Toeplitz (type=TOEPH) structure for variance-covariance structure.<br>3. In the event of that this model still fails to converge, alternative correlation structures may be considered such as type=CSH or CS. |
| **Model Results Presentation** |
| • The point estimates of LS mean Hgb during the primary efficacy evaluation period for each treatment will be presented with the associated standard errors and 95% CIs. For non-inferiority assessment at a one-sided significance level of 2.5%, the estimate of the treatment difference, standard error, its 95% CI, and a non-inferiority p-value will be provided.<br>• Non-inferiority will be established if the lower limit of the 95% CI for the treatment difference (daprodustat - darbepoetin alfa) of the mean Hgb during the primary efficacy evaluation period is greater than -1.0 g/dL (i.e., a p-value is smaller than 0.025). |
| **Subgroup Analyses** |
| • Treatment differences (daprodustat - darbepoetin alfa) of the mean Hgb during the primary efficacy evaluation period, standard errors, and the associated 95% CIs will be provided by each subgroup (See Section 5.4.2).<br>• The subgroup analyses will be based on the ITT population.<br>• The same statistical analysis method (using MMRM described as above) will be applied to estimate the mean Hgb during the primary efficacy evaluation period for each subgroup. If there is a problem with convergence for a certain subgroup, the result of the subgroup will not be displayed.<br>• Graphical summaries for the treatment differences of the mean Hgb during the primary efficacy evaluation period and the associated 95% CIs will be produced using a forest plot. |

### 7.1.6. Sensitivity and Supportive Analyses

To assess the robustness of the primary efficacy results, the primary efficacy analyses will be repeated using following sensitivity and supplementary approaches:

- ***mITT/PP Population***; the primary efficacy analyses will be repeated for the mITT and PP populations as the supplementary analysis.

- ***Evaluable Hgb***; if there are Hgb considered to be impacted by blood transfusion or marketed rhEPO/ESAs, supplementary analysis excluding the Hgb values from the analyses of primary endpoint will be conducted.

- ***Analysis of covariance (ANCOVA)***; it will be conducted as supplementary analysis to MMRM. This model includes treatment group and baseline Hgb. The analysis population will be the mITT population and the analysis will be repeated in the PP population.

- ***Tipping point analysis***; based on multiple imputation it will be conducted as sensitivity and supplementary analysis to missing data assumption. This analysis explores points where non-inferiority is not confirmed (tipping points) by changing assumption to missing data and repeating imputations. The analysis population will

be the ITT population and the analysis will be repeated in the mITT and PP populations.

#### 7.1.6.1. Evaluable Hgb

The analyses will be based on the ITT population, unless otherwise specified. In a strategy for intercurrent event of blood transfusion and commercial ESA medication, the following hypothetical scenario is considered to assess what would have happened if the event did not occur. Non-evaluable Hgb (described in 15.6.3), which is caused by this event, will be treated as missing, and will be analyzed based on missing at random assumption (the observations of missing depend on just observed values, not on unobserved values).

**Model Specification**

- Evaluable Hgb defined in Section 15.6.3 will be used for the analysis. Non-evaluable Hgb will be treated as missing.
- Analyses will be conducted by MMRM. See Section 7.1.5.1 for the detail.

**Model Results Presentation**

- The point estimates of adjusted mean Hgb during the primary efficacy evaluation period for each treatment will be presented with the associated standard errors and 95% CIs. The treatment difference, standard error, its 95% CI, and the non-inferiority p-value (described in Section 7.1.5.1, Model Specification) will also be presented.

#### 7.1.6.2. Analysis of Covariance (ANCOVA)

The analyses will be based on the mITT and PP populations, unless otherwise specified. In a strategy for intercurrent event of study withdrawal, a subject who has the event before Week 40 will not be included in analyses. If a subject has the event on or after Week 40, the event is taken to be irrelevant to the mean Hgb during primary efficacy evaluation period (i.e., observed values will be used for the analysis).

**Model Specification**

- A subject must have at least one Hgb measurement during the primary efficacy evaluation period (Week 40 to Week 52) to be included in this analysis.
- Analyses will be conducted by an ANCOVA model as follows:

$$\text{mean}(Hgb_i) = \beta_0 + \beta_{baseline} * Baseline_i + \beta_j + \varepsilon$$

$\text{mean}(Hgb_i) = (Hgb_{i,Week\ 40} + Hgb_{i,Week\ 44} + Hgb_{i,Week\ 48} + Hgb_{i,Week\ 52})/4$:
mean Hgb during the primary efficacy evaluation period for subject i
$\beta_0$: Intercept
$\beta_{baseline}$: baseline Hgb effect
$Baseline_i$: Hgb measurement for subject i
$\beta_j$: treatment effect (j= daprodustat, darbepoetin alfa)

ε: random error
i: subject (i = 1, 2, …, N)
N: number of subjects included in the analysis

- LS means for treatment j will be calculated as follows:

$\mu_j = \beta_0 + \beta_{baseline} * \mu_{baseline} + \beta_j$

$\mu_j$: LS mean for treatment j
$\mu_{baseline}$: mean for baseline Hgb

- The treatment difference for mean Hgb during the primary efficacy evaluation period will be calculated as follows:

$\mu_{daprodustat} - \mu_{darbepoetin\ alfa} = \beta_{daprodustat} - \beta_{darbepoetin\ alfa}$

- P-value for non-inferiority test will be based on the following *t* test statistic (Mascha, 2011):

$t = (\mu_{daprodustat} - \mu_{darbepoetin\ alfa} - \delta)/s$

$\delta$: non-inferiority margin (= -1.0 g/dL)

s: standard error of treatment difference

The non-inferiority p-value is the probability of observing a larger value of *t* in a *t* distribution with degrees of freedom of residual

**Model Checking & Diagnostics**

- Not applicable

**Model Results Presentation**

- The point estimates of adjusted mean Hgb for each treatment will be presented with the associated standard errors and 95% CIs. The treatment difference, standard error, its 95% CI, and a non-inferiority p-value (described in Section 7.1.5.1, Model Specification) will also be presented.

**Subgroup Analyses**

- The subgroup analyses will be based on the modified ITT population.
- The same statistical analysis method (using ANCOVA described as above) will be applied to estimate the mean Hgb during the primary efficacy evaluation period for each subgroup.
- Graphical summaries for the treatment differences of the mean Hgb during the primary efficacy evaluation period and the associated 95% CIs will be produced using a forest plot.

### 7.1.6.3. Tipping Point Analysis

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

Tipping point sensitivity analyses will be conducted under a range of missing data assumptions to determine how extreme assumptions need to be for non-inferiority conclusions to change. Assumptions about missing Hgb values on the daprodustat and darbepoetin alfa arm will vary independently, and will include scenarios where subjects with missing data on daprodustat have worse outcomes than subjects with missing data on darbepoetin alfa. If the tipping point scenario is clinically plausible, the conclusion under missing at random may be questionable.

In a strategy for intercurrent event of study withdrawal, a hypothetical scenario is considered to assess what would have happened if the event did not occur. For this hypothesis, the missing data due to this event would occur at not-at-random manner, that is the observations of missing depend on unobserved values, which will be mimicked with delta-adjustment analysis in this study.

**Model Specification**

- A tipping point is the critical point that reverses the study conclusion (i.e., non-inferiority test).
- Tipping point analysis for this study takes following steps:
  1. multiple imputation
  2. delta adjustment
  3. analyses for each imputed complete dataset.
  4. making combined results

  As a reference, programming codes for tipping point analysis are described by Yang, 2014 as %midata macro in the appendix.

1. *Multiple Imputation Strategy*

- Imputations will be conducted by a multiple imputation method using the SAS PROC MI procedure.
  - The number of imputations will be set to 200.
  - The seed for reproducibility is set to 201754.
- Initially, to obtain a monotone missing dataset from a non-monotone missing dataset, the imputation for intermittent missing values will be done using MCMC by treatment.
- After obtaining the dataset with only the monotone missing patterns, imputation based on MAR assumption can be performed by treatment in a sequential manner. Assume that repeated measures variables $Y_1,\ldots, Y_n$ are included in the imputation model (linear regression model with a covariate of baseline Hgb). The $Y_1$ is imputed first based on the covariate, then $Y_2$ would be imputed using the covariate and $Y_1$, and so on for each variable until $Y_n$ is imputed using the covariate and $Y_1,\ldots,Y_{n-1}$.

2. *Delta ($\Delta$) Adjustment Strategy*

- Based on MAR assumption ($\Delta$=0), monotone missing data that occured before Week 52 will be imputed as shown above. To mimic missing not at random manner, sequentially increasing $\Delta$ will be added to imputed values where $\Delta$ represents a change in Hgb over 4-week interval. No $\Delta$ adjustments will be done for intermittent missing values.
  - Sequentially increasing $\Delta$ adjustment is to add n*$\Delta$ value on the imputed value of nth monotone missing data. The longer the period of time with monotone missing, the larger $\Delta$ value will be added. Suppose a subject who has withdrawn at Week 40 visit, in other words, this subject has monotone missing data from Week 44 to Week 52. Imputations are conducted on missing data of Week 44, 48, and 52 and then $\Delta$ is added to an imputed value on Week 44, 2$\Delta$ on Week 48, and 3$\Delta$ on Week 52.
- Initially, the $\Delta$ values will be explored for both arms and will range from -4.0 to 4.0 g/dL with a 1.0 g/dL increment. Once the "rough" tipping point is found with the large increment (=1.0 g/dL), the exploration will be done with smaller increments to find the more precise tipping points. Low and high cutoffs at Hgb values of 7.0 g/dL and 14.0 g/dL will be utilized on

| |
|---|
| delta-adjusted imputed values. To reduce computationally intensive iterations, the further worsening scenarios beyond a range from -4.0 to 4.0 g/dL will not be examined.<br>*3. Analysis Strategy for Each Imputed Complete Dataset*<br>• The analysis using a MMRM (described in Section 7.1.5.1) will be applied and will be repeated for each imputed complete dataset. The calculation of the denominator degrees of freedom may be simplified (e.g., between-within degrees of freedom) for the imputed complete dataset. The mean differences between the mean Hgb during the primary efficacy evaluation will be estimated for each imputed complete dataset.<br>*4. Combine results of m datasets*<br>• For each pair of deltas (one independently assigned delta for each treatment arm), Rubin's rules (Rubin, 1987) will be used to combine results of all imputed datasets using SAS PROC MIANALYZE procedure. As a result, for each pair of delta values, a single estimated treatment difference and its standard error will be produced, with which a one-sided non-inferiority p-value can be calculated using non-adjusted degree of freedom. |
| **Model Checking & Diagnostics** |
| • For the model checking & diagnostics of MMRM analyses, see the Section 7.1.5.1 |
| **Model Results Presentation** |
| • Graphics depicting treatment difference and non-inferiority p-value surfaces will be produced using an enhanced tipping point approach (Liublinska, 2014); A colored heat map that illustrates the gradual change of non-inferiority p-values will be produced.<br>  • In a display, colored grids highlight delta combinations that result in rejecting the null hypothesis (i.e., non-inferiority established). |
| **Sensitivity and Supplementary Analyses** |
| • The analysis will be repeated for the mITT and PP populations. |

## 7.2. Principal Secondary Efficacy Analyses

### 7.2.1. Endpoint / Variables

| [Endpoint / Parameter/ Display Type] | Absolute | | | | | | |
|---|---|---|---|---|---|---|---|
| | Stats Analysis | | | Summary | | Individual | |
| | T | F | L | T | F | F | L |
| **Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period** | | | | | | | |
| (Principal Secondary) Logistic Regression mITT Population | Y | | | | | | |
| Logistic Regression ITT Population | Y | | | | | | |
| Logistic Regression PP Population | Y | | | | | | |
| Logistic Regression mITT Population By Subgroup | Y | Y[1] | | | | | |

**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] Forest plots

### 7.2.2. Summary Measure

*Number (%) of subjects with mean Hgb in target range during the primary efficacy evaluation period*

The number and percentage of responders, who are subjects with observed mean Hgb within the target range during the primary efficacy evaluation period, will be summarized. Odds ratio will be estimated by using a logistic regression and provided along with its 95% CI and a superiority one-sided p-value. Analysis will be repeated for the ITT and PP populations in the same manner. The subgroup analysis based on the mITT population will also be produced using tables and a forest plot.

### 7.2.3. Population of Interest

The principal secondary efficacy analyses will be based on the mITT population, unless otherwise specified.

### 7.2.4. Strategy for Intercurrent (Post-Randomization) Events

| Intercurrent events | Strategy |
|---|---|
| Study withdrawal | The occurrence of the event is taken to be a component of response to treatment. If a subject has no available Hgb data during Week 40 to 52 due to early withdrawal, the subject is deemed as a non- |

| Intercurrent events | Strategy |
|---|---|
| | responder. If a subject has at least one available Hgb data during Week 40 to 52, a response to treatment will be defined by whether the mean Hgb during Week 40 to 52 using observed Hgb values within target range. |
| Prohibited medications (except for commercial ESA medications) | Basically, the occurrence of the event is taken to be irrelevant. Subjects with long-term use of prohibited medications will be excluded from the PP population. |
| Blood transfusion and/or commercial ESA medication | The occurrence of the event is taken to be irrelevant. |
| Intermittent missing | The occurrence of the event is taken to be irrelevant. |

### 7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

#### 7.2.5.1. Statistical Methodology Specification

**Endpoint / Variables**

- Number (%) of subjects with mean Hgb in the target range (10.0-12.0 g/dL) during the primary efficacy evaluation period (Week 40 to 52)

**Model Specification**

- The percentage of subjects with observed mean Hgb during the primary efficacy evaluation period within the target range will be derived from the average of observed Hgb values during the primary efficacy evaluation period for individuals.
- Analyses will be conducted by a logistic regression model as follows:

$$\text{logit}(\pi) = \beta_0 + \beta_{baseline} * Baseline_i + \beta_j + \varepsilon$$

$\pi_i$: treatment success (mean($Hgb_i$) is within the target range or not)
$\beta_0$: Intercept
$\beta_{baseline}$: baseline Hgb effect
$Baseline_i$: Hgb measurement for subject i
$\beta_j$: treatment effect (j= daprodustat, darbepoetin alfa)
$\varepsilon$: random error
i: subject (i = 1, 2, …, N)

N: number of subjects included in the analysis

- The mean Hgb during the primary efficacy evaluation period will be calculated for each individual and confirmed if the values are in the target range or not. Therefore, subjects who have at least one Hgb measurement during the evaluation period will be included in this analysis. A subject who has missing data of the mean Hgb during the primary evaluation period due to intercurrent events will be regarded as a non-responder.
- The odds ratio (daprodustat/darbepoetin alfa) will be obtained as follows:
  $OR = \exp(\beta_{daprodustat} - \beta_{darbepoetin\ alfa})$
  The odds ratio, the Wald-type 95% CI and a superiority one-sided p-value based on a z-score will be provided together.

**Model Checking & Diagnostics**

- If the logistic regression cannot be applicable due to all responders or all non-responders, the odds ratio and the associated statistics will not be provided.

**Model Results Presentation**

- The superiority assessment will be performed only if the primary endpoint achieved non-inferiority.
- The number and percentage of subjects with observed mean Hgb during the primary efficacy evaluation period within the target range (10.0-12.0 g/dL) will be presented by treatment group. If available, the odds ratio (daprodustat/darbepoetin alfa), the associate 95% CI, and a superiority one-sided p-value will also be provided, otherwise 'NC'(not calculated) will be provided for odds ratios and the associated statistics.
- Superiority will be established if the lower limit of the 95% CI for the odds ratio is greater than 1.0 (i.e., a p-value is smaller than 0.025).

**Subgroup Analyses**

- The subgroup analyses will be based on the mITT population by each subgroup (See Section 5.4.2).
- The statistical analysis method uses the same logistic model, unless the logistic model is not applicable due to all responders or all non-responders.
- Graphical summaries for odds ratios and the associated 95% CIs will be produced using a forest plot. If the logistic model is not applicable, 'NC'(not calculated) label will be provided.

**Sensitivity and Supplementary Analyses**

- The mITT Population will be used for this logistic analysis, and the supplementary analysis using same logistic model will be repeated in the ITT and PP Population to evaluate the robustness of the conclusion. In the ITT population, subjects who have no available Hgb after Week 40 will be considered as non-responder.
- The logistic regression will be performed by a set of pre-specified subgroups (Section 5.4.2). These subgroup analyses are considered exploratory to assess for consistency with the overall results.

## 7.3. Secondary Efficacy Analyses

### 7.3.1. Endpoint / Variables

| [Endpoint / Parameter/ Display Type] | Absolute | | | | | |
|---|---|---|---|---|---|---|
| | Stats Analysis | | Summary | | Individual | |
| | T | F | T | F | F | L |
| **Hgb** | | | | | | |
| Hgb (g/dL) at each assessment visit | | | Y | Y | | Y |
| Hgb (g/dL) at each assessment visit<br>by prior ESA type, prior ESA dose, and ERI | | | Y | | | |
| Change from baseline in Hgb (g/dL) at each assessment visit | | | Y | Y | | |
| Change from baseline in Hgb (g/dL) at each assessment visit<br>by prior ESA type, prior ESA dose, and ERI | | | Y | | | |
| Number (%) of subjects by Hgb change from baseline category at Week 4 [1] [2] | | | Y | | | |
| Number (%) of subjects by Hgb change from baseline category at Week 4 [1] [2]<br>by prior ESA type, prior ESA dose, and ERI | | | Y | | | |
| Number (%) of subjects with Hgb level within the target range at each assessment visit [3] | | | Y | Y | | |
| Time (%) in Hgb target range during the primary efficacy evaluation period [4] | | | Y | | | Y |
| Number (%) of subjects who have an Hgb level of less than 7.5 g/dL [5] | | | Y | | | Y |
| Number (%) of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks | | | Y | | | Y |
| Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes [5] | | | Y | | | Y |
| Hemocue Hgb | | | | | | Y |
| Scatter Plot of Hgb Assessments: Central Laboratory vs. HemoCue | | | | Y | | |
| **Dose adjustment [6]** | | | | | | |
| Dose (mg or μg) at each assessment visit / final visit | | | Y | | | Y |
| Dose (mg or μg) at each assessment visit / final visit<br>by prior ESA type, prior ESA dose, and ERI | | | Y | | | |
| Number (%) of subjects with each dose at each assessment visit | | | Y | Y | | |
| Number (%) of subjects with each dose at each assessment visit<br>by prior ESA type, prior ESA dose, and ERI | | | Y | Y | | |
| Duration (days) of treatment interruption due to Hgb >13.0 g/dL [1] [5] | | | Y | | | Y |
| Dose adjustment [1] | | | Y | | | |

| [Endpoint / Parameter/ Display Type] | Absolute | | | | | |
|---|---|---|---|---|---|---|
| | Stats Analysis | | Summary | | Individual | |
| | T | F | T | F | F | L |
| **Subject Profiles** | | | | | | |
| Hgb and Dose over Time | | | | | 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] A summary will be produced for only daprodustat group

[2] <=-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, and >2 g/dL. In addition, within ±1 g/dL and over ±2 g/dL

[3] Not only within the target range, but also with above and below target range will be assessed.

[4] Rosendaal method will be used (See Section 15.6.3).

[5] On-therapy Hgb values observed at scheduled visits will be included in a summary. On-therapy Hgb values observed at unscheduled visits will be included if specified (See Section 7.3.2).

[6] Summaries for dose adjustment will based on HemoCue Hgb values including those of unscheduled visits.

### 7.3.2. Summary Measure

*Hgb at each assessment visit*

The values will be summarized using mean, standard deviation, 95% CI, minimum, P25, median, P75, and maximum at each assessment visit by treatment group. Graphical summaries will be provided using mean and 95% CI over time. This will also be summarized by prior ESA type, prior ESA dose, and ERI subgroup.

*Change from baseline at each assessment visit*

The values will be summarized using mean, standard deviation, 95% CI, minimum, P25, median, P75, and maximum at each assessment visit by treatment group. Graphical summaries will be provided using mean and 95% CI over time. This will also be summarized by prior ESA type, prior ESA dose, and ERI subgroup.

*Number (%) of subjects by Hgb change from baseline category at Week 4 - daprodustat*

The number and percentage of subjects within each category will be provided only for daprodustat group and the categories will be classified into 6 (i.e., ≤-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, >2 g/dL). In addition, 'within ±1 g/dL (i.e., ≤-1 and ≥1)' and 'over ±2 g/dL (i.e., <-2 and >2)' categories will be provided. This will also be summarized by prior ESA type, prior ESA dose, and ERI subgroup.

*Number (%) of subjects with Hgb within the target range at each assessment visit*

The number and percentage of subjects with Hgb within, above and below the target range will be summarized at each assessment visit by treatment group. Graphical summaries over time will also be produced.

*Time (%) in the Hgb target range during the primary efficacy evaluation period*

The time (weeks and percentage) within/above/below the target range will be summarized by treatment group using mean, standard deviation, minimum, P25, median, P75, and maximum. Treatment differences (daprodustat – darbepoetin alfa) and the associated 95% CIs for the time (weeks and percentage) within the target range will also be provided. See Section 15.6.3 for details.

*Number (%) of subjects who have an Hgb level of less than 7.5 g/dL*

The number and percentage of subjects who have an Hgb level of less than 7.5 g/dL during the treatment period will be summarized by treatment group. On-therapy Hgb values observed in both scheduled and unscheduled visits will be included in the summary.

*Number (%) of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks*

The number and percentage of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks during the treatment period will be summarized by treatment group. The odds ratio (daprodustat/darbepoetin alfa) will also be provided with its 95% CI. On-therapy Hgb values will be used for the summary. See Section 15.6.3 for details.

*Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes*

The number and percentage of subjects who have an Hgb level of more than 13.0 g/dL during the treatment period and number of episodes will be summarized by treatment group. On-therapy Hgb values observed in both scheduled and unscheduled visits will be included in the summary.

*Scatter plot of Hgb assessments: Central Laboratory vs. HemoCue*

A scatter plot of Hgb values measured by Central Laboratory versus Hgb values measured by Hemocue will be produced along with Pearson's correlation coefficient. Regardless of visit and treatment group, all available pairs of Hgb (i.e. non-missing values in both from central laboratory and from the corresponding HemoCue measurement) will be used.

- **Dose adjustment**

The dose adjustment algorithm is described in Section 15.6.3, based on HemoCue Hgb values.

*Dose at each assessment visit/ final visit*

Dose at each assessment visit and final visit will be summarized using mean, standard deviation, minimum, P25, median, P75, mode, and maximum at each assessment visit by treatment. The final visit will be the last visit of treatment exposure for each subject.

Mean dose during Week 40 to 52 will also be summarized and includes subjects who has at least one exposure record during Week 40 to 52. This will also be summarized by prior ESA type, prior ESA dose, and ERI subgroup.

*Number (%) of subjects with each dose at each assessment visit*

The number and percentage of subjects with each dose (mg or µg) will be provided by treatment. Graphical summaries of histogram will be provided with the number of subjects in each dose by treatment. Dose categories will be classified into 10; N/A (not administered), 0 mg (treatment interruption), 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 18 mg, and 24 mg for daprodustat and classified into 9; N/A, 0 µg, 10 µg, 15 µg, 20 µg, 30 µg, 40 µg, 60 µg for darbepoetin alfa. This will also be summarized by prior ESA type, prior ESA dose, and ERI subgroup.

*Duration (days) of treatment interruption due to Hgb >13.0 g/dL - daprodustat*

The number and percentage of subjects who have a period of treatment interruption due to Hgb >13.0 g/dL will be summarized. On subjects who have a period of treatment interruption due to Hgb >13 g/dL, the duration (in days) of treatment interruption due to Hgb >13.0 g/dL per subject will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. On-therapy Hgb values observed in both scheduled and unscheduled visits will be counted in the summary.

*Dose adjustment - daprodustat*

The number and percentage of subjects with dose adjustments will be provided. Number of dose adjustments will be summarized using mean, standard deviation, minimum, median, mode, and maximum. For dose adjustments frequency, the number and percentage of subjects will be provided by the number of dose adjustments (i.e. zero, one, two, three, four, …, ten, eleven, and twelve or more; these categories may be refined) during the whole treatment period and Week 40 to 52, respectively. For the timing of dose adjustments, the number and percentage of subjects with dose adjustments by each assessment visit will be provided.

### 7.3.3. Population of Interest

The secondary efficacy analyses will be based on the ITT population, unless otherwise specified.

### 7.3.4. Strategy for Intercurrent (Post-Randomization) Events

Any intercurrent events are taken to be irrelevant for secondary endpoints. The secondary endpoints will be summarized based on available and observed data.

### 7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

## 7.4. Exploratory Efficacy Analyses

### 7.4.1. Endpoint / Variables

| [Endpoint / Parameter/ Display Type] | Absolute | | | | | |
|---|---|---|---|---|---|---|
| | Stats Analysis | | Summary | | Individual | |
| | T | F | T | F | F | L |
| **Iron Use** | | | | | | |
| Dose of IV iron (mg) during the treatment period and the primary efficacy evaluation period (Week 40 to 52) | | | Y | | | |
| Dose of IV iron (mg) during the treatment period and the primary efficacy evaluation period (Week 40 to 52) by Baseline Iron Use | | | Y | | | |
| Number (%) of subjects who use iron during the treatment period and the primary efficacy evaluation period (Week 40 to 52) | | | Y | | | |
| Number (%) of subjects who use iron during the treatment period and the primary efficacy evaluation period (Week 40 to 52) by Baseline Iron Use | | | Y | | | |
| **Iron Parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC)** | | | | | | |
| Raw observed value at each assessment visit | | | Y | Y | | Y |
| Raw observed value at each assessment visit by Baseline Iron Use | | | Y | Y | | |
| Change from baseline at each assessment visit | Y | Y | Y | | | |
| Change from baseline at each assessment visit by Baseline Iron Use | Y | Y | Y | | | |
| **Other** | | | | | | |
| Scatter plot of change from baseline in Hgb at Week 4 vs. covariates of interest – Daprodustat | | | | Y | | |
| Scatter plot of mean dose during Week 40 to 52 vs. covariates of interest – Daprodustat | | | | 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.

### 7.4.2. Summary Measure

- **Iron Use**

*Dose of IV iron (mg) during the treatment period and the primary efficacy evaluation period*

Monthly average IV iron dose by quarter (See Section 15.6.6) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. Quarter 1 (Day 1 to Week 12), Quarter 2 (Week 12 to Week 24), Quarter 3 (Week 24 to Week 40), Quarter 4 (Week 40 to Week 52), and whole treatment period will be used and the Quarter 4 represents the primary efficacy evaluation period. This will also be summarized by baseline iron use defined in Section 5.4.2.

*Number (%) of subjects who use iron during the treatment period and the primary efficacy evaluation period*

The number and percentage of subjects who use iron during the treatment period and the primary efficacy evaluation period will be summarized separately. These will also be summarized by baseline iron use defined in Section 5.4.2.

- **Iron Parameter (ferritin, TSAT, hepcidin, serum iron, and TIBC)**

Based on literature review the distributions of TSAT and hepcidin are skewed and require a log-transformation (See Section 5.2).

*Raw observed value at each assessment visit*

Ferritin, serum iron, and TIBC values will be summarized by treatment group using mean, standard deviation, 95% CI, minimum, P25, median, P75, and maximum at each assessment visit. TSAT and hepcidin values will be summarized by treatment group using geometric mean, standard error, coefficient of variation, and 95% CI based on log-transformed parameters, median, minimum, and maximum based on original scale at each assessment visit. These will also be summarized by baseline iron group. Graphical summaries will also be provided for each iron parameter.

*Change from baseline at each assessment visit*

Change from baseline in Ferritin, serum iron, and TIBC values will be summarized by treatment group using mean, standard deviation, 95% CI, minimum, P25, median, P75, and maximum at each assessment visit. Percent Change from baseline in TSAT and hepcidin values (Section 5.2) will be summarized by treatment group using geometric mean, coefficient of variation, and 95% CI based on log-transformed parameters, minimum, median, and maximum based on original scale at each assessment visit.

Treatment differences (daprodustat – darbepoetin alfa) and the associated 95% CIs for change from baseline will be provided at each assessment (See Section 7.4.5.1). For ferritin, serum iron, and TIBC change from baseline, graphical summaries will be provided by treatment group using the adjusted means and the associated 95% CIs over time. For TSAT and hepcidin percent change from baseline, graphical summaries will be provided using adjusted geometric means percent change from baseline and the associated 95% CIs over time. These will also be summarized by baseline iron group.

- **Other**

*Scatter plot of change from baseline in Hgb at Week 4 vs. covariates of interest*

Scatter plot of change from baseline in Hgb at Week 4 versus following covariates of interest, body weight, baseline Hgb, prior ESA dose will be produced only for daprodustat. See Section 15.6.3 for the detailed derivations.

*Scatter plot of mean dose during Week 40 to 52 vs. covariates of interest*

Scatter plot of mean dose during Week 40 to 52 versus following covariates of interest, body weight, baseline Hgb, prior ESA dose will be produced only for daprodustat. See Section 15.6.3 for the detailed derivations.

### 7.4.3. Population of Interest

The exploratory efficacy analyses will be based on the ITT population, unless otherwise specified.

### 7.4.4. Strategy for Intercurrent (Post-Randomization) Events

Any intercurrent events are taken to be irrelevant for exploratory endpoints and the exploratory endpoints will be summarized based on available and observed data.

Analysis of change from baseline in the respective iron parameter at each assessment visit will follow the strategy below.

| Intercurrent events | Strategy |
|---|---|
| Study withdrawal / Intermittent missing | The following hypothetical scenario is considered to assess what would have happened if the event did not occur. Analysis using MMRM assume missing at random mechanism, that is the observations of missing depend on just observed values, not on unobserved values. |

### 7.4.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables presented in Section 7.4.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

### 7.4.5.1. Statistical Methodology Specification

**Endpoint / Variables**

- Change from baseline in the respective iron parameter at each assessment visit

**Model Specification**

- Analyses will be repeated for each iron parameter (ferritin/TSAT/hepcidin/serum iron/TIBC) using MMRM as follows:

  $Iron_{ik} = \beta_0 + \beta_{baseline} * Baseline_i + \beta_j + \beta_k + \beta_{jk} + \beta_{baseline*j} * Baseline_i + \varepsilon_{ik}$

  $Iron_{i, week}$: each iron measurement for subject i at visit k
  $\beta_0$: Intercept
  $\beta_{baseline}$: baseline effect of each iron parameter
  $Baseline_i$: the baseline value of each iron parameter for subject i
  $\beta_j$: treatment effect (j= daprodustat, darbepoetin alfa)
  $\beta_k$: visit effect (k = Week 4, Week 16, Week 28, Week 40, Week 52)
  $\beta_{jk}$: treatment-by-visit interaction
  $\beta_{baseline*j}$: baseline-by-visit interaction
  $\varepsilon_{ik}$: random error for subject i at visit k
  i: subject (i = 1, 2, …, N)
  N: number of subjects included in the analysis
- The model parameters will be estimated using Restricted Maximum Likelihood (method=REML) with the Newton-Raphson algorithm.
- The Kenward-Roger method for calculating the denominator degrees of freedom will be used.
- The variance-covariance structures for repeated measures within the individual subject will be unstructured (type=UN).
- LS means for treatment j at visit k will be calculated as follows for each iron parameter as adjusted mean change from baseline.

  $\mu_{jk} = \beta_0 + \beta_{baseline} * \mu_{baseline} + \beta_j + \beta_k + \beta_{jk} + \beta_{baseline*k} * \mu_{baseline}$
  $\mu_{jk}$: LS mean for treatment j at visit k
  $\mu_{baseline}$: mean for the baseline value of each iron parameter
- The treatment difference at visit k for model based mean change from baseline will be calculated as follows for each iron parameter as adjusted treatment difference

  $\mu_{daprodustat*k} - \mu_{darbepoetin\ alfa*k} = \beta_{daprodustat} - \beta_{darbepoetin\ alfa} + \beta_{daprodustat*k} - \beta_{darbepoetin\ alfa*k}$

- Note that log-transformed values will be used for TSAT and hepcidin in the MMRM analysis. The LS means for treatment j at visit k and the adjusted treatment difference at visit k will be exponentially back-transformed to the original scale and provided as follows:

  Adjusted geometric mean percent change from baseline = $100*(\exp(\mu_{jk}) - 1)$
  Adjusted ratio for percent change from baseline = $\exp(\mu_{daprodustat*k} - \mu_{darbepoetin\ alfa*k})$

| Model Checking & Diagnostics |
|---|
| • In case there is a problem with convergence of the unstructured (type=UN) variance-covariance, the following strategy will be examined.<br>1. Use Fisher's scoring algorithm for the estimation method.<br>2. Set Heterogeneous Toeplitz (type=TOEPH) structure for variance-covariance structure.<br>3. In the event of that this model still fails to converge, alternative correlation structures may be considered such as type=CSH or CS. |
| **Model Results Presentation** |
| • For ferritin, serum iron, and TIBC, the adjusted mean change from baseline will be presented with the associated 95% CIs by treatment at each assessment visit. The adjusted treatment difference (daprodustat – darbepoetin alfa) for change from baseline will also be presented with the associated 95% CI at each assessment visit.<br>• For TSAT and hepcidin, the adjusted geometric mean percent change from baseline will be presented with the associated 95% CIs by treatment at each assessment visit. The adjusted ratio (daprodustat / darbepoetin alfa) for percent change from baseline will also be presented with the associated 95% CI at each assessment visit. |
| **Subgroup Analyses** |
| • For all of the respective iron parameter, the above analysis will be repeated by baseline iron use subgroup (See Section 5.4.2) in the same manner.<br>• The subgroup analyses will be based on the ITT population.<br>• If there is a problem with convergence for a subgroup, the result of the subgroup will not be displayed. |

# 8. SAFETY ANALYSES

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

## 8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), serious adverse events (SAEs), and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

Medical device incidents fulfilling the definition of an AE/SAE will follow the same processes for collecting AE and SAE information and will not be summarized particularly.

| Endpoint / Parameter/ Display Type | Absolute | | |
|---|---|---|---|
| | Summary | | Individual |
| | T | F | L |
| **Adverse Events (AEs)** | | | |
| On-Therapy AEs by SOC and PT | Y | | Y |
| On-Therapy AEs by SOC and PT and Maximum Intensity | Y | | |
| On-Therapy AEs by SOC and PT by onset | Y | | |
| On-Therapy AEs up to Week 4 by SOC and PT | Y | | |
| On-Therapy AEs up to Week 4 by SOC and PT and Maximum Intensity | Y | | |
| Post-Therapy AEs by SOC and PT | Y | | Y |
| Post-Therapy AEs by SOC and PT and Maximum Intensity | Y | | |
| On-Therapy Drug-Related AEs by SOC and PT | Y | | |
| On-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity | Y | | |
| On-Therapy Drug-Related AEs up to Week 4 by SOC and PT | Y | | |
| On-Therapy Drug-Related AEs up to Week 4 by SOC and PT and Maximum Intensity | Y | | |
| Post-Therapy Drug-Related AEs by SOC and PT | Y | | |
| Post-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity | Y | | |
| On-Therapy Common (>= 2 %) AEs by Overall Frequency | Y | Y [1] | |
| On-Therapy Common (>= 5 %) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences) | Y | | |
| On-Therapy Non-Serious Drug-Related AEs | Y | | |
| Subject Numbers for Individual AEs | | | Y |
| Relationship Between AE SOCs, PT & Verbatim Text | | | Y |
| **Serious and Other Significant AEs** | | | |
| Fatal Serious AEs | | | Y |
| Non-Fatal Serious AEs | | | Y |
| On-Therapy Serious AEs | Y | | |
| Post-Therapy Serious AEs | Y | | |
| On-Therapy Serious Drug-Related AEs | Y | | |
| Serious AEs in Screening Period [2] | | | Y |
| Reasons for Considering as a Serious AE | | | Y |
| On-Therapy Serious AEs by SOC and PT (Subjects & No. of Occurrences) | Y | | |
| AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study | Y | | Y |

| Endpoint / Parameter/ Display Type | Absolute | | |
|---|---|---|---|
| | Summary | | Individual |
| | T | F | L |
| Treatment by SOC and PT | | | |
| CV Events | | | Y |

**NOTES:**

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF 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] Plot of common AEs and relative risk will be generated by treatment.
[2] Listing will be based on All Screening Population.

### 8.1.1. Planned Adverse Events Analyses Displays

- **Adverse Events**

*AEs by SOC and PT*

The number and percentage of subjects reporting at least one AE will be provided by treatment group. These events will be summarized by primary system organ class and preferred term. On-therapy AEs, on-therapy AEs up to Week 4, and post-therapy AEs will be summarized separately.

On-therapy AEs by onset (<=Week 4, >Week 4 to <=Week 16, >Week 16 to <=Week 28, >Week 28 to <=Week 40, >Week 40) will also be summarized separately. The number of subjects reporting the first occurrence of each AE will be provided by onset time by primary system organ class and preferred term.

*AEs by SOC and PT and Maximum Intensity*

AEs will be summarized by treatment group; by maximum intensity (not applicable, mild, moderate, severe) by primary system organ class and preferred term. Subjects who experience the same event several times with different intensities will only be counted with the maximum intensity in the order of (not applicable < mild < moderate < severe). On-therapy AEs, on-therapy AEs up to Week 4, and post-therapy AEs will be summarized separately.

*Drug-Related AEs by SOC and PT*

The number and percentage of subjects reporting at least one drug-related AE will be provided by treatment group. These events will be summarized by primary system organ class and preferred term. On-therapy AEs, on-therapy AEs up to Week 4, and post-therapy AEs will be summarized separately.

*Drug-Related AEs by SOC and PT and Maximum Intensity*

Drug-related AEs will be summarized by treatment group; by maximum intensity (not applicable, mild, moderate, severe) by primary system organ class and preferred term.

Subjects who experience the same event several times with different intensities will only be counted with the maximum intensity in the order of (not applicable < mild < moderate < severe). On-therapy, up to Week 4, and post-therapy AEs will be summarized separately.

*On-Therapy Common (>= 2%) AEs by Overall Frequency*

The number and percentage of subjects with on-therapy common (>= 2% in any treatment group) adverse events by overall frequency will be provided by treatment group. These events will be summarized by preferred term.

A graph will be produced which displays both AE incidence rates and relative risks.

*On-Therapy Common (>= 5%) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)*

The number and percentage of subjects reporting at least one on-therapy common (>= 5% in any treatment group) non-serious AE will be provided by treatment group. The number of on-therapy non-serious AE occurrences will also be provided. These events will be summarized by primary system organ class and preferred term.

*On-Therapy Non-Serious Drug-Related AEs*

The number and percentage of subjects with on-therapy non-serious drug-related AEs will be summarized by preferred term.

- **Serious and Other Significant AEs**

*Serious AEs*

The number and percentage of subjects reporting at least one Serious AE will be provided by treatment group. These events will be summarized by primary system organ class and preferred term. On- and post-therapy serious AEs will be summarized separately.

*On-Therapy Serious Drug-Related AEs*

The number and percentage of subjects with on-therapy serious drug-related AEs will be summarized by preferred term.

*On-Therapy Serious AEs by SOC and PT (Subjects & No. of Occurrences)*

The number and percentage of subjects reporting at least one on-therapy serious AE will be provided by treatment group. The number of on-therapy serious AE occurrences will also be provided. These events will be summarized by primary system organ class and preferred term.

*AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT*

The number and percentage of subjects reporting an on-therapy AE leading to discontinuation of study treatment will be summarized by treatment group. These events will be summarized by primary system organ class and preferred term.

## 8.2. Adverse Events of Special Interest Analyses

A comprehensive list based on clinical review will be used to identify each type of event. AEs of special interest will be manually-selected before unblinding at patient-level (i.e. following case-by-case review by members of the Safety Review Team (SRT) including representatives from the local Japan team) and not at preferred term level. The details of the planned displays are provided in Appendix 10: List of Data Displays.

| Endpoint / Parameter/ Display Type | Absolute | | |
|---|---|---|---|
| | Summary | | Individual |
| | T | F | L |
| **AEs of special interest** [1] | | | |
| On-Therapy AEs of special interest | Y | | Y |
| Post-therapy AEs of special interest | Y | | Y |

**NOTES:**

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF 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] Refer to Section 15.6.4

### 8.2.1. Planned Adverse Events of Special Interest Analyses Displays

- **AEs of Special Interest (AESIs)**

*AEs of Special Interest*

The number and percentage of subjects reporting at least one AESI will be provided by treatment group. These events will be summarized by each AESI term (See Section 15.6.4). On-therapy and post-therapy AESIs will be summarized separately.

## 8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry/ Hematology/Other Laboratory tests, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

| Endpoint / Parameter/ Display Type | Absolute | | | Change from BL | | |
|---|---|---|---|---|---|---|
| | Summary | | Individual | Summary | | Individual |
| | T | F | L | T | F | L |
| **Chemistry** | | | | | | |
| Chemistry Values by Visit | Y | | Y | Y | | |
| Percent Change from Baseline in Lipid Parameters [1] (total cholesterol, LDL cholesterol, HDL cholesterol, and LDL/HDL cholesterol ratio) by Visit | | | Y | Y | Y | |
| Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline | Y | | | | | |
| Worst Case Chemistry Results Relative to PCI Criteria Post-Baseline Relative to Baseline | Y | | | | | |
| **Hematology** | | | | | | |
| Hematology Values by Visit | Y | | Y | Y | | |
| Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline | Y | | | | | |
| Worst Case Hematology Results Relative to PCI Criteria Post-Baseline Relative to Baseline | Y | | | | | |
| **Iron Parameters** | | | | | | |
| Iron Values by Visit [2] | Y | | Y | Y | | |
| Worst Case Iron Results Relative to Normal Range Post-Baseline Relative to Baseline | Y | | | | | |
| Worst Case Iron Results Relative to PCI Criteria Post-Baseline Relative to Baseline | Y | | | | | |
| **Other Laboratory Tests [3]** | | | | | | |
| Other Laboratory Values by Visit | Y | | Y | Y | | |
| Worst Case Other Laboratory Results Relative to Normal Range Post-Baseline Relative to Baseline | Y | | | | | |
| Worst Case Other Laboratory Results Relative to PCI Criteria Post-Baseline Relative to Baseline | Y | | | | | |
| **Hepatobiliary (Liver)** | | | | | | |
| Liver Monitoring/Stopping Event Reporting | Y | | | | | |
| Hepatobiliary Laboratory Abnormalities | Y | | | | | |
| Medical Conditions for Subjects with Liver Stopping Events | | | Y | | | |
| Substance Use for Subjects with Liver Stopping Events | | | Y | | | |
| Scatter Plot of Maximum vs. Baseline for ALT | | Y | | | | |
| Scatter Plot of Maximum ALT vs Maximum Total Bilirubin | | Y | | | | |
| **All Laboratory** | | | | | | |
| All Laboratory Data for Subjects with any Value of Potential Clinical Concern/PCI | | | Y | | | |
| Laboratory Values of PCI | | | Y | | | |

**NOTES:**

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- 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] Lipid parameters will be log-transformed and the percent change from baseline will be reported.
[2] Transferrin and UIBC will be included for this summary and other iron parameters will be provided as efficacy endpoints.
[3] Only iPTH will be collected as other laboratory tests.

### 8.3.1. Planned Clinical Laboratory Analyses Displays

LDL/HDL cholesterol ratio will be derived from LDL and HDL cholesterol (see Section 15.6.4), and handled as one of chemistry laboratory tests and lipid parameters.

- ***Chemistry/Hematology/Iron Parameter/Other Laboratory Tests***

*Clinical Laboratory Values by Visit*

The values will be summarized using mean, standard deviation, median, minimum, and maximum at each assessment visit and baseline by treatment group. Chemistry, hematology, iron parameter, and other laboratory values will be summarized separately.

*Percent Change from Baseline in Lipid Parameters*

Lipid parameters (including LDL/HDL cholesterol ratio) will be log-transformed and the percent change from baseline will be reported. The percent change from baseline in each lipid parameter, including baseline values, will be summarized using geometric mean, 95% CI, minimum, median, and maximum at each assessment visit by treatment group. In baseline values, the coefficient of variation will also be provided.

*Clinical Laboratory Changes from Baseline by Visit*

The values will be summarized using mean, standard deviation, median, minimum, and maximum at each assessment visit. Change from baseline in chemistry (excluding LDL/HDL cholesterol ratio), hematology, iron parameter, and other laboratory will be summarized separately.

*Worst Case Laboratory Results Relative to Normal Range/PCI Criteria Post-Baseline Relative to Baseline*

The number of subjects with worst case laboratory results relative to normal range/potential clinical importance (PCI) criteria which are post-baseline relative to baseline, including unscheduled assessments, will be summarized by test and category by treatment group. Summaries for normal range and PCI will be provided separately. The categories for normal range are: To Low, To Normal or No Change, To High; the categories for PCI criteria are: To Low, To w/in Range or No Change, To High. The categorization is determined by comparing the baseline category to the worst case post-baseline category. PCI criteria is described in Appendix 8.

- ***Hepatobiliary (Liver)***

Details of liver chemistry stopping criteria are described in the protocol.

Liver monitoring/stopping events will be summarized by treatment group.

Hepatobiliary laboratory abnormalities will be summarized by treatment group.

A scatter plot of maximum on-therapy ALT values versus baseline ALT values will be produced if larger data permit.

A scatter plot of maximum total bilirubin (xULN) versus maximum ALT (xULN) values on-therapy will be produced if larger data permit.

## 8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

| Endpoint / Parameter/ Display Type | Absolute | | | Change from BL | | |
|---|---|---|---|---|---|---|
| | Summary | | Individual | Summary | | Individual |
| | T | F | L | T | F | L |
| **ECG** | | | | | | |
| ECG Findings | Y | | Y | | | |
| ECG Values by Visit | | | Y | Y | | |
| Abnormal ECG Findings | | | Y | | | |
| **Vital Signs** | | | | | | |
| Vital Signs by Visit | Y | | Y | Y | | |
| Worst Case Vital Sign Results Relative to PCI Criteria Post-Baseline Relative to Baseline | Y | | | | | |
| All Vital Signs for Subjects with Any Values of PCI | | | Y | | | |
| **Ophthalmology** | | | | | | |
| Prior-Therapy Ophthalmologic Exams | Y | | Y | | | |
| On-Therapy Ophthalmologic Exams | Y | | Y | | | |
| **Change in Anti-Hypertensive Medications** | | | | | | |
| Number (%) of Subjects Who Have Any Change in Anti-Hypertensive Medications During the Treatment Period | Y | | Y | | | |

**NOTES:**

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- 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.

### 8.4.1. Planned Other Safety Analyses Displays

- ***ECG***

ECG findings ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will be summarized by assessment visit for each treatment group. Change from baseline in ECG values will be summarized using mean, standard deviation, minimum, median, and maximum by assessment visit for each treatment group. Findings without regard to visits (labelled “Worst Case Post-Baseline”, only the worst case finding for each subject) will also be provided. All ECG measures (heart rate, PR interval, QRS duration, QT [uncorrected] interval and QTcB [calculated], result of ECG) will be included in listings.

- ***Vital Signs***

Vital sign values will be summarized using mean, standard deviation, minimum, median, and maximum by assessment visit for each treatment group. Separate summary statistics of pre- and post-dialysis vital signs will be provided for raw values and change from baseline. In a summary of change from baseline, each baseline value (i.e. pre- and post-dialysis baseline) will be used for calculation (Section 5.2).

The number of subjects with worst case vital sign results relative to PCI criteria which are post-baseline relative to baseline, including unscheduled assessments, will also be summarized by test and category by treatment group. The categories for PCI criteria are: To Low, To w/in Range or No Change, To High. The categorization is determined by comparing the baseline category to the worst case post-baseline category.

- ***Ophthalmology Exams***

The responses to each question and any questions will be summarized using number and percentage at each assessment visit by treatment group. The response will be classified into 'Yes' and 'No'. A summary of ophthalmology exams at screening and at on-therapy will be produced separately. The number and percentage of subjects with worst case after-screening ophthalmology exams (i.e., the response is 'Yes' at least once during whole treatment period, including unscheduled visits) will also be summarized by each question by treatment group.

- ***Change in Anti-Hypertensive Medications***

The number and percentage of subjects who have any change at least once in anti-hypertensive medications (type and/or dose) due to increased blood pressure during whole treatment period will be summarized by treatment group.

# 9. PATIENT REPORTED OUTCOME ANALYSES

## 9.1. Endpoint / Variables

| Endpoint / Parameter/ Display Type | Absolute | | | | | |
|---|---|---|---|---|---|---|
| | Stats Analysis | | Summary | | Individual | |
| | T | F | T | F | F | L |
| **Patient Reported Outcome** | | | | | | |
| SF-36 HR-QoL Scores (PCS, MCS, 8 subscales) | | | Y | | | Y |
| Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 subscales) | Y | | Y | | | |
| EQ-5D-5L Scores | | | Y | | | Y |
| EQ-5D-5L Index Values | | | Y | | | Y |
| Changes from Baseline in EQ-5D-5L Index Value | Y | | Y | | | |
| EQ VAS | | | Y | | | Y |
| Changes from Baseline in EQ VAS | Y | | 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.

## 9.2. Summary Measure

Scoring derivations are described in Section 15.6.7.

*SF36 HR-QoL Scores and Changes from Baseline (PCS, MCS, 8 subscales)*

The summary scores (PCS and MCS) and the domain scores (Physical Functioning [PF], Role-Physical [RP], Bodily Pain [BP], General Health [GH], Vitality [VT], Social Functioning [SF], Role-Emotional [RE], and Mental Health [MH]) will be summarized using mean, standard deviation, median, minimum, and maximum at each assessment visit by treatment group. For changes from baseline, the adjusted treatment difference and the 95% CIs will also be provided (See Section 15.6.7).

*EQ-5D-5L / EQ VAS Scores and Changes from Baseline in EQ-5D-5L Index Value / EQ VAS*

The number and percentage of subjects with each score within each category will be displayed at each assessment visit by treatment group. EQ-5D-5L index values and EQ VAS scores will be provided using mean, standard deviation, median, minimum, and maximum at each assessment visit by treatment group. For changes from baseline, the adjusted treatment difference and the 95% CIs will also be provided (See Section 15.6.7).

## 9.3. Population of Interest

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

## 9.4. Strategy for Intercurrent (Post-Randomization) Events

Any intercurrent events are taken to be irrelevant for the endpoints and the endpoints will be summarized based on available and observed data.

Analysis of change from baseline in the respective QoL parameter at each assessment visit will follow the strategy below.

| **Intercurrent events** | **Strategy** |
|---|---|
| Study withdrawal / Intermittent missing | The following hypothetical scenario is considered to assess what would have happened if the event did not occur. Analysis using MMRM assume missing at random mechanism, that is the observations of missing depend on just observed values, not on unobserved values. |

## 9.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

### 9.5.1. Statistical Methodology Specification

| **Endpoint / Variables** |
|---|
| • Change from baseline in the respective QoL parameter at each assessment visit |
| **Model Specification** |
| • Analyses will be repeated for each QoL parameter (SF-36 HR-QoL scores/EQ-5D-5L index value/EQ-VAS score) using MMRM as specified in Section 7.4.5.1:<br>• Note that the QoL parameters are no need to be log-transformed as opposed to some of the iron parameters. |
| **Model Results Presentation** |
| • The adjusted mean change from baseline will be presented with the associated 95% CIs by treatment at each assessment visit. The adjusted treatment difference (daprodustat – darbepoetin alfa) for change from baseline will also be presented with the associated 95% CI at each assessment visit. |
| **Subgroup Analyses** |
| • Not applicable |

# 10. PHARMACOKINETIC ANALYSES

## 10.1. Pharmacokinetic Analyses

### 10.1.1. Endpoint / Variables

The details of the planned displays are presented in Appendix 10: List of Data Displays.

| Endpoints | Untransformed | | | | Log-Transformed | | | |
|---|---|---|---|---|---|---|---|---|
| | Summary | | Individual | | Summary | | Individual | |
| | F | T | F | L | F | T | F | L |
| Plasma Concentrations of Daprodustat | Y [1] [2] | Y | Y [1] | Y | | | | |
| Derived PK Parameters | Y [3] | Y [3] | Y[3] | Y | | Y[3] | | |
| Dose Normalized PK Parameters | Y [3] | Y [3] | Y[3] | Y | | Y[3] | | |

**NOTES :**

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

1. Linear and Semi-Log plots will be created on the same display.
2. Separate Mean (± SD) and Median plots will be generated.
3. Individual PK parameters calculated based on less than 4-time point concentrations or any time deviated concentration will be omitted from summaries and figures.

#### 10.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 15.5.3 Reporting Standards for Pharmacokinetic)

Concentrations of daprodustat in plasma will be listed and summarized by dose group and nominal time. Individual plasma concentration-time profiles and median/mean profiles by dose group will be plotted. Each of figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. a log-linear plot).

#### 10.1.1.2. Derived Pharmacokinetic Parameters

Derivation of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Pharmacology & Science Promotion Office, GlaxoSmithKline K.K.

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin (version 6.3 or higher). All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma daprodustat concentration-time data, as data permits.

| Parameter | Parameter Description |
|---|---|
| AUC(0-4) | Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(last)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the linear trapezoidal for each decremental trapezoid.<br>The concentration at 0 hr will be set to 0. |
| Cmax | Maximum observed concentration, determined directly from the concentration-time data. |
| Tmax | Time to first occurrence of Cmax will be obtained directly from the concentration-time data. |

**NOTES:**

- Additional parameters may be included as required.
- C(last) is expected to be the concentration observed at 4 hours after the most recent dose.

### 10.1.2. Summary Measure

Refer to Section 15.5.3 for the display standards.

- ***Plasma Daprodustat Concentrations***

Non-transformed and log-transformed plasma concentration at every scheduled time point will be summarized at Week 12, Week 24, and all visits (i.e., pooled analysis of Week 12 and Week 24) by dose level. Non-transformed plasma concentration of daprodustat will be summarized using mean, 95% CI, standard deviation, median, minimum, and maximum. Log-transformed plasma concentration of daprodustat will be summarized using geometric mean, 95% CI of geometric mean, standard deviation of log-transformed data and between subject coefficient of variation (%CVb).

- ***PK Parameters***

Non-transformed and log-transformed PK parameters will be summarized at Week 12, Week 24, and all visits (i.e., pooled analysis of Week 12 and Week 24) by dose level. Non-transformed PK parameters of daprodustat (AUC(0-4), Cmax, and Tmax) will be summarized using mean, 95% CI, standard deviation, median, minimum, and maximum. Log-transformed PK parameters of daprodustat (AUC(0-4), Cmax, and Tmax) will be summarized using geometric mean, 95% CI of geometric mean, standard deviation of log-transformed data and between subject coefficient of variation (%CVb).

Dose normalized PK parameters (non-transformed and log-transformed) will also be summarized in the same manner by dose level. In summary of dose normalized PK parameters, summary tables by tablet strength (non-transformed and log-transformed) will be provided.

### 10.1.3. Population of Interest

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

### 10.1.4. Strategy for Intercurrent (Post-Randomization) Events

Any intercurrent events are taken to be irrelevant for pharmacokinetic endpoints. The pharmacokinetic endpoints will be summarized based on available and observed data.

# 11. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

No population pharmacokinetics analyses are planned for this study, but the pharmacokinetic data may be used for a separate report.

# 12. PHARMACODYNAMIC ANALYSES

No pharmacodynamics analyses are planned for this study, but the pharmacodynamic data may be used for a separate report.

# 13. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

No pharmacokinetic / pharmacodynamic analyses are planned for this study, but the pharmacokinetic / pharmacodynamic data may be used for a separate report.

# 14. REFERENCES

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# 15. APPENDICES

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

### 15.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

| Number | Exclusion Description |
|---|---|
| 01 | Informed Consent in Deviation Category |
| 02 | Eligibility Criteria Not Met in Deviation Category |
| 03 | Not Withdrawn After Developing Withdrawal Criteria in Deviation Category |
| 04 | Wrong study treatment or assignment administered in Deviation Subcategory |
| 05 | Randomization procedures (e.g. subject randomized out of order) in Deviation Subcategory |
| 06 | Less than 3 out of 4 scheduled evaluable Hgb values from the primary efficacy evaluation period [1] |
| 07 | Subject received prohibited medication for more than 14 days during study period [2] |
| 08 | Non-compliance with randomized medication (compliance category of under compliant or over compliant) [3] during the primary efficacy evaluation period, based on eCRF randomized medication exposure and compliance forms |

**NOTES:**

[1] Evaluable Hgb values are described in Section 15.6.3.

[2] Prohibited mediations include strong inhibitors of CYP2C8 (e.g., gemfibrozil) and strong inducers of CYP2C8 (e.g., rifampin/rifampicin), not include erythropoietin (e.g., epoetin/ darbepoetin alfa/ epoetin beta pegol, excluding darbepoetin alfa supplied by GSK).

[3] See Section 15.6.2; Over compliant: <80%, compliant: ≥80% and ≤120%, over compliant: >120%

# 15.2. Appendix 2: Schedule of Activities

## 15.2.1. Protocol Defined Schedule of Events

| Phase | Screening | Treatment | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit<br>**All assessments pre-dialysis, unless noted.** | -4～-2 [11] | Day 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 |
| Allowance range (days) | ±3 | - | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 |
| Informed consent | X | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | | | | | | | |
| Medical history, demography, height, weight [1] | X | | | | | | | | | | | | | | | |
| IWRS call | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Study medication dispensing [2, 3] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Study treatment compliance | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs (before and after dialysis) [4] | X | X | | X | | | | | | X | | | | | | X |
| Ophthalmology [5] | ← | | | | | | ← | | → | | | | | | | |
| ECG | X | | | | | | | | | | | | | X | | |
| HemoCue Hgb | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology | X | X | | X | | Hgb only | | Hgb only | | X | | Hgb only | | Hgb only | | X |
| Clinical chemistry | X | X | | X | | | | | | X | | | | | | X |
| Pregnancy test (serum hCG) [6] | X | X | | X | | | | | | X | | | | | | X |
| Estradiol, FSH [7] | X | | | | | | | | | | | | | | | |
| PK [8] | | | | | | | | X | | | | | | X | | |
| Ferritin, TSAT | X | X | | X | | | | | | X | | | | | | X |
| Serum iron, TIBC, UIBC, serum transferrin, hepcidin | | X | | X | | | | | | X | | | | | | X |
| iPTH | | X | | | | | | | | | | | | | | X |
| HR-QoL (SF-36, EQ-5D-5L/ EQ-VAS) | | X | | | | | | X | | | | | | | | X |
| Genetics sample [9] | | X | | | | | | | | | | | | | | |
| AE assessment [10] | X [12] | ← | | | | | | | | | | | | | | → |
| Concomitant Medications Review | ← | | | | | | | | | | | | | | | → |

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| Phase | Treatment | | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit<br>**All assessments pre-dialysis, unless noted.** | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 | Early withdrawal [13] | 2 weeks after Week 52 or early withdrawal |
| Allowance range (days) | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | - | ±3 |
| Informed consent | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | | | | | | | | | | | | | | |
| Medical history, demography, height, weight [1] | | | | | | | | | | | | | | |
| IWRS call | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Study medication dispensing [2, 3] | X | X | X | X | X | X | X | X | X | X | X | | | |
| Study treatment compliance | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs (before and after dialysis) [4] | | | | | | X | | | | | | X | X | X |
| Ophthalmology [5] | | | | | | | | | | ← | — | → | ↔ | |
| ECG | | | | | | | | | | | | X | | |
| HemoCue Hgb | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Hematology | | Hgb only | | Hgb only | | X | | Hgb only | | Hgb only | | X | X | X |
| Clinical chemistry | | | | | | X | | | | | | X | X | X |
| Pregnancy test (serum hCG) [6] | | | | | | X | | | | | | X | X | X |
| Estradiol, FSH [7] | | | | | | | | | | | | | | |
| PK [8] | | | | | | | | | | | | | | |
| Ferritin, TSAT | | | | | | X | | | | | | X | X | |
| Serum iron, TIBC, UIBC, serum transferrin, hepcidin | | | | | | X | | | | | | X | X | |
| iPTH | | | | | | | | | | | | X | | |
| HR-QoL | | | | | | | | | | | | X | X | |
| Genetics sample [9] | | | | | | | | | | | | | | |
| AE assessment [10] | ← | — | — | — | — | — | — | — | — | — | — | — | — | → |
| Concomitant Medications Review | ← | — | — | — | — | — | — | — | — | — | — | — | — | → |

1. Body weight is measured after dialysis.
2. Daprodustat/placebo will be dispensed once every 4 weeks, and darbepoetin alfa/placebo will be dispensed once every 2 weeks
3. If a subject visit the study site only to receive study medication, only the IWRS call, study medication dispensing, and study medication compliance will be required.
4. At visits without dialysis, only one measurement of each parameter will be obtained.
5. Ophthalmology exams should be conducted at the following time points.

6. Screening: anytime after consenting and prior to first dose of study medication (Day 1)
7. Week 12: window from weeks 10-14 (inclusive)
8. End of study: window from weeks 48-52 (inclusive)
9. Early study medication discontinuation: withdrawal eye exam as close to the last dose as possible (the repeat exams are not required if one has been performed within the 2 prior weeks).
10. Performed in females of childbearing potential.
11. Measured in female subjects only to determine the menopausal status (see Section 5.1 in protocol.)
12. See Table 11 in protocol.
13. Informed consent for optional Genetic research should be obtained before collecting a sample (see Section 7.6 in protocol.).
14. See Section 7.4.1.1. in protocol. The interval between screening and Day 1 should be 4 weeks in subjects treated with epoetin beta pegol every 4 weeks or darbepoetin alfa every 4 weeks in the prior ESA therapy.
15. Only SAEs assessed as related to study participation or a GSK product are collected.
16. For withdrawn subjects, specified assessments should be done wherever possible.

## 15.3. Appendix 3: Assessment Windows

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Permissible range at each visit was specified in time & event table (See Appendix 2). Records in the eCRF unscheduled visit will not be slotted to a particular time point, but remain as unscheduled if they are either summarized or listed unless otherwise specified.

Regarding the visits where only HemoCue Hgb is available (i.e., Week 2, Week 6, Week 10, etc. See Appendix 2.), the Hgb values will not be used for any analyses but presented in the listing unless otherwise specified.

### 15.3.1. Definitions of Assessment Windows for Analyses

| Analysis Time Point | Definitions |
|---|---|
| Screening [1] | Data collected in Screening visit<br>If multiple records are present, the latest record will be used for analysis. |
| Day 1 [1] | Data collected in Day 1 visit<br>If multiple records are present, the latest record will be used for analysis. |
| Week 2 | Data collected in Week 2 visit |
| Week 4 | Data collected in Week 4 visit |
| Week 6 | Data collected in Week 6 visit |
| … | … |
| Week 48 | Data collected in Week 48 visit |
| Week 50 | Data collected in Week 50 visit |
| Week 52 | Data collected in Week 52 visit |
| Follow-up | Data collected in Follow-up visit |

**Note:**
Any unscheduled visit will not be slotted to a particular time point.
[1] For rescreened subjects, data collected in screening-pass visit (i.e., screening and day 1 visit where the subject has passed a screening test) will be used for analysis. They may have multiple records at Screening and/or Day 1 visit, which associates with a screening pass visit and screening failure visit(s) (See Section 15.6.1)

## 15.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

### 15.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to randomization date and treatment stop date.

Treatment stop date is defined in Section 15.6.1.

#### 15.4.1.1. Study Phases for Hgb Data

| Treatment State | Definition |
|---|---|
| Pre-therapy | Date ≤ Randomization Date |
| On-therapy | Randomization Date < Date ≤ Treatment Stop Date + 1 day |
| Post-therapy | Date > Treatment Stop Date + 1 day |

**NOTES:**

- If randomization date is missing then the assessment will be considered to be pre-therapy

#### 15.4.1.2. Study Phases for AE Data

On-therapy AEs will be treated as treatment emergent AEs, therefore, treatment emergent flag for AEs will be derived from on-therapy treatment state.

| Treatment State | Definition |
|---|---|
| Pre-therapy | AE Start Date < Randomization Date |
| On-therapy | Randomization Date ≤ AE Start Date ≤ Treatment Stop Date + 1 day |
| Post-therapy | AE Start Date > Treatment Stop Date + 1 day |
| Duration (Days) | AE Resolution Date – AE Onset Date + 1 day |
| Drug-related | If relationship is marked 'YES' on eCRF or value is missing. |

**NOTES:**

- If randomization date is missing then the assessment will be considered to be pre-therapy

#### 15.4.1.3. Study Phases for Concomitant Medication

| Treatment State | Definition |
|---|---|
| Pre-therapy | Concomitant medications that meet either following conditions will be regarded as pre-therapy.<br>• Concomitant Medication Start Date < Randomization Date [a, b, c, j, n]<br>• Concomitant Medication Start Date is missing [g, h, i, m, o]<br>• Randomization Date is missing |
| On-therapy | Concomitant medications that meet either following conditions will be regarded as on-therapy.<br>• Randomization Date ≤ Concomitant Medication Start Date ≤ Treatment Stop Date + 1 [d, e, k, p, q, r, s, v]<br>• (Concomitant Medication Start Date < Randomization Date) AND (Randomization Date ≤ Concomitant Medication Stop Date) [b, c, n] |

| Treatment State | Definition |
|---|---|
| | • (Concomitant Medication Start Date < Randomization Date) AND (Concomitant Medication Stop Date is missing) [j]<br>• (Concomitant Medication Start Date is missing) AND (Concomitant Medication Stop Date ≥ Randomization Date) [h, i, o]<br>• (Concomitant Medication Start Date is missing) AND (Concomitant Medication Stop Date is missing) [m] |
| Post-therapy | Concomitant medications that meet either following conditions will be regarded as post-therapy.<br>• Concomitant Medication Stop Date > Treatment Stop Date [c, e, f, l, r, t, v]<br>• Concomitant Medication Stop Date is missing [j, k, l, m, s, u] |

**NOTES:**

- Data of concomitant medication includes ESA, iron, and blood products and blood supportive care products.
- Alphabets in brackets after the conditions correspond to each case in following illustrations.

Illustrations of the pre-therapy, on-therapy, and post-therapy for concomitant medications are included below:

| | Pre-therapy | On-therapy | | | Post-therapy | | Pre-therapy medication | On-therapy medication | Post-therapy medication |
|---|---|---|---|---|---|---|---|---|---|
| | | Randomization Date | | Treatment Stop Date | Treatment Stop Date + 1 Days | | | | |
| (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 |

x = start/stop date of medication
? = missing start/stop date of medication
* If a medication is stopped on-therapy or post-therapy and no start date is recorded it will be assumed that the medication was ongoing from the pre-therapy phase
** If a medication is started pre-therapy or on-therapy and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study
*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the pre-therapy phase to the post-therapy phase

# 15.5. Appendix 5: Data Display Standards & Handling Conventions

## 15.5.1. Reporting Process

| | |
|---|---|
| **Software** | |
| • The currently supported versions of SAS software and S-Plus will be used. | |
| **Reporting Area** | |
| HARP Server | : uk1salx00175 |
| HARP Compound | : /arenv/arprod/gsk1278863/mid201754/final_01 |
| QC Spreadsheet | : /arenv/arprod/gsk1278863/mid201754/final_01/documents |
| **Analysis Datasets** | |
| • Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & ADaM IG Version 1.0. If the Study Data Standardization Plan (SDSP) exists for a study, ensure the CDISC versions are consistent. | |
| **Generation of RTF Files** | |
| • RTF files will not be generated. | |

## 15.5.2. Reporting Standards

| |
|---|
| **General** |
| • The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):<br>  • 4.03 to 4.23: General Principles<br>  • 5.01 to 5.08: Principles Related to Data Listings<br>  • 6.01 to 6.11: Principles Related to Summary Tables<br>  • 7.01 to 7.13: Principles Related to Graphics<br>• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should locate in the modular appendices as ICH or non-ICH listings |
| **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, unless otherwise stated.<br>• Numeric data will be reported at the precision collected on the eCRF.<br>• 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:<br>  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.<br>  • 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.<br>  • Scheduled visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings, figures, summaries and statistical analyses.<br>• Reporting for Data Listings:<br>  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).<br>  • Unscheduled or unplanned readings will be presented within the subject's listings. |

| **Unscheduled Visits** | |
|---|---|
| • Unscheduled visits will not be included in summary tables and/or figures.<br>  • If unscheduled visits are included, details of how summaries will be displayed will be provided in the RAP.<br>• All unscheduled visits will be included in listings. | |
| **Descriptive Summary Statistics** | |
| Continuous Data | Refer to IDSL Statistical Principle 6.06.1: This does not apply to the output of statistical models or when the standard list is inappropriate.<br>• For cases where the standard may not be applied, see the display details in Section 6 to Section 10. |
| Categorical Data | N, n, frequency, % |
| **Graphical Displays** | |
| • Refer to IDSL Statistical Principals 7.01 to 7.13. | |

### 15.5.3. Reporting Standards for Pharmacokinetic

| **Pharmacokinetic Concentration Data** | |
|---|---|
| PC Windows Non-Linear (WNL) File | PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GUI_51487.<br>Note: Concentration values will be imputed as per GUI_51487 |
| Descriptive Summary Statistics, Graphical Displays and Listings | Refer to IDSL PK Display Standards.<br>Refer to IDSL Statistical Principle 6.06.1.<br>Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only. |
| **Pharmacokinetic Parameter Derivation** | |
| PK Parameter to be Derived by Programmer | The following PK parameters will be derived by the Programmer:<br>• Dose-Normalized PK parameters |
| **Pharmacokinetic Parameter Data** | |
| Is NQ impacted PK Parameters Rule Being Followed | Yes, refer to Standards for Handling NQ Impacted PK Parameters. |
| Descriptive Summary Statistics, Graphical Displays and Listings | Each pharmacokinetic parameter (AUC(0-4), Cmax, and Tmax) will be summarized using the minimum set of summary statistics (IDSL statistical display principle 6.06.1).<br>For each pharmacokinetic parameter (AUC(0-4), Cmax, and Tmax), the log-transformed parameter will be summarized using the summary statistics. The summary statistics are: N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log-transformed data and between subject coefficient of variation (CVb (%)) will be reported.<br>[1] $CV_b$ (%) = $\sqrt{}$ (exp($SD^2$) - 1) * 100<br>(SD = SD of log transformed data) |

# 15.6. Appendix 6: Derived and Transformed Data

## 15.6.1. General

| **Multiple Measurements at One Analysis Time Point** |
|---|
| • Subjects having both High and Low values for Normal Ranges at any post-baseline visit 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 PCI summary tables.<br>• For multiple measurements at Screening and/or Day 1 visit, the screening-pass visit record will be used for analysis (See Appendix 3). |
| **Study Day** |
| • Calculated as the number of days from Randomization Date:<br>  • Ref Date = Missing → Study Day = Missing<br>  • Ref Date < Randomization Date → Study Day = Ref Date – Randomization Date<br>  • Ref Data ≥ Randomization Date → Study Day = Ref Date – (Randomization Date) + 1 |
| **Unique Subject ID** |
| • All subjects have unique subject ID for analyses even if a subject was enrolled after rescreened. Tables/figures/listings will be produced based on unique subject ID.<br>• For a rescreened subject, the unique subject ID will be derived from the first-assigned subject number though he or she seems to have different subject numbers in eCRF by screening assessments. |
| **Rescreening Subjects** |
| • For rescreened subjects, data collected in screening-pass visit will be used for analysis. They may have multiple records at Screening and/or Day 1 visit, which associates with a screening-pass visit and screening failure visit(s)<br>• Regarding a listing of SAEs in screening period, all pre-therapy SAEs captured in eCRF will be provided including screen failure records of rescreened subjects. |
| **Treatment Start Date** |
| • First randomized treatment start date |
| **Treatment Stop Date - Daprodustat** |
| • Calculated as the latest randomized treatment stop date |
| **Treatment Stop Date – Darbepoetin Alfa** |
| • Following definition will be based on "assumed" treatment stop date because the treatment stop date is not captured in eCRF.<br>**Definition:**<br>• If a subject has completed the treatment period (i.e., Week 52 visit record is present), treatment stop date will be calculated as Week 52 visit date<br>  ○ Week 52 visit date will be based on laboratory Hgb date. HemoCue Hgb date will be used when laboratory Hgb date is unavailable.<br>• If a subject has withdrawn from the treatment period (i.e., Week 52 visit record is missing), treatment stop date will be calculated as the latest treatment start date + 6 days (1 day before the next treatment start date if a subject hadn't withdrawn)<br>  • Subjects are intended to have weekly injection of darbepoetin alfa, therefore assumed treatment stop date could include "+ 6 days" to mimic weekly dosing. |

| Subgroup Definition |
|---|
| • For general considerations, see Section 5.4.2.<br>• Regarding prior ESA type and prior ESA dose, see Section 15.6.2<br>• Period of time on dialysis (years) will be defined as follows:<br>  ○ (Randomization Date – Date of Dialysis Initiation + 1) / 365.25<br>• Baseline iron use = use or non-use of pre-therapy iron medications (including Riona and P-TOL, see Section 15.6.6)<br>• History of diabetes will be derived from the current history diabetes (Yes/No) in medical history records. |
| **Time Definitions (per GSK standard principles)** |
| • 1 week = 7 days<br>• 1 month = 30.4375 days<br>• 1 year = 365.25 days |

## 15.6.2. Study Population

| Subject Disposition and Study Population |
|---|
| **Rescreened Subjects** |
| • Screening status and reason for screening failure for a subject who has multiple subject numbers will be unique in the unique subject ID.<br>  ○ The screening status of a subject who failed screening but passed rescreening will be 'enrolled', and the reason for failure will not be counted.<br>  ○ The screening status of a subject who failed more than one screening and never passed will be 'failed', and the reason for failure will be derived from the latest failure record.<br>• Study population of subjects will be derived from the above unique screening status. |

| Demographics and Baseline Characteristics |
|---|
| **Age** |
| • GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:<br>  ○ A date and month will be imputed as '30th June' as it will not be captured.<br>• Randomization date will be used as reference date of calculation.<br>  ○ If randomization date is missing, screening date will be used. |
| **Body Mass Index (BMI)** |
| • Calculated as Weight (kg) / [Height (m)]$^2$ |
| **Type of Prior ESA** |
| • For this study, prior ESA dose can be administered in several different ways, which are categorized by GSK drug codes as follows. |

| Prior ESA | Epoetin | Epoetin beta pegol | Darbepoetin alfa |
|---|---|---|---|
| CMDRGCOL | 00928302<br>00928303<br>00928305 | 53876201 | 50520401 |

| |
|---|
| • Dosing route (IV or SC) will be derived from eCRF. |
| **Prior ESA Dose (IU/week) at Baseline** |
| • During screening, subjects may be receiving ESA in multiple ways, including epoetin IV or SC, darbepoetin alfa IV or SC, or epoetin beta pegol IV or SC. The dose of ESA at screening visit will be |

**Demographics and Baseline Characteristics**

standardized to obtain a continuous single unit prior ESA dose in terms of epoetin IV (IU/week). The standardization will be carried with the following formula based on literature review:

- For subjects taking epoetin IV
  - Standardized mean prior ESA dose (IU/week) = epoetin IV dose (IU/week)
- For subjects taking epoetin SC
  - Standardized mean prior ESA dose (IU/week) = (161/113)*epoetin SC dose(IU/week): [Besarab. 2002]
- For subjects taking darbepoetin alfa IV or SC
  - Standardized mean prior ESA dose (IU/week) = 250*darbepoetin alfa dose (μg/week)
- For subjects taking epoetin beta pegol IV or SC
  - Standardized mean prior ESA dose (IU/week) = 208*epoetin beta pegol dose (μg/week)

- Prior ESA dose will be calculated using a weighted mean:
  - Mean prior ESA dose (μg/week or IU/week) = $([dose\_w]_1*[duration_1] + ... + [dose\_w]_n*[duration]_n)] / [[duration]_1 + ... + [duration]_n]$
    where
    - $[Dose\_w]_n = [dose]_n * [frequency]_n$
    - $[Duration]_n = [Prior\ ESA\ start\ date]_{n+1} – [prior\ ESA\ start\ date]_n$*
      or
      [Randomization date] – $[prior\ ESA\ start\ date]_n$*
      when $n^{th}$ record is the last prior ESA dose

      *Using "[end date] – [start date] +1' may be inappropriate because the start date may be identical with the end date in case the dose frequency is once daily or twice daily, etc.

    Note: Frequency is defined as follows:
    If subject receives prior ESA x times per week → frequency = x
    If subject receives prior ESA every x weeks → frequency = 1/x
    If subject receives prior ESA x times per month → frequency = x * 7 / 30.4375
    If subject receives prior ESA x times per day → frequency = x * 7/duration
    once daily (QD) = 1 time per day, twice daily (BID) = 2 times per day, etc…

- Prior ESA dose during the period of 12 weeks prior to randomization will be used for calculation.
- To obtain this, some records may be converted for calculation because some dosing records may include both before and after the period or may not include the period.
  - If a start date of dosing is before 12 weeks prior to randomization (i.e., study day < -84), the start date will be replaced to the date of study day = -84 for the calculation.
  - This conversion makes the records before 12 weeks prior to randomization ignorable because the records will lose their information and weighting of duration before the period.

**Demographics and Baseline Characteristics**

Illustration of Standardized Mean Prior ESA calculation (ex: epoetin IV)

| Record# | Visit | Start Date | Dose (IU) | Frequency. [unit] | Duration (days) | Dose_w (IU / week) |
|---|---|---|---|---|---|---|
| 1 | Screening | 06Feb2017 | 750 | Once daily | 2 | 750*7/2 = 2625 |
| 2 | Screening | 08Feb2017 | 750 | Once daily | 2 | 750*7/2 = 2625 |
| 3 | Screening | 10Feb2017 | 1500 | Once daily | 3 | 1500*7/3 = 3500 |
| 4 | Screening | 13Feb2017 | 750 | 3 [times/week] | 9 | 750*3 = 2250 |
| - | Day 1 | 22Feb2017 [Randomization Date] | | | Weighted mean (IU/week) =2578.1 | |

**Erythropoietin Resistance Index (ERI) at Baseline**

- Calculated as standardized mean prior ESA dose (IU/week) divided by dry weight (kg) at screening visit and then divided by the achieved Day 1 Hgb (g/dL).

**Exposure**

**Blinded Dose Level**

- Blinded dose level of each visit will be linked with prescribed dose according to the protocol:

| Dose level | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Treatment | Prescribed Dose | | | | | | | | |
| Daprodustat / Placebo | 0 mg | 1 mg | 2 mg | 4 mg | 6 mg | 8 mg | 12 mg | 18 mg | 24 mg |
| Darbepoetin Alfa / Placebo | 0 μg | 10 μg | 15 μg | 20 μg | 30 μg | 40 μg | 60 μg | NA | NA |

- In darbepoetin alfa / placebo treatment, prescribed dose will be associated with exposure records. Two records of exposure within a certain visit form have a certain blinded dose level.

**Prescribed Dose and Actual Dose**

- Prescribed dose will be derived from blinded dose level captured in eCRF.
- Actual dose will be derived from container number(s) captured in eCRF. Note that unscheduled (additional) bottles will not be taken into account. In principle, actual dose will be the same as prescribed dose except for a case in which inconsistency between a prescribed dose and actual bottle(s) occurs. If such an inconsistency occurs, it may not be possible to determine what dose was actually taken. In these cases, the actual dose may be changed from the prescribed dose to a more plausible value based on the available information (e.g., IRT data).

**Extent of Exposure of Daprodustat**

- Subjects who were randomized but did not report a treatment start date will be categorized as having zero days of exposure.
- Time on study treatment will be calculated based on the following formula:
  Time on study treatment (days)
  = [Study Treatment Stop date] – [Study Treatment Start date] + 1 day
  The time on study treatment does not exclude dose interruptions.

**Exposure**

- Cumulative dose will be based on the formula using actual dose:
  Cumulative Dose = Sum of ([Exposure Duration] x [Actual Dose]) at Each Visit
  where Exposure duration = [Treatment Stop date] – [Treatment Start date] +1 day
- Subject daily dose (= Cumulative Dose / Time on study treatment) is calculated for each subject using actual dose and the summary statistics are calculated based on the subject average daily dose.
- Distribution of the dose level
  Dose level will be classified into 9 categories; 0 mg (i.e. treatment interruption), 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 18 mg, 24 mg according to actual dose.

**Extent of Exposure of Darbepoetin Alfa**

- Subjects who were randomized but did not report a treatment start date will be categorized as having zero days of exposure.
- Time on study treatment will be calculated based on the following formula:
  Time on study treatment (days)
  = [Study Treatment Stop date] – [Study Treatment Start date] + 1 day
  The time on study treatment does not exclude dose interruptions.
- Cumulative dose will be based on the formula using actual dose:
  Cumulative Dose = Sum of Actual Dose at Each Visit
- Subject weekly dose (= Cumulative Dose / Time on study treatment) is calculated for each subject using actual dose and the summary statistics are calculated based on the subject average weekly dose.
- Distribution of the dose level
  Dose will be classified into 7 categories; 0 μg (i.e. treatment interruption), 10 μg, 15 μg, 20 μg, 30 μg, 40 μg, 60 μg according to actual dose.

**Treatment Compliance of Daprodustat**

- Treatment compliance will be calculated for daprodustat as follows:
  - Compliance (%) = [(Total # of tablets actual taken) / (Total # of tablets planned taken)] * 100
    where
    Total # of tablets actual taken = Sum of (Numbers of Tablets Taken at Each Visit)
    Total # of tablets planned taken = Sum of [(Treatment Stop Date – Treatment Start Date + 1 day) x Planned # of tablet / day in Each Visit]
  - Daprodustat compliance will also be categorized based on calculated compliance:
    Calculated compliance < 80% → Under Compliant
    Calculated compliance ≥ 80% and ≤ 120% → Compliant
    Calculated compliance > 120% → Over Compliant

  Where a container number is available, planned # of tablet/day is defined as follows according to the protocol:
  - 0 mg → 1 tablet/day (i.e., subjects takes placebo tablets)
  - 1 mg → 1 tablet/day
  - 2 mg → 1 tablet/day
  - 4 mg → 1 tablet/day
  - 6 mg → 1 tablet/day
  - 8 mg → 2 tablets/day
  - 12 mg → 2 tablets/day
  - 18 mg → 3 tablets/day
  - 24 mg → 4 tablets/day

  where dose record is derived from prescribed dose.

  Where a container number is not available (i.e., bottles not delivered to a subject), planned # of tablet/day will be 0 so that the treatment compliance will not be calculated.

**Exposure**

Where unscheduled (additional) bottles are being captured, the total # of tablets actual taken will be slotted to the corresponding scheduled visit.

**Treatment Compliance of Darbepoetin Alfa**

- Treatment compliance of darbepoetin alfa will be based on dosing records (weekly doses are captured) and categorized as Under Compliant, Compliant, and Over Compliant, and will be defined as follows:
  - Calculated compliance < 80% → Under Compliant
  - Calculated compliance ≥ 80% and ≤ 120% → Compliant
  - Calculated compliance > 120% → Over Compliant
- Calculated compliance will just be carried to derive compliance category, not provided for any displays. It will be carried using the following formula:
  - Calculated compliance (%) = [(Total # of dosing records with container number) / (Total # of planned dosing)] * 100

  where

  Total # of planned dosing = [Time on study treatment (days)] / 7

  where Time on study treatment (days) = Treatment Stop Date – Treatment Start date + 1

  When a container number is available in a visit, subjects will receive an injection in the visit (i.e., dosing records may be available even when subjects don't receive injections).
- For compliance up to Week 4, following formulae will be used:

  Total # of actual dosing up to Week 4 = Sum of (Number of dosing records with container number before Week 4 visit)

  Total # of planned dosing up to Week 4 = [Time on study treatment (days) up to Week 4] / 7
  - Time on study treatment (days) up to Week 4
    = [Week 4 Dosing Date] – [Treatment Start date] + 1 day
    If Week 4 dosing date is missing (i.e., withdrawal before Week 4), treatment stop date will be used instead.
- For compliance during the primary efficacy evaluation period, following formulae will be used:

  Total # of actual dosing during the EP = Sum of (Number of dosing records with container number on and after Week 40 visit).

  Total # of planned dosing during the EP = [Time on study treatment (days) during the EP] / 7
  - Time on study treatment (days) during the EP
    = [Treatment Stop Date] – [Week 40 Dosing Date] + 1 day
    If Week 40 dosing date is missing (i.e., withdrawal before Week 40), the compliance will not be calculated.

## 15.6.3. Efficacy

**Hgb Values**

**Central Laboratory and HemoCue Hgb Values**

- For reporting purposes, central laboratory Hgb values will be used, unless otherwise specified. However, if a central laboratory Hgb value is missing, a corresponding non-missing HemoCue Hgb value, which is associated with the identical subject number and visit, will be used.

**Evaluable Hgb Values**

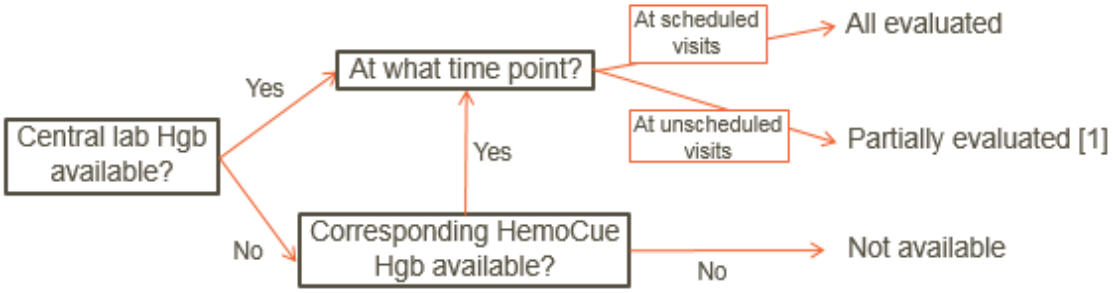
- It will be used for reporting sensitivity analysis results and Hgb listings.
- Evaluable Hgb values will be based on on-therapy central laboratory and/or HemoCue Hgb values that are not taken within the 8 weeks following a transfusion or within the 8 weeks following a non-

**Hgb Values**

randomized ESA medication (except protocol-specified ESA treatment in screening period).
If an Hgb record meets at least one following criteria, the Hgb record will be regarded as non-evaluable.

- Blood Product Administration Date < Date ≤ Blood Product Administration Date + 56 (days)
- ESA Start Date < Date of Hgb data ≤ ESA Stop Date + 56 (days)

**Flowchart for Hgb Analyses**




- This flowchart will be applicable, unless otherwise specified
- Basically, scheduled visits between Day 1 and Week 52 will be applicable to this flowchart, but analyses including by-visit summaries may include other schedued visits (ie. screening and follow-up visit).

[1] Regarding partially evaluated Hgb values, the following summaries of Hgb will include unscheduled visits:

- Summary of Time (weeks and %) within Hgb target range during the primary efficacy evaluation period
- Summary of Number (%) of subjects who have an Hgb level of less than 7.5 g/dL
- Summary of Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes

**Hgb Increase of More than 2.0 g/dL over Any 4 Weeks**

- For this reporting purpose, Hgb values from central laboratory will be used as previously described.
- A subject who has at least one record with Hgb increase of more than 2.0 g/dL over any 4 weeks will be counted and all episodes will be listed.
- Hgb increase will be calculated for scheduled visits between Day 1 and Week 52 if available (i.e. Week 4 Hgb - Day 1 Hgb, Week 8 Hgb - Week 4 Hgb, ...)

Illustration of calculation (example in case of Week 12 missing, until Week 24 visit)

| Hgb (g/dL) | Lab Date | Study Day | Visit | Hgb increase |
|---|---|---|---|---|
| 9.1 | 01FEB2017 | 1 | Day 1 | Not calculated |
| 9.8 | 02MAR2017 | 30 | Week 4 | 0.7 |
| 11.9 | 02APR2017 | 61 | Week 8 | 2.1 |
| 12.6 | 07JUN2017 | 127 | Week 16 | Not calculated |
| 12.7 | 08JUL2017 | 158 | Week 20 | 0.1 |
| 12.3 | 02AUG2017 | 183 | Week 24 | -0.4 |

- Odds ratio and its 95% CI will be obtained using the same statistical model described in Section 7.2.5.
- When the odds ratio is undefined, it will not be presented.

**Scatter Plot of Hgb Assessments: Central Laboratory vs. HemoCue**

- All available pairs of Hgb (i.e. non-missing values in both from central laboratory and from the

**Hgb Values**

corresponding HemoCue measurement) will be used, regardless of treatment groups and visits. The figure will include a linear regression line with 95% CI band, R-squared, and Pearson's correlation coefficient.

**Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Covariates of Interest**

- The following scatter plot figures will be produced for overall:
  - Change from Baseline in Hgb at Week 4 vs. Body Weight at Screening
  - Change from Baseline in Hgb at Week 4 vs. Baseline Hgb
  - Change from Baseline in Hgb at Week 4 vs. Prior ESA Dose
- Vertical axis will indicate the change from baseline in Hgb (g/dL) at Week 4, horizontal axis will indicate the covariates of interest; dry body weight (kg) at screening, baseline Hgb (g/dL), or prior ESA dose (IU/week).
- Only individual plots will be provided unlike the scatter plot of Hgb assessments.

**Scatter Plot of Mean Dose During Week 40 to 52 vs. Covariates of Interest**

- The following scatter plot figures will be produced for overall:
  - Mean Dose during Week 40 to 52 vs. Body Weight at Screening
  - Mean Dose during Week 40 to 52 vs. Baseline Hgb
  - Mean Dose during Week 40 to 52 vs. Prior ESA dose
- Vertical axis will indicate the mean dose (mg), horizontal axis will indicate the covariates of interest; dry body weight (kg) at screening, baseline Hgb (g/dL), or prior ESA dose (IU/week).
- Mean dose will be calculated from the arithmetic mean using the latest 3 exposure records (i.e., for completers Week 40, 44, and 48), which are based on the actual doses and the scheduled visits.
- Subjects who has less than 3 dosing records will be excluded from the figures.
- Mean dose during Week 40 to 52 will also be summarized and listed.
- Only individual plots will be provided unlike the scatter plot of Hgb assessments.

**Time in Target Range**

**Time (weeks and percentage) in Target Range During the Primary Efficacy Evaluation Period**

- For this reporting purpose, on-therapy Hgb values of central laboratory during Week 40 to Week 52, including unscheduled visits, will be used. However, if a central laboratory Hgb value is missing, a corresponding non-missing HemoCue Hgb value, which is associated with the identical subject number and visit, will be used.
- Number of days that a subject's Hgb is within the analysis range of 10.0-12.0 g/dL inclusive between Week 40 and 52, including any on-therapy Hgb values that were taken during this time period. Linear interpolation is used to estimate Hgb between visits, if a subject has an intermittent missing value (Rosendaal, 1993).

Illustration of calculation

| Hgb (g/dL) | Lab Date | Visit | Ref Day | Hgb Shift | Total shift (%) within range | Time in range (weeks) |
|---|---|---|---|---|---|---|
| 9.9 | 01AUG2017 | Week 40 | 0 | NC | NC | NC |
| 10.8 | 01SEP2017 | Week 44 | 31 | 0.9 (=10.8-9.9) | total shift: 0.8 0.8/0.9=88.89% | (31-0)*0.8889/7 =27.56/7 (weeks) |
| missing | 01OCT2017 | Week 48 | 61 | NA | NA | NC |

**Time in Target Range**

| | | | | | | |
|---|---|---|---|---|---|---|
| 12.4 | 01NOV2017 | Week 52 | 92 | 1.6 (=12.4-10.8) | total shift: 1.2 1.2/1.6=75% | (92-31)*0.75/7 =45.75/7 (weeks) |
| Overall time in the target range = (27.56 + 45.75)/7 = 73.31/7 = 10.47 (weeks)<br>Percent time in the target range = 10.47/(92/7) = 79.68% | | | | | | |

NC: Not calculated, NA: Not available

- Hgb laboratory assessment date will be used to calculate a duration (Ref Day) between assessments.
  - Duration between assessments = [Hgb lab date] – [Hgb lab date of the previous measurement]

  If a subject was withdrawn from the treatment before Week 40 so that the duration between Week 40 to Week 52 cannot be calculated, the subject will not be included in a summary.

  Basically, the duration should be [Week 52 lab date – Week 40 lab date] unless a subject was withdrawn before Week 52. In this case, treatment stop date will be used instead of Week 52.
- As an above example, suppose a subject has Hgb reading 9.9 g/dL on August 1st (Week 40), then reading if 10.8 g/dL on September 1st. The assumption is made that the week, between these scheduled assessments the subjects Hgb increases from 9.9 to 10.8 g/dL in a linear manner. The following steps are taken to calculate the time (days) the subject's Hgb was within target range (10.0 to 12.0 g/dL).
  1. Calculate amount of Hgb shift (9.9 to 10.8 = 0.9 shift) and Hgb shift within range (0.8 out of shift is within range of 10.0 – 12.0)
  2. Calculate percent of total shift (%) within range (0.8/0.9 = 88.89%)
  3. Estimate the number of weeks since last visit within range (88.89% x duration between assessments = 88.89% x 31/7 weeks = 3.94 weeks within range)

  If a subject has an intermittent missing Hgb assessment (on-therapy), the linear interpolation will be done by ignoring missing Hgb data.

  To calculate overall time (weeks) in Hgb target range, the total days in range for each time period are added together and divided by 7.

  The % of time in range between Week 40 and Week 52 for a subject will be calculated by calculating overall time (weeks) within range and dividing by the total duration (weeks) between Week 40 to Week 52. Similarly, the % of time above Hgb target range and % of time above and below Hgb target range will be calculated,

**Dose Adjustment**

**Dose Adjustment Algorithm**

- Note that dose adjustment summaries will be produced only for daprodustat group.
- Dose adjustment algorithm will be based on HemoCue Hgb values at scheduled visits. No Hgb values measured at unscheduled visits will be included.
- Dose will be derived from actual dose associated with container numbers.
- The following table illustrates the algorithm using analysis flags as below:
  - (FL_A): Adjustment flags will be counted if actual dose is changed from that of the previous visit.
  - (FL_B): Over 13.0 g/dL flags will be counted if HemoCue Hgb >13.0 g/dL is observed.
  - (FL_C): Interruption flags will be counted if actual dose is zero.

  Treatment durations will be calculated based on the following formula:
  - Duration (days) = Treatment Stop Date – Treatment Start Date + 1 day

**Dose Adjustment**

Illustration of dose adjustment algorithm (24-week case)

| Visit (Example) | Treatment Start date/ Stop date | Duration | HemoCue Hgb (g/dL) | Dose (mg) | (FL_A) Adjust-ment | (FL_B) Over 13 g/dL | (FL_C) Inter-ruption |
|---|---|---|---|---|---|---|---|
| Day 1 | 01FEB2017/ 01MAR2017 | 29 | 11.1 | 4 | N | N | N |
| Week 4 | 02MAR2017/ 15MAR2017 | 14 | 11.4 | 4 | N | N | N |
| Week 8 | 02APR2017/ 01MAY2017 | 30 | 11.8 | 2 | Y | N | N |
| Week 12 | 02MAY2017/ 01JUN2017 | 31 | 13.4 | 0 | Y | Y | Y |
| Week 16 | 02JUN2017/ 01JUL2017 | 30 | 12.6 | 0 | N | N | Y |
| Week 20 | 02JUL2017/ 01AUG2017 | 31 | 11.7 | 1 | Y | N | N |
| Week 24 | - | - | 12.3 | - | - | N | - |

For programmers, note that the flags are for the purposed of illustration, and are not intended to imply any type of requirement.

For summary tables, further details are described within the next items;

- 'Duration (days) of treatment interruption due to Hgb >13.0 g/dL'
- 'Dose adjustment'

**Duration (days) of Treatment Interruption due to Hgb >13.0 g/dL**

Calculation of duration of treatment interruption due to Hgb >13.0 g/dL will be based on the dose adjustment algorithm defined in the protocol.

- Duration (days) = Sum of $[Duration]_n$

  where

  $[Duration]_n$ represents exposure duration at visit n to meet the following.

  - Treatment interruption is made due to HemoCue Hgb over 13.0 g/dL and consecutive until treatment is resumed.

  In the above illustration, duration = 61 (days), from Week 12 and 16 visit records.

**Dose Adjustment**

Calculation of frequency of dose adjustment will be based on the above algorithm.

- Number of dose adjustment will be counted for each subject as follows:
  - Counts of adjustment flag = 'Y'

## 15.6.4. Safety

| Adverse Events |
|---|
| **AE up to Week 4** |
| Cut-off date of Week 4 for individuals will be based on Week 4 visit date which is associated with the earliest date throughout Week 4 records (i.e., SDTM.SV.STDTC). |
| **AEs of Special Interest (AESIs)** |
| AESIs are manually-selected at patient-level (i.e. following case-by-case review by members of the SRT including representatives from the local Japan team) and not at preferred term level.<br><br>AESI categories are classified as follows:<br>• Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis<br>• Death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access<br>• Cardiomyopathy<br>• Pulmonary artery hypertension<br>• Cancer-related mortality and tumor progression and recurrence<br>• Esophageal and gastric erosions<br>• Proliferative retinopathy, macular edema, choroidal neovascularization<br>• Exacerbation of rheumatoid arthritis<br><br>Thrombosis and tissue ischemia events will be considered to be secondary to excessive erythropoiesis if during the window of [AE start date – 30 days, AE start date +15 days] any one of the following 3 events occurs:<br>• Any Hgb value > 13 g/dL<br>• Hgb increase > 2 g/dL over 2 weeks<br>• Hgb increase > 4 g/dL over 4 weeks<br>Note: Thrombosis and tissue ischemia events that need to be considered against the above 3 Hgb events will be identified by the case-by-case review.<br>Note: HemoCue and central laboratory values will be considered separately. Unscheduled Hgb values will also be used in the assessment of secondary to excessive erythropoiesis if available.<br>Note: For the second two bullets, all Hgb values that have an assessment date within the window of [AE start date – 58 days, AE start date + 15 days] will be considered. |

| Laboratory Parameters |
|---|
| **Imputation** |
| • 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.<br>o Example 1: 2 Significant Digits = '< x' becomes x – 0.01<br>o Example 2: 1 Significant Digit = '> x' becomes x + 0.1<br>o Example 3: 0 Significant Digits = '< x' becomes x – 1<br>• The following laboratory values will not be applicable for this imputation:<br>o Hgb, serum iron, serum ferritin, serum transferrin, TIBC, UIBC, TSAT, and Hepcidin |

| Laboratory Parameters |
|---|
| • The default convention for reporting of clinical laboratory units will be the international system of units (SI units). |
| **Lipid Parameters** |
| • LDL/HDL cholesterol ratio will be derived from the following equation.<br>o LDL/HDL cholesterol ratio = LDL cholesterol (mmol/L) / HDL cholesterol (mmol/L) |
| **Log-Transformation** |
| • Lipid parameters will be log-transformed and the percent change from baseline will be reported. Based on literature review the distributions of hepcidin and TSAT are skewed and require a log-transformation. Other endpoints may also be log-transformed if deemed appropriate (See Section 5.2). |
| **Others** |
| • For summaries of the absolute neutrophils and lymphocytes count, PCI cutoffs will be calculated by multiplying the percentages given for each subject by the absolute white blood count. |

### 15.6.5. Pharmacokinetic

| General |
|---|
| **Dose Level** |
| • Summaries by dose level and used tablet strength will be based on an actual dose associated with a container number. (See Section 15.6.2). Tablet strength is defined as follows:<br>o Actual dose = 1 mg → 1 mg tablet strength<br>o Actual dose = 2 mg → 2 mg tablet strength<br>o Actual dose = 4 mg → 4 mg tablet strength<br>o Actual dose = 6 mg → 6 mg tablet strength<br>o Actual dose = 8 mg → 4 mg tablet strength<br>o Actual dose = 12 mg → 6 mg tablet strength<br>o Actual dose = 18 mg → 6 mg tablet strength<br>o Actual dose = 24 mg → 6 mg tablet strength<br>• Dose level which is actually provided to subjects will be derived from an actual dose of the visit (including unscheduled visit) which meets the following:<br>o Treatment Start Date ≤ Date of last dose taken prior to PK sampling ≤ Treatment Stop Date |
| **Others** |
| • Dose normalized PK parameters will be derived from [PK parameters / actual dose (mg)].<br>• In aggregated analyses, data collected in Week 12 and Week 24 will be aggregated.<br>• For the PK parameters calculation, the concentration at 0 hr will be set to 0 and assign zero to NQ values.<br>• Individual's PK parameters calculated less than 4-time point concentrations or any time deviated (beyond ± 30 min of scheduled timepoints) concentrations will be omitted from summaries and figures, but presented in a listing. |

### 15.6.6. Exploratory Endpoint

| Iron Endpoints |
|---|
| **Subjects Who Used IV and Oral Iron** |
| • Number of subjects who used IV and/or oral iron will be summarized<br>• Subjects who used IV and oral iron will be defined as follows: |

- Subjects with on-therapy IV and/or oral iron medication collected in a specific eCRF form (CONMEDS-IRON).
- Subjects who used Riona (GSK drug code=00752601) will also be regarded as baseline iron use subjects in a subgroup analysis and also counted for oral iron use in this summary.
- Regarding oral iron use, the number of subjects who used Riona and other than Riona will also be counted respectively.

**IV Iron Dose by Quarter**

- Records of on-therapy iron medication will be used for the following calculations
- Monthly average IV iron during the treatment period = Total IV iron dose (mg) during the treatment period / (duration in the treatment period (days) / 30.4375 days)
- Monthly average IV iron by quarter = Total IV iron dose during each quarter (mg) / (duration in a quarter (days) / 30.4375 days).
- Total IV iron dose during each quarter (mg) will be carried with the following formula using each record. Duration will be derived from iron medication start/stop date:
  - Total IV iron dose during each quarter (mg) = (iron dose$_1$*frequency$_1$*duration$_1$) + ... + (iron dose$_n$*frequency$_n$*duration$_n$)
  - Duration (days) = (stop date$_1$ - start date$_1$ + 1) + ... + (stop date$_n$ - start date$_n$ + 1)

  Frequency is defined as follows:
  - If subject receives iron dose with once daily → frequency = 1
  - If subject receives iron dose with BID → frequency = 2
  - If subject receives iron dose with TID → frequency = 3
  - If subject receives iron dose with QID → frequency = 4
  - If subject receives iron dose with every x week → frequency = 1/(7*x)If subject receives iron dose with every x week → frequency = 1/(7*x)
  - If subject receives iron dose with x times per week → frequency = x/7
  - If subject receives iron dose with x times per month → frequency = 1/(30.4375*x)

  Total IV iron during the treatment period will be carried in the same manner.
- Quarters will be defined as follows:

| | **Start Date** | **End Date** |
|---|---|---|
| Treatment period | Randomization Date | Treatment Stop Date |
| Quarter 1 | Randomization Date | Treatment Start Date at Week 12 - 1 day |
| Quarter 2 | Treatment Start Date at Week 12 | Treatment Start Date at Week 24 - 1 day |
| Quarter 3 | Treatment Start Date at Week 24 | Treatment Start Date at Week 40 - 1 day |
| Quarter 4[1] | Treatment Start Date at Week 40 | Treatment Stop Date |

**NOTES:**

- A Quarter End Date will be replaced with treatment stop date (see Section 15.6.1) when treatment start date at Week 12, 24, or 40 is missing (i.e. early withdrawal before Week 12, 24, or 40). In this case, the subsequent Quarter(s) will not be generated.
- Iron medication start/stop date will be defined newly for the analyses in addition to Quarter start/end date to derive amount of iron dose within a specified Quarter (analysis flags may be used to judge which quarters the iron records should belong to).

[1] Quarter 4 represents the primary efficacy evaluation period.

- If iron medication start date < randomization date, the iron medication start date will be replaced with randomization date for the analysis.
- If iron medication end date > Treatment Stop Date, the iron medication stop date will be replaced with

Treatment Stop Date for the analysis.

- If iron medication start date and stop date step over quarters, the iron medication record will be divided; the end date in the former record and the start date in the latter record will be replaced with the quarter end date and the next quarter start date, respectively.

| Quarter State of Iron Medication | Definition |
|---|---|
| Quarter n<br>(n=1,2,3, & 4) | Quarter n Start Date ≤ Iron Medication Start Date<br>and<br>Iron Medication End Date ≤ Quarter n End Date |
| Quarter n & n+1 (will be divided as described above)<br>(n=1,2, & 3) | Iron Medication Start Date ≤ Quarter n End Date<br>and<br>Quarter [n+1] Start Date ≤ Iron Medication Stop Date |

**NOTES:**

- Only on-therapy iron medication will be evaluated.
- If no start or stop date is recorded on iron medication, the date will be replaced with Randomization Date or Treatment Stop Date, respectively.

**TIBC**

- TIBC will be calculated automatically by the central laboratory using:
  - TIBC = UIBC + total iron

**TSAT**

- Based on literature review the distribution of TSAT is skewed and requires a log-transformation. Calculation of statistics on log-transformed data are described in Section 5.2.
- TSAT will be calculated automatically by the central laboratory using:
  - TSAT = 100 * (Serum Iron/TIBC)

**Hepcidin**

- Based on literature review the distribution of hepcidin is skewed and requires a log-transformation. Calculation of statistics on log-transformed data are described in Section 5.2

**Iron Use Subgroup**

- Subjects who used Riona will also be regarded as baseline iron use subjects in a subgroup analysis.
- The baseline iron use will be defined as follows:
  - A subject takes a pre-therapy iron medication and/or a pre-therapy medication of the GSK drug code = 00752601 (FERRIC CITRATE; Riona).

## 15.6.7. Patient Reported Outcome

The original version of instructions and questionnaire items for the study are written in Japanese. In displays, the items will be translated into English version (can be found at http://www.qualitymetric.com for SF-36v2, EuroQol products for EQ-5D-5L).

**SF-36v2**

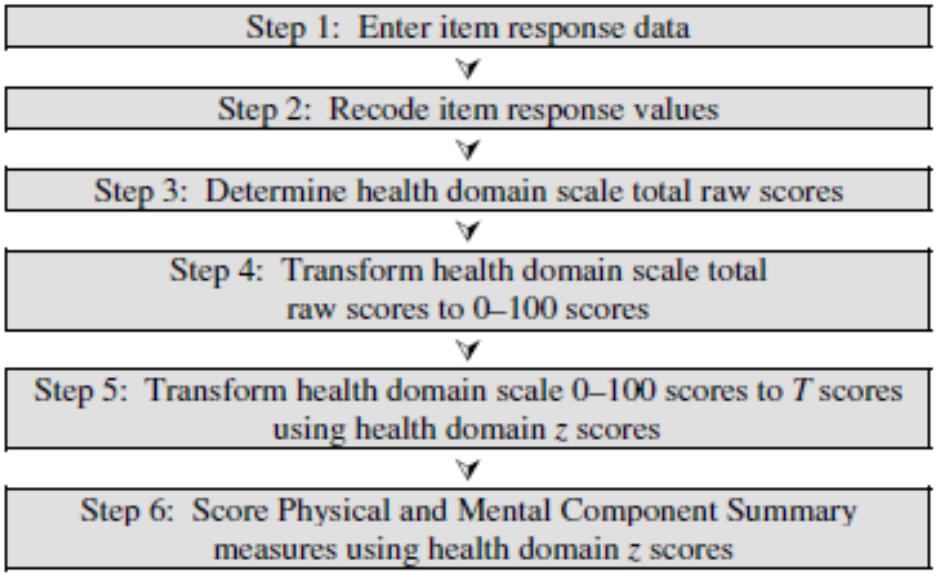
**Overview of Scoring Algorithm**

- Scores will be calculated by Optum PRO CoRE. Refer to "User's Manual for the SF-36v2 Health Survey Third Edition, 2011" for further details.
- Three sets of summary scores will be calculated based on responses to each item on the SF-36:
  - Physical Component Summary (PCS) score
  - Mental Component Summary (MCS) score

**SF-36v2**

- Domain scores based on the following eight domains
  - Physical Functioning
  - Role-Physical (i.e., role limitations due to physical health)
  - Bodily Pain
  - General Health
  - Vitality
  - Social Functioning
  - Role-Emotional (i.e., role limitations due to mental/emotional health)
  - Mental Health

The scoring process is summarized in the following figure (Refer to Figure 5.1 in User's Manual for the SF-36v2 Health Survey Third Edition, 2011).




Before submitting an SF-36v2 response set for scoring, the following points will be ensured.

- SF-36v2 Acute is being used for this study.
- Missing values will be estimated using the *Maximum Data Recovery Mode*.
- 2009 U.S. general population will be set for scoring.

**EQ-5D-5L / EQ-VAS**

**Scoring Algorithm**

- EQ-VAS scores will be summarized based on the numbers participants have written in the box.
- Index values will be calculated based on responses to each item on the EQ-5D-5L:
  - Mobility (level 1 to 5; e.g., level 1 = "I have no problems in waling about")
  - Self-Care (level 1 to 5; e.g., level 1 = "I have no problems washing or dressing myself")
  - Usual Activities (level 1 to 5; e.g., level 1 = "I have no problems doing my usual activities")
  - Pain / Discomfort (level 1 to 5; e.g., level 1 = "I have no pain or discomfort")
  - Anxiety / Depression (level 1 to 5; e.g., level 1 = "I am not anxious or depressed")
- Based on the EQ-5D-5L profile, the index value will be carried out using "EQ-5D-5L_Crosswalk_Index_Value_Calculator.v2" (can be downloaded from the EuroQol website). Japan specific value sets will be used.

# 15.7. Appendix 7: Reporting Standards for Missing Data

## 15.7.1. Premature Withdrawals

| Element | Reporting Detail |
|---|---|
| General | • Subject study completion (i.e. as specified in the protocol) was defined as follows: A completed subject is one who has completed all periods of the study including the follow-up visit.<br>• Withdrawn subjects were not replaced in the study.<br>• 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. |

## 15.7.2. 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:<br>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.<br>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, if applicable. |

### 15.7.2.1. Handling of Missing and Partial Dates

| Element | Reporting Detail |
|---|---|
| General | • Partial dates will be displayed as captured in subject listing displays. |
| Concomitant Medications/ Medical History | • Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:<br>o When only the start year is provided, a '01' will be used for the day and 'Jan' will be used for the month<br>o When only the start month and year is provided, a ‘01’ will be used for the day.<br>o When only the stop year is provided, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.<br>o When only the stop month and year is provided, a ‘28/29/30/31’ will be used for the day (dependent on the month and year).<br>• The recorded partial date will be displayed in listings. |
| Adverse Events | • The CRF does not allow for the possibility of partial dates. |

## 15.8. Appendix 8: Values of Potential Clinical Importance

### 15.8.1. Laboratory Values

| Chemistry | | | |
|---|---|---|---|
| **Laboratory Parameter** | **Units** | **Clinical Concern Range** | |
| | | **Low Flag** | **High Flag** |
| Albumin (serum) | g/L | < 30 g/L | >55 g/L |
| Aspartate Aminotransferase | IU/L | N/A | ≥ 3x ULRR |
| Alanine Aminotransferase | IU/L | N/A | ≥ 3x ULRR |
| Bilirubin (total) | μmol/L | N/A | ≥ 2x ULRR |
| Calcium (albumin-adjusted) | mmol/L | < 1.87 mmol/L | > 2.56 mmol/L |
| Bicarbonate (total) | mmol/L | < 20 mmol/L | > 32 mmol/L |
| Inorganic phosphate | mmol/L | < 0.81 mmol/L | > 1.77 mmol/L |
| Potassium (serum) | mmol/L | > 0.5 mmol/L below LLRR | > 1.0 mmol/L above ULRR |
| Sodium (serum) | mmol/L | < 130 mmol/L | > 150 mmol/L |

| Hemotology | | | |
|---|---|---|---|
| **Laboratory Parameter** | **Units** | **Clinical Concern Range** | |
| | | **Low Flag** | **High Flag** |
| Platelet Count | GI/L | < 80 GI/L | > 500 GI/L |
| *WBC Count* | GI/L | > 1x LLRR | >5x ULRR |
| Neutrophils | GI/L | < 1.0 GI/L | N/A |
| Lymphocytes | GI/L | < 0.5 GI/L | N/A |

| Iron Parameters | | | |
|---|---|---|---|
| **Laboratory Parameter** | **Units** | **Clinical Concern Range** | |
| | | **Low Flag** | **High Flag** |
| Ferritin | μg/L | < 100 μg/L | > 1200 μg/L |
| TSAT | % | <15 % | >40 % |

| Other Parameters | | | |
|---|---|---|---|
| **Laboratory Parameter** | **Units** | **Clinical Concern Range** | |
| | | **Low Flag** | **High Flag** |
| iPTH | ng/L | N/A | > 9x ULRR |

### 15.8.2. Vital Signs

| Vital Sign Parameter (Absolute) | Units | Clinical Concern Range | |
|---|---|---|---|
| | | Lower | Upper |
| Systolic Blood Pressure | mmHg | < 85 mmHg | > 180 mmHg |
| Diastolic Blood Pressure | mmHg | < 45 mmHg | > 110 mmHg |
| Heart Rate | beats/min | < 40 beats/min | > 110 beats/min |

# 15.9. Appendix 9: Abbreviations & Trade Marks

## 15.9.1. Abbreviations

| Abbreviation | Description |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| AIC | Akaike's Information Criteria |
| A&R | Analysis and Reporting |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | Confidence Interval |
| CPMS | Clinical Pharmacology Modelling & Simulation |
| CS | Clinical Statistics |
| CSR | Clinical Study Report |
| CTR | Clinical Trial Register |
| $CV_b$ / $CV_w$ | Coefficient of Variation (Between) / Coefficient of Variation (Within) |
| DBF | Database Freeze |
| DBR | Database Release |
| DOB | Date of Birth |
| DP | Decimal Places |
| eCRF | Electronic Case Record Form |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Clinical Results Disclosure Requirements |
| GSK | GlaxoSmithKline |
| Hgb | Hemoglobin |
| HRQoL | Health-Related Quality of Life |
| IA | Interim Analysis |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IDSL | Integrated Data Standards Library |
| IMMS | International Modules Management System |
| IP | Investigational Product |
| ITT | Intent-To-Treat |
| MMRM | Mixed Model Repeated Measures |
| PCI | Potential Clinical Importance |
| PD | Pharmacodynamic |
| PDMP | Protocol Deviation Management Plan |
| PK | Pharmacokinetic |
| PP | Per Protocol |
| PopPK | Population PK |
| QC | Quality Control |
| QTcF | Frederica's QT Interval Corrected for Heart Rate |
| QTcB | Bazett's QT Interval Corrected for Heart Rate |
| RAP | Reporting & Analysis Plan |
| RAMOS | Randomization & Medication Ordering System |
| SAC | Statistical Analysis Complete |
| SDSP | Study Data Standardization Plan |
| SDTM | Study Data Tabulation Model |

| Abbreviation | Description |
|---|---|
| SOP | Standard Operation Procedure |
| SRT | Safety Review Team |
| TA | Therapeutic Area |
| TFL | Tables, Figures & Listings |
| TIBC | Total Iron Binding Capacity |
| TSAT | Transferrin Saturation |
| UIBC | Unsaturated Iron Binding Capacity |
| UN | Unstructured |
| VAS | Visual Analog Scale |
| WBC | Whole Blood Cell |

### 15.9.2. Trademarks

| Trademarks of the GlaxoSmithKline Group of Companies |
|---|
| NONE |

| Trademarks not owned by the GlaxoSmithKline Group of Companies |
|---|
| HemoCue |
| Optum PRO CoRE |
| P-TOL |
| Riona |
| SAS |
| S-Plus |
| WinNonlin |

# 15.10. Appendix 10: List of Data Displays

## 15.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

| Section | Tables | Figures |
|---|---|---|
| Study Population | 1.1 to 1.27 | Not applicable |
| Efficacy | 2.1 to 2.58 | 2.1 to 2.43 |
| Safety | 3.1 to 3.50 | 3.1 to 3.2 |
| Patient Reported Outcome | 4.1 to 4.10 | Not applicable |
| Pharmacokinetic | 5.1 to 5.8 | 5.1 to 5.15 |
| **Section** | **Listings** | |
| ICH Listings | 1 to 33 | |
| Other Listings | 34 to 71 | |
| Patient Profile Listings | 72 to 81 | |

## 15.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

| Section | Figure | Table | Listing |
|---|---|---|---|
| Study Population | POP_Fn | POP_Tn | POP_Ln |
| Efficacy | EFF_Fn | EFF_Tn | EFF_Ln |
| Safety | SAFE_Fn | SAFE_Tn | SAFE_Ln |
| Patient Reported Outcome | PRO_Fn | PRO_Tn | PRO_Ln |
| Pharmacokinetic | PK_Fn | PK_Tn | PK_Ln |

**NOTES:**

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

### 15.10.3. Table of Contents for Headline Results Deliverable

The numbering of displays will match with that of final statistical analysis.

| Headline Results Analysis | | | | |
|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** |
| **Headline Tables** | | | | |
| **Study Population** | | | | |
| 1.1 | Randomized | ES8 | Summary of Subject Status and Reason for Study Withdrawal | |
| 1.10 | Safety | DM1 | Summary of Demographic Characteristics - Safety | |
| **Efficacy** | | | | |
| 2.1 | ITT | EFF_T1 | Summary of Hgb (g/dL) by Visit | |
| 2.2 | ITT | EFF_T1 | Summary of Change from Baseline in Hgb (g/dL) by Visit | |
| 2.3 | mITT | EFF_T2 | Summary of Mean Hgb (g/dL) Based on Observed Cases During the Primary Efficacy Evaluation Period | |
| 2.4 | ITT | EFF_T3 | Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – ITT | |
| 2.15 | mITT | EFF_T5 | Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period - mITT | |
| **Safety** | | | | |
| 3.1 | Safety | AE1 | Summary of On-Therapy AEs by SOC and PT | |
| 3.8 | Safety | AE1 | Summary of On-Therapy Drug-Related AEs by SOC and PT | |
| 3.17 | Safety | AE1 | Summary of On-Therapy Serious AEs | |
| 3.21 | Safety | AE1 | Summary of On-Therapy AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT | |
| 3.22 | Safety | SAFE_T2 | Summary of On-Therapy AEs of Special Interest | |

| Headline Results Analysis | | | | |
|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** |
| 3.48 | Safety | SAFE_T6 | Summary of Ophthalmologic Exams at Screening | |
| 3.49 | Safety | SAFE_T7 | Summary of On-Therapy Ophthalmologic Exams | |
| **Headline Listings** | | | | |
| 30 | Safety | SAFE_L1 | Listing of Adverse Events of Special Interest | |
| 64 | Safety | SAFE_L2 | Listing of Ophthalmologic Exams | |

## 15.10.4. Table of Contents for SAC Deliverable

### 15.10.4.1. Study Population Tables

| Study Population Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Subject's Disposition** | | | | | |
| 1.1. | Randomized | ES8 | Summary of Subject Status and Reason for Study Withdrawal | ICH E3, GSK CTR, FDAAA, EudraCT | Y |
| 1.2. | Safety | SD1 | Summary of Treatment Status and Reasons for Discontinuation of Study Treatment | ICH E3 | Y |
| 1.3. | All Screening | ES6 | Summary of Screening Status and Reasons for Screen Failure | Journal Requirements | Y |
| 1.4. | Enrolled | NS1 | Summary of Subjects Enrolled by Country and Site ID | EudraCT/clinical operations | Y |
| **Protocol Deviations** | | | | | |
| 1.5. | Randomized | DV1 | Summary of Important Protocol Deviations | ICH E3 | Y |
| 1.6. | Randomized | IE1 | Summary of Inclusion/Exclusion Criteria Deviations | ICH E3 | Y |
| **Population Analyzed** | | | | | |
| 1.7. | Randomized | SP1 | Summary of Study Populations | IDSL | Y |
| 1.8. | mITT | SP2 | Summary of Exclusions from Per Protocol Population | IDSL | Y |
| **Demographic and Baseline Characteristics** | | | | | |
| 1.9. | ITT | DM1 | Summary of Demographic Characteristics - ITT | ICH E3, GSK CTR, FDAAA, EudraCT | Y |
| 1.10. | Safety | DM1 | Summary of Demographic Characteristics – Safety | ICH E3, GSK CTR, FDAAA, EudraCT | Y |
| 1.11. | ITT | POP_T1 | Summary of Prior ESA – ITT | | Y |
| 1.12. | Safety | POP_T1 | Summary of Prior ESA - Safety | | Y |
| 1.13. | Enrolled | DM11 | Summary of Age Ranges | EudraCT | Y |
| 1.14. | Safety | DM5 | Summary of Race and Racial Combinations | ICH E3, GSK CTR, FDAAA, EudraCT | Y |

| Study Population Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 1.15. | Safety | FH1 | Summary of Family History for CV Risk Factors | IDSL | Y |
| 1.16. | Safety | SU1 | Summary of Substance Use (History of Tobacco Use, Alcohol Intake) | IDSL | Y |
| **Dialysis** | | | | | |
| 1.17. | Safety | POP_T2 | Summary of Baseline Mode of Dialysis | | Y |
| 1.18. | Safety | POP_T3 | Summary of Baseline Mode of Vascular Access | | Y |
| **Medical Conditions and Concomitant Medications** | | | | | |
| 1.19. | Safety | MH4 | Summary of Current Medical Conditions | ICH E3 | Y |
| 1.20. | Safety | MH4 | Summary of Past Medical Conditions | ICH E3 | Y |
| 1.21. | Safety | CM1 | Summary of Concomitant Medications (Pre-Therapy) | ICH E3 | Y |
| 1.22. | Safety | CM1 | Summary of Concomitant Medications (On-Therapy) | ICH E3 | Y |
| 1.23. | Safety | CM1 | Summary of Concomitant Medications (Post-Therapy) | ICH E3 | Y |
| 1.24. | Safety | CM1 | Summary of Other Concomitant Medications (On-Therapy) | | Y |
| 1.25. | Safety | POP_T4 | Summary of Blood Products and Blood Supportive Care Products (On-Therapy) | | Y |
| **Exposure and Treatment Compliance** | | | | | |
| 1.26. | Safety | EX1 | Summary of Exposure to Study Treatment | | Y |
| 1.27. | Safety | POP_T5 | Summary of Treatment Compliance | | Y |

### 15.10.4.2. Efficacy Tables

| Efficacy: Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Hgb - General** | | | | | |
| 2.1. | ITT | EFF_T1 | Summary of Hgb (g/dL) by Visit | | Y |
| 2.2. | ITT | EFF_T1 | Summary of Change from Baseline in Hgb (g/dL) by Visit | | Y |
| **Mean Hgb based on observed Hgb During the Primary Efficacy Evaluation Period** | | | | | |
| 2.3. | mITT | EFF_T2 | Summary of Mean Hgb (g/dL) Based on Observed Cases During the Primary Efficacy Evaluation Period | | Y |
| **Primary Efficacy Analyses: Model based Mean Hgb During the Primary Efficacy Evaluation Period** | | | | | |
| 2.4. | ITT | EFF_T3 | Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – ITT | | Y |
| 2.5. | mITT | EFF_T3 | Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – mITT | | Y |
| 2.6. | PP | EFF_T3 | Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – PP | | Y |
| 2.7. | ITT | EFF_T3 | Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – Subgroup | | Y |
| **Sensitivity Analyses** | | | | | |
| 2.8. | ITT | EFF_T3 | Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using Evaluable Hgb | | Y |
| 2.9. | mITT | EFF_T3 | Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using ANCOVA – mITT | | Y |
| 2.10. | PP | EFF_T3 | Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using ANCOVA – PP | | Y |

| Efficacy: Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 2.11. | mITT | EFF_T3 | Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using ANCOVA - Subgroup | | Y |
| 2.12. | ITT | EFF_T4 | Tipping Point Summary for Non-Inferiority Test (Daprodustat vs Darbepoetin Alfa) – ITT | | Y |
| 2.13. | mITT | EFF_T4 | Tipping Point Summary for Non-Inferiority Test (Daprodustat vs Darbepoetin Alfa) – mITT | | Y |
| 2.14. | PP | EFF_T4 | Tipping Point Summary for Non-Inferiority Test (Daprodustat vs Darbepoetin Alfa) - PP | | Y |
| **Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period** | | | | | |
| 2.15. | mITT | EFF_T5 | Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period - mITT | | Y |
| 2.16. | PP | EFF_T5 | Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period – PP | | Y |
| 2.17. | ITT | EFF_T5 | Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period - ITT | | Y |
| 2.18. | mITT | EFF_T5 | Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period – Subgroup | | Y |
| **Hgb** | | | | | |
| 2.19. | ITT | EFF_T6 | Summary of Number (%) of Subjects by Hgb Change from Baseline Category at Week 4 - Daprodustat | | Y |
| 2.20. | ITT | EFF_T7 | Summary of Number (%) of Subjects with Hgb within Target Range by Visit | Screening visit will not be included | Y |
| 2.21. | ITT | EFF_T8 | Summary of Time (%) in Hgb Target Range During the Primary Efficacy Evaluation Period | | Y |

| Efficacy: Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 2.22. | ITT | EFF_T9 | Summary of Number (%) of Subjects Who Have Hgb Level of Less than 7.5 g/dL | | Y |
| 2.23. | ITT | EFF_T9 | Summary of Number (%) of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 weeks | | Y |
| 2.24. | ITT | EFF_T10 | Summary of Number (%) of Subjects Who Have Hgb Level of More than 13.0 g/dL and Number of Episodes | | Y |
| **Dose Adjustment** | | | | | |
| 2.25. | ITT | EFF_T11 | Summary of Dose by Visit | | Y |
| 2.26. | ITT | EFF_T12 | Summary of Number (%) of Subjects with Each Dose (/day) by Visit - Daprodustat | | Y |
| 2.27. | ITT | EFF_T13 | Summary of Number (%) of Subjects with Each Dose (/week) by Visit – Darbepoetin Alfa | | Y |
| 2.28. | ITT | EFF_T14 | Summary of Duration (days) of Treatment Interruption due to Hgb >13.0 g/dL – Daprodustat | | Y |
| 2.29. | ITT | EFF_T15 | Summary of Dose Adjustment – Daprodustat | | Y |
| **Iron Use During the Treatment Period** | | | | | |
| 2.30. | ITT | EFF_T16 | Summary of IV Iron Dose (mg) During the Treatment Period | | Y |
| 2.31. | ITT | EFF_T17 | Summary of Number (%) of Subjects with Iron Use During the Treatment Period | | Y |
| 2.32. | ITT | EFF_T16 | Summary of IV Iron Dose (mg) During the Treatment Period by Baseline Iron Use | | Y |
| 2.33. | ITT | EFF_T17 | Summary of Number (%) of Subjects with Iron Use During the Treatment Period by Baseline Iron Use | | Y |

| Efficacy: Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Iron Parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC)** | | | | | |
| 2.34. | ITT | LB1 | Summary of Ferritin (ug/L) by Visit | | Y |
| 2.35. | ITT | LB1 | Summary of Ferritin (ug/L) Change from Baseline by Visit | | Y |
| 2.36. | ITT | EFF_T18 | Summary of Transferrin Saturation (%) by Visit | | Y |
| 2.37. | ITT | EFF_T19 | Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit | | Y |
| 2.38. | ITT | EFF_T18 | Summary of Hepcidin (nmol/L) by Visit | | Y |
| 2.39. | ITT | EFF_T19 | Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit | | Y |
| 2.40. | ITT | LB1 | Summary of Serum Iron (umol/L) by Visit | | Y |
| 2.41. | ITT | LB1 | Summary of Serum Iron (umol/L) Change from Baseline by Visit | | Y |
| 2.42. | ITT | LB1 | Summary of Total Iron Binding Capacity (umol/L) by Visit | | Y |
| 2.43. | ITT | LB1 | Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit | | Y |
| 2.44. | ITT | LB1 | Summary of Ferritin (ug/L) by Visit by Baseline Iron Use | | Y |
| 2.45. | ITT | LB1 | Summary of Ferritin (ug/L) Change from Baseline by Visit by Baseline Iron Use | | Y |
| 2.46. | ITT | EFF_T18 | Summary of Transferrin Saturation (%) by Visit by Baseline Iron Use | | Y |
| 2.47. | ITT | EFF_T19 | Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit by Baseline Iron Use | | Y |
| 2.48. | ITT | EFF_T18 | Summary of Hepcidin (nmol/L) by Visit by Baseline Iron Use | | Y |
| 2.49. | ITT | EFF_T19 | Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit by Baseline Iron Use | | Y |

| Efficacy: Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 2.50. | ITT | LB1 | Summary of Serum Iron (umol/L) by Visit by Baseline Iron Use | | Y |
| 2.51. | ITT | LB1 | Summary of Serum Iron (umol/L) Change from Baseline by Visit by Baseline Iron Use | | Y |
| 2.52. | ITT | LB1 | Summary of Total Iron Binding Capacity (umol/L) by Visit by Baseline Iron Use | | Y |
| 2.53. | ITT | LB1 | Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit by Baseline Iron Use | | Y |
| **Hgb – Prior ESA subgroup** | | | | | |
| 2.54. | ITT | EFF_T1 | Summary of Hgb (g/dL) by Visit by Prior ESA Type, Prior ESA Dose, and ERI | repeat Table 2.1 for prior ESA type, prior ESA dose, and ERI subgroup | Y |
| 2.55. | ITT | EFF_T1 | Summary of Change from Baseline in Hgb (g/dL) by Prior ESA Type, Prior ESA Dose, and ERI | repeat Table 2.2 for prior ESA type, prior ESA dose, and ERI subgroup | Y |
| 2.56. | ITT | EFF_T5 | Summary of Number (%) of Subjects by Hgb Change from Baseline Category at Week 4 by Prior ESA Type, Prior ESA Dose, and ERI - Daprodustat | repeat Table 2.16 for prior ESA type, prior ESA dose, and ERI subgroup for daprodustat group | Y |
| 2.57. | ITT | EFF_T11 | Summary of Dose (/day) by Visit by Prior ESA Type, Prior ESA Dose, and ERI - Daprodustat | repeat Table 2.22 for prior ESA type, prior ESA dose, and ERI subgroup for daprodustat group | Y |
| 2.58. | ITT | EFF_T12 | Summary of Number (%) of Subjects with Each Dose (/day) by Visit by Prior ESA Type, Prior ESA Dose, and ERI – Daprodustat | repeat Table 2.23 for prior ESA type, prior ESA dose, and ERI subgroup for daprodustat group | Y |

### 15.10.4.3. Efficacy Figures

| Efficacy: Figures | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Raw Mean Hgb** | | | | | |
| 2.1. | ITT | EFF_F1 | Plot of Mean Change from Baseline in Hgb (g/dL) and 95% CIs over Time by Treatment | | Y |
| 2.2. | ITT | EFF_F1 | Plot of Mean Hgb (g/dL) and 95% CIs over Time by Treatment | | Y |
| **Model-Based Mean Hgb During the Primary Efficacy Evaluation Period** | | | | | |
| 2.3. | ITT | EFF_F2 | Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment – ITT | | Y |
| 2.4. | mITT | EFF_F2 | Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment - mITT | | Y |
| 2.5. | PP | EFF_F2 | Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment - PP | | Y |
| 2.6. | ITT | EFF_F2 | Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment – Evaluable Hgb | | Y |
| 2.7. | ITT | EFF_F3 | Forest Plot of Model-Adjusted Treatment Difference (Daprodustat vs Darbepoetin Alfa) for Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period by Subgroup – MMRM | | Y |
| 2.8. | mITT | EFF_F3 | Sensitivity Forest Plot of Model-Adjusted Treatment Difference (Daprodustat vs Darbepoetin Alfa) for Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period by Subgroup - ANCOVA | | Y |
| 2.9. | ITT | EFF_F4 | Tipping Point Display for Non-Inferiority Test (Daprodustat vs Darbepoetin Alfa) – ITT | | Y |

| Efficacy: Figures | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 2.10. | ITT | EFF_F4 | Tipping Point Display for Non-Inferiority Test (Daprodustat vs Darbepoetin Alfa) – mITT | | Y |
| 2.11. | ITT | EFF_F4 | Tipping Point Display for Non-Inferiority Test (Daprodustat vs Darbepoetin Alfa) - PP | | Y |
| **Number (%) of Subjects with Mean Hgb in Target Range During Primary Efficacy Evaluation Period** | | | | | |
| 2.12. | ITT | EFF_F5 | Forest Plot of Model-Adjusted Odds Ratio (Daprodustat / Darbepoetin Alfa) for Proportion of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period by Subgroup | | Y |
| **Hgb** | | | | | |
| 2.13. | ITT | EFF_F6 | Histogram of Number (%) of Subjects with Hgb within Target Range over Time | Like Fig. 2.7.6.2.3.1-2 in NESP CTD 2.7.6<br>Screening and follow-up visit will not be included | Y |
| 2.14. | ITT | EFF_F7 | Scatter Plot of Hgb Assessments: Central Laboratory vs. HemoCue | | Y |
| **Dose Adjustment** | | | | | |
| 2.15. | ITT | EFF_F8 | Histogram of Dose by Visit | | Y |
| 2.16. | ITT | EFF_F8 | Histogram of Dose by Visit by Prior ESA Type, Prior ESA Dose, and ERI | | Y |
| **Subject Listing** | | | | | |
| 2.17. | ITT | EFF_F9 | Subject Profiles of Hgb and Dose over Time | Provided based on active treatment group | Y |
| **Iron Parameters** | | | | | |
| 2.18. | ITT | EFF_F1 | Plot of Mean Ferritin (ug/L) Change from Baseline and 95% CI over Time | | Y |

| Efficacy: Figures | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 2.19. | ITT | EFF_F1 | Plot of Geometric Mean Transferrin Saturation Percent Change from Baseline and 95% CI over Time | | Y |
| 2.20. | ITT | EFF_F1 | Plot of Geometric Mean Hepcidin Percent Change from Baseline and 95% CI over Time | | Y |
| 2.21. | ITT | EFF_F1 | Plot of Mean Serum Iron (umol/L) Change from Baseline and 95% CI over Time | | Y |
| 2.22. | ITT | EFF_F1 | Plot of Mean Total Iron Binding Capacity (umol/L) Change from Baseline and 95% CI over Time | | Y |
| 2.23. | ITT | EFF_F1 | Plot of Mean Ferritin (ug/L) Change from Baseline and 95% CI over Time by Baseline Iron Use | | Y |
| 2.24. | ITT | EFF_F1 | Plot of Geometric Mean Transferrin Saturation Percent Change from Baseline and 95% CI over time by Baseline Iron Use | | Y |
| 2.25. | ITT | EFF_F1 | Plot of Geometric Mean Hepcidin Percent Change from Baseline and 95% CI over Time by Baseline Iron Use | | Y |
| 2.26. | ITT | EFF_F1 | Plot of Mean Serum Iron (umol/L) Change from Baseline and 95% CI over Time by Baseline Iron Use | | Y |
| 2.27. | ITT | EFF_F1 | Plot of Mean Total Iron Binding Capacity (umol/L) Change from Baseline and 95% CI over Time by Baseline Iron Use | | Y |
| 2.28. | ITT | EFF_F1 | Plot of Mean Ferritin (ug/L) and 95% CI over Time | | Y |
| 2.29. | ITT | EFF_F1 | Plot of Geometric Mean Transferrin Saturation (%) and 95% CI over Time | | Y |
| 2.30. | ITT | EFF_F1 | Plot of Geometric Mean Hepcidin (nmol/L) and 95% CI over Time | | Y |
| 2.31. | ITT | EFF_F1 | Plot of Mean Serum Iron (umol/L) and 95% CI over Time | | Y |

| Efficacy: Figures | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 2.32. | ITT | EFF_F1 | Plot of Mean Total Iron Binding Capacity (umol/L) and 95% CI over Time | | Y |
| 2.33. | ITT | EFF_F1 | Plot of Mean Ferritin (ug/L) and 95% CI over Time by Baseline Iron Use | | Y |
| 2.34. | ITT | EFF_F1 | Plot of Geometric Mean Transferrin Saturation (%) and 95% CI over time by Baseline Iron Use | | Y |
| 2.35. | ITT | EFF_F1 | Plot of Geometric Mean Hepcidin (nmol/L) and 95% CI over Time by Baseline Iron Use | | Y |
| 2.36. | ITT | EFF_F1 | Plot of Mean Serum Iron (umol/L) and 95% CI over Time by Baseline Iron Use | | Y |
| 2.37. | ITT | EFF_F1 | Plot of Mean Total Iron Binding Capacity (umol/L) and 95% CI over Time by Baseline Iron Use | | Y |
| **Other** | | | | | |
| 2.38. | ITT | EFF_F10 | Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Body Weight – Daprodustat | | Y |
| 2.39. | ITT | EFF_F10 | Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Baseline Hgb – Daprodustat | | Y |
| 2.40. | ITT | EFF_F10 | Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Prior ESA Dose – Daprodustat | | Y |
| 2.41. | ITT | EFF_F10 | Scatter Plot of Mean Dose During Week 40 to 52 vs. Body Weight – Daprodustat | | Y |
| 2.42. | ITT | EFF_F10 | Scatter Plot of Mean Dose During Week 40 to 52 vs. Baseline Hgb – Daprodustat | | Y |
| 2.43. | ITT | EFF_F10 | Scatter Plot of Mean Dose During Week 40 to 52 vs. Prior ESA Dose – Daprodustat | | Y |

### 15.10.4.4. Safety Tables

| Safety Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Adverse Events (AEs)** | | | | | |
| 3.1. | Safety | AE1 | Summary of On-Therapy AEs by SOC and PT | ICH E3 | Y |
| 3.2. | Safety | AE5 | Summary of On-Therapy AEs by SOC and PT and Maximum Intensity | ICH E3 | Y |
| 3.3. | Safety | AE1 | Summary of On-Therapy AEs up to Week 4 by SOC and PT | | Y |
| 3.4. | Safety | AE5 | Summary of On-Therapy AEs up to Week 4 by SOC and PT and Maximum Intensity | | Y |
| 3.5. | Safety | SAFE_T1 | Summary of On-Therapy Common (>=2%) AEs by SOC and PT by Onset | J-CTD; Not cumulative summary | Y |
| 3.6. | Safety | AE1 | Summary of Post-Therapy AEs by SOC and PT | ICH E3 | Y |
| 3.7. | Safety | AE5 | Summary of Post-Therapy AEs by SOC and PT and Maximum Intensity | ICH E3 | Y |
| 3.8. | Safety | AE1 | Summary of On-Therapy Drug-Related AEs by SOC and PT | ICH E3 | Y |
| 3.9. | Safety | AE5 | Summary of On-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity | ICH E3 | Y |
| 3.10. | Safety | AE1 | Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT | | Y |
| 3.11. | Safety | AE5 | Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT and Maximum Intensity | | Y |
| 3.12. | Safety | AE1 | Summary of Post-Therapy Drug-Related AEs by SOC and PT | | Y |
| 3.13. | Safety | AE5 | Summary of Post-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity | | Y |

| Safety Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 3.14. | Safety | AE3 | Summary of On-Therapy Non-Serious Drug-Related AEs | Required for Plain Language Summary | Y |
| 3.15. | Safety | AE3 | Summary of On-Therapy Common (>=2%) AEs by Overall Frequency | ICH E3 | Y |
| 3.16. | Safety | AE15 | Summary of On-Therapy Common (>=5%) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences) | FDAAA, EudraCT | Y |
| **Serious and Other Significant AEs** | | | | | |
| 3.17. | Safety | AE1 | Summary of On-Therapy Serious AEs | GSK CTR | Y |
| 3.18. | Safety | AE1 | Summary of Post-Therapy Serious AEs | GSK CTR | Y |
| 3.19. | Safety | AE3 | Summary of On-Therapy Serious Drug-Related AEs | Required for Plain Language Summary | Y |
| 3.20. | Safety | AE16 | Summary of On-Therapy Serious AEs by SOC and PT (Subjects & No. of Occurrences) | FDAAA, EudraCT | Y |
| 3.21. | Safety | AE1 | Summary of On-Therapy AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT | IDSL | Y |
| **AEs of Special Interest** | | | | | |
| 3.22. | Safety | SAFE_T2 | Summary of On-Therapy AEs of Special Interest | | Y |
| 3.23. | Safety | SAFE_T2 | Summary of Post-Therapy AEs of Special Interest | | Y |
| **Laboratory: Chemistry** | | | | | |
| 3.24. | Safety | LB1 | Summary of Chemistry Values by Visit | ICH E3<br>Includes Baseline values | Y |
| 3.25. | Safety | LB1 | Summary of Chemistry Changes from Baseline by Visit | ICH E3 | Y |
| 3.26. | Safety | SAFE_T3 | Summary of Percent Change from Baseline in Lipid Parameters (Total Cholesterol, LDL Cholesterol, HDL Cholesterol, LDL/HDL Cholesterol Ratio) by Visit | | Y |

| Safety Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 3.27. | Safety | LB15 | Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline | ICH E3 | Y |
| 3.28. | Safety | LB17 | Summary of Worst Case Chemistry Results Relative to PCI Criteria Post-Baseline Relative to Baseline | ICH E3 | Y |
| **Hematology** | | | | | |
| 3.29. | Safety | LB1 | Summary of Hematology Values by Visit | ICH E3<br>Includes Baseline values | Y |
| 3.30. | Safety | LB1 | Summary of Hematology Changes from Baseline by Visit | ICH E3 | Y |
| 3.31. | Safety | LB15 | Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline | ICH E3 | Y |
| 3.32. | Safety | LB17 | Summary of Worst Case Hematology Results Relative to PCI Criteria Post-Baseline Relative to Baseline | ICH E3 | Y |
| **Iron Parameters** | | | | | |
| 3.33. | Safety | LB1 | Summary of Iron Parameter by Visit | ICH E3<br>Includes Baseline values | Y |
| 3.34. | Safety | LB1 | Summary of Iron Parameter Changes from Baseline by Visit | ICH E3 | Y |
| 3.35. | Safety | LB15 | Summary of Worst Case Iron Parameter Results Relative to Normal Range Post-Baseline Relative to Baseline | ICH E3 | Y |
| 3.36. | Safety | LB15 | Summary of Worst Case Iron Parameter Results Relative to PCI Criteria Post-Baseline Relative to Baseline | ICH E3 | Y |
| **Other Laboratory Tests** | | | | | |
| 3.37. | Safety | LB1 | Summary of Other Laboratory Values by Visit | ICH E3<br>Includes Baseline values | Y |
| 3.38. | Safety | LB1 | Summary of Other Laboratory Changes from Baseline by Visit | ICH E3 | Y |

| Safety Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 3.39. | Safety | LB15 | Summary of Worst Case Other Laboratory Results Relative to Normal Range Post-Baseline Relative to Baseline | ICH E3 | Y |
| 3.40. | Safety | LB17 | Summary of Worst Case Other Laboratory Results Relative to PCI Criteria Post-Baseline Relative to Baseline | ICH E3 | Y |
| **Hepatobiliary (Liver)** | | | | | |
| 3.41. | Safety | LIVER1 | Summary of Liver Monitoring/Stopping Event Reporting | IDSL | Y |
| 3.42. | Safety | LIVER10 | Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria | IDSL | Y |
| **ECG** | | | | | |
| 3.43. | Safety | EG1 | Summary of ECG Findings | IDSL | Y |
| 3.44. | Safety | EG2 | Summary of Change from Baseline in ECG Values by Visit | IDSL | Y |
| **Vital Signs** | | | | | |
| 3.45. | Safety | SAFE_T4 based on VS1 | Summary of Vital Signs by Visit | Summarized by each assessment status (i.e. pre- and post-dialysis) | Y |
| 3.46. | Safety | SAFE_T4 based on VS1 | Summary Change from Baseline in Vital Signs by Visit | Summarized by each assessment status (i.e. pre- and post-dialysis) | Y |
| 3.47. | Safety | SAFE_T5 based on VS7 | Summary of Worst Case Vital Sign Results Relative to PCI Criteria Post-Baseline Relative to Baseline | Summarized by each assessment status (i.e. pre- and post-dialysis) | Y |
| **Ophthalmology** | | | | | |
| 3.48. | Safety | SAFE_T6 | Summary of Ophthalmologic Exams at Screening | | Y |
| 3.49. | Safety | SAFE_T7 | Summary of On-Therapy Ophthalmologic Exams | | Y |
| **Change in Anti-Hypertensive Medications** | | | | | |
| 3.50. | Safety | SAFE_T8 | Summary of Change in Anti-Hypertensive Medications Due to Increased Blood Pressure | | Y |

### 15.10.4.5. Safety Figures

| Safety Figures | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Adverse Events** | | | | | |
| 3.1. | Safety | AE10 | Common (>=2%) On-Therapy AEs Sorted by Relative Risk | IDSL | Y |
| **Clinical Laboratory Analyses** | | | | | |
| 3.2. | Safety | SAFE_F1 | Plot of Percent Change from Baseline in Lipid Parameters (Total Cholesterol, LDL Cholesterol, HDL Cholesterol, LDL/HDL Cholesterol Ratio) over Time | Geometric mean and its 95% CI will be presented. | Y |

### 15.10.4.6. Patient Reported Outcome Tables

| Efficacy: Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Patient Reported Outcome** | | | | | |
| 4.1. | ITT | SF2 | Summary of SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) | including PCS and MCS | Y |
| 4.2. | ITT | SF4 | Summary of Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) | including PCS and MCS | Y |
| 4.3. | ITT | PRO_T1 | Summary of EQ-5D-5L Score | | Y |
| 4.4. | ITT | PRO_T2 | Summary of EQ-5D-5L Index Value | | Y |
| 4.5. | ITT | PRO_T2 | Summary of Changes from Baseline in EQ-5D-5L Index Value | | Y |
| 4.6. | ITT | PRO_T3 | Summary of EQ Visual Analog Scale (VAS) | | Y |
| 4.7. | ITT | PRO_T3 | Summary of Changes from Baseline in EQ Visual Analog Scale (VAS) | | Y |
| 4.8. | ITT | PRO_T4 | Analysis of Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) | | Y |
| 4.9. | ITT | PRO_T5 | Analysis of Changes from Baseline in EQ-5D-5L Index Value | | Y |
| 4.10. | ITT | PRO_T5 | Analysis of Changes from Baseline in EQ Visual Analog Scale (VAS) | | Y |

### 15.10.4.7. Pharmacokinetic Tables

| Pharmacokinetic Tables | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Plasma Daprodustat Concentrations** | | | | | |
| 5.1. | PK | PK01 | Summary of Daprodustat Plasma Concentration by Dose Level (non-transformed) | | Y |
| 5.2. | PK | PK_T1 based on PK05 | Summary of Daprodustat Plasma Concentration by Dose Level (loge-transformed) | | Y |
| **PK parameters** | | | | | |
| 5.3. | PK | PK03 | Summary of Daprodustat Pharmacokinetic Parameters by Dose Level (non-transformed) | | Y |
| 5.4. | PK | PK05 | Summary of Daprodustat Pharmacokinetic Parameters by Dose Level (loge-transformed) | | Y |
| 5.5. | PK | PK03 | Summary of Dose Normalized Daprodustat Pharmacokinetic Parameters by Dose Level (non-transformed) | | Y |
| 5.6. | PK | PK05 | Summary of Dose Normalized Daprodustat Pharmacokinetic Parameters by Dose Level (loge-transformed) | | Y |
| 5.7. | PK | PK03 | Summary of Dose Normalized Daprodustat Pharmacokinetic Parameters by Used Tablet Strength (non-transformed) | | Y |
| 5.8. | PK | PK05 | Summary of Dose Normalized Daprodustat Pharmacokinetic Parameters by Used Tablet Strength (loge-transformed) | | Y |

### 15.10.4.8. Pharmacokinetic Figures

| Pharmacokinetic Figures | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Plasma Daprodustat Concentrations** | | | | | |
| 5.1. | PK | PK24 | Individual Daprodustat Plasma Concentration-Time Plots | (Linear and Semi-Log) (by Dose) | Y |
| 5.2. | PK | PK17 | Mean Daprodustat Plasma Concentration-Time Plots | (Linear and Semi-Log) (by Dose) | Y |
| 5.3. | PK | PK19 | Mean (+SD) Daprodustat Plasma Concentration-Time Plots | (Linear and Semi-Log) (by Dose) | Y |
| 5.4. | PK | PK20 | Median Daprodustat Plasma Concentration-Time Plots | (Linear and Semi-Log) (by Dose) | Y |
| **PK parameters** | | | | | |
| 5.5. | PK | PK_F1 | Individual Plot of Daprodustat Dose Level and PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.6. | PK | PK_F2 | Mean (+SD) Plot of Daprodustat Dose Level and PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.7. | PK | PK_F3 | Median Plot of Daprodustat Dose Level and PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.8. | PK | PK_F1 | Individual Plot of Daprodustat Dose Level and Dose Normalized PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.9. | PK | PK_F2 | Mean (+SD) Plot of Daprodustat Dose Level and Dose Normalized PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.10. | PK | PK_F3 | Median Plot of Daprodustat Dose Level and Dose Normalized PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.11. | PK | PK_F4 | Box Plot of Daprodustat Dose Level and Dose Normalized PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.12. | PK | PK_F1 | Individual Plot of Daprodustat Used Tablet Strength and Dose Normalized PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.13. | PK | PK_F2 | Mean (+SD) Plot of Daprodustat Used Tablet Strength and Dose | will provide only pooled data | Y |

| Pharmacokinetic Figures | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| | | | Normalized PK Parameters (AUC(0-4) and Cmax) | | |
| 5.14. | PK | PK_F3 | Median Plot of Daprodustat Used Tablet Strength and Dose Normalized PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |
| 5.15. | PK | PK_F4 | Box Plot of Daprodustat Used Tablet Strength and Dose Normalized PK Parameters (AUC(0-4) and Cmax) | will provide only pooled data | Y |

### 15.10.4.9. ICH Listings

| ICH Listings | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Study Population** | | | | | |
| **Subject Disposition** | | | | | |
| 1. | Randomized | ES2 | Listing of Reasons for Study Withdrawal | ICH E3 | Y |
| 2. | Safety | SD2 | Listing of Reasons for Study Treatment Discontinuation | ICH E3 | Y |
| 3. | All Screening | ES7 | Listing of Reasons for Screen Failure | CONSORT Diagram | Y |
| 4. | Randomized | BL1 | Listing of Subjects for Whom the Treatment Blind was Broken | ICH E3 | Y |
| 5. | Safety | TA1 | Listing of Planned and Actual Treatments | GSK CSR | Y |
| **Protocol Deviations** | | | | | |
| 6. | Randomized | DV2 | Listing of Important Protocol Deviations | | Y |
| 7. | Randomized | IE3 | Listing of Subjects with Inclusion/Exclusion Criteria Deviations | | Y |
| **Population Analyzed** | | | | | |
| 8. | Randomized | SP3 | Listing of Subjects Excluded from Any Population | Subjects excluded from Safety, ITT, mITT, and PP will be included. | Y |
| 9. | mITT | SP3 | Listing of Subjects Excluded from Per Protocol Population | Include the exclusion categories | Y |
| **Demographic and Baseline Characteristics** | | | | | |
| 10. | Safety | DM2 | Listing of Demographic Characteristics | ICH E3 | Y |
| 11. | Safety | POP_L1 | Listing of Other Baseline Characteristics | | Y |
| 12. | Safety | CM2 | Listing of Prior ESA | | Y |
| 13. | Safety | DM9 | Listing of Race | ICH E3 | Y |

| ICH Listings | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Exposure and Treatment Compliance** | | | | | |
| 14. | Safety | POP_L2 | Listing of Exposure Data - Daprodustat | ICH E3<br>Include placebo daprodustat treatment | Y |
| 15. | Safety | POP_L3 | Listing of Exposure Data - Darbepoetin Alfa | ICH E3<br>Include placebo darbepoetin alfa treatment | Y |
| 16. | Safety | POP_L4 | Listing of Study Medication Compliance | ICH E3<br>Include compliance of placebo treatment | Y |
| **Efficacy** | | | | | |
| **Hgb** | | | | | |
| 17. | ITT | EFF_L1 | Listing of Hgb Data | | Y |
| 18. | ITT | EFF_L2 | Listing of Subjects Who Have an Hgb Level of Less than 7.5 g/dL | | Y |
| 19. | ITT | EFF_L2 | Listing of Subjects Who Have an Hgb Increase of More than 2.0 g/dL over Any 4 weeks | | Y |
| 20. | ITT | EFF_L2 | Listing of Subjects Who Have an Hgb Level of More than 13.0 g/dL | | Y |
| 21. | ITT | EFF_L3 | Listing of Subjects with Treatment Interruption due to Hgb > 13 g/dL | | Y |
| **Safety** | | | | | |
| **Adverse Events** | | | | | |
| 22. | Safety | AE8 | Listing of All Adverse Events | ICH E3 | Y |
| 23. | Safety | AE7 | Listing of Subject Numbers for Individual Adverse Events | ICH E3 | Y |
| 24. | Safety | AE2 | Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text | IDSL | Y |

| ICH Listings | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Serious and Other Significant Adverse Events** | | | | | |
| 25. | Safety | AE8 | Listing of Fatal Serious Adverse Events | ICH E3 | Y |
| 26. | Safety | AE8 | Listing of Non-Fatal Serious Adverse Events | ICH E3 | Y |
| 27. | All Screening | AE8 | Listing of Serious AEs in Screening Period | | Y |
| 28. | Safety | AE8 | Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment | ICH E3 | Y |
| 29. | Safety | AE14 | Listing of Reasons for Considering as a Serious Adverse Event | ICH E3 | Y |
| 30. | Safety | SAFE_L1 | Listing of Adverse Events of Special Interest | ICH E3<br>Displays will be produced with AESI category in addition of AE8 template. | Y |
| **All Laboratory** | | | | | |
| 31. | Safety | LB5 | Listing of All Chemistry Data for Subjects with Any Value Outside of Normal Range/of PCI | ICH E3 | Y |
| 32. | Safety | LB5 | Listing of All Hematology Data for Subjects with Any Value Outside of Normal Range/of PCI | ICH E3 | Y |
| 33. | Safety | LB5 | Listing of All Other Laboratory Data for Subjects with Any Value Outside of Normal Range/of PCI | ICH E3 | Y |

## 15.10.4.10. Other Listings

| Other Listings | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Study Population** | | | | | |
| **Demographic and Baseline Characteristics** | | | | | |
| 34. | Safety | FH4 | Listing of Family Members with History of Cardiovascular Risk Factors | | Y |
| 35. | Safety | SU2 | Listing of Substance Use History | | Y |
| **Medical Conditions and Concomitant Medication** | | | | | |
| 36. | Safety | MH2 | Listing of Medical Conditions | | Y |
| 37. | Safety | CM2 | Listing of Concomitant Medications | | Y |
| 38. | Safety | POP_L5 | Listing of ESA Concomitant Medications (On-, Post-Therapy) | | Y |
| 39. | Safety | POP_L6 | Listing of Iron Concomitant Medications | | Y |
| 40. | Safety | POP_L7 | Listing of Anti-Hypertensive Concomitant Medications | | Y |
| 41. | Safety | POP_L8 | Listing of Blood Products and Blood Supportive Care Products | | Y |
| **Dialysis** | | | | | |
| 42. | Safety | POP_L9 | Listing of Baseline Mode of Dialysis | | Y |
| 43. | Safety | POP_L9 | Listing of Subjects with Changes in Hemodialysis | | Y |
| 44. | Safety | POP_L10 | Listing of Baseline Mode of Vascular Access | | Y |
| 45. | Safety | POP_L11 | Listing of Subjects with Vascular Therapeutic Procedures | | Y |
| 46. | Safety | POP_L11 | Listing of Subjects with Vascular Access Intervention / Revision | | Y |

| Other Listings | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Safety** | | | | | |
| **Suicidality-Related Adverse Event** | | | | | |
| 47. | Safety | IDSL standard | Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1-Section 2) | | Y |
| 48. | Safety | IDSL standard | Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3) | | Y |
| 49. | Safety | IDSL standard | Listing of Possible Suicidality-Related Adverse Event Data: (Section 4) | | Y |
| 50. | Safety | IDSL standard | Listing of Possible Suicidality-Related Adverse Event Data: (Section 5-8) | | Y |
| **Clinical Laboratory, ECG, Vital Sign, and Ophthalmology Exam** | | | | | |
| 51. | Safety | LB5 | Listing of Chemistry Data | | Y |
| 52. | Safety | LB5 | Listing of Hematology Data | | Y |
| 53. | Safety | LB5 | Listing of Other Laboratory Data | | Y |
| 54. | Safety | MH2 | Listing of Medical Conditions for Subjects with Liver Stopping Events | This listing is required for medical review of subjects with liver stopping events. | Y |
| 55. | Safety | SU2 | Listing of Substance Use for Subjects with Liver Stopping Events | This listing is required for medical review of subjects with liver stopping events. | Y |
| 56. | Safety | LIVER5 | Listing of Liver Monitoring/Stopping Event Reporting | | Y |
| 57. | Safety | LIVER6 | Listing of Liver Stopping Event Information for RUCAM Score | | Y |
| 58. | Safety | LIVER7 | Listing of Liver Biopsy Details | | Y |
| 59. | Safety | LIVER8 | Listing of Liver Imaging Details | | Y |
| 60. | Safety | EG3 | Listing of ECG Values | | Y |

| Other Listings | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| 61. | Safety | EG5 | Listing of ECG Findings | Delete column of 'Clinically Significant Change from Baseline?' from EG5 template | Y |
| 62. | Safety | VS4 | Listing of Vital Signs | | Y |
| 63. | Safety | VS4 | Listing of All Vital Signs for Subjects with Values of PCI | | Y |
| 64. | Safety | SAFE_L2 | Listing of Ophthalmologic Exams | | Y |
| 65. | Safety | SAFE_L3 | Listing of Subjects Who Have Any Change in Anti-Hypertensive Medications | | Y |
| **Other** | | | | | |
| 66. | Safety | PREG1a | Listing of Subjects Who Became Pregnant During the Study | | Y |
| **Exploratory Endpoints** | | | | | |
| 67. | Safety | LB5 | Listing of Iron Parameter Data | All iron parameters will be included. | Y |
| **Patient Reported Outcome** | | | | | |
| 68. | ITT | PRO_L1 | Listing of SF-36v2 Summary Scores and Domain Scores | Including PCS, MCS and 8 subscales | Y |
| 69. | ITT | PRO_L2 | Listing of Individual Scores of EQ-5D-5L / VAS | | Y |
| **Pharmacokinetic Parameters** | | | | | |
| 70. | PK | PK07 | Listing of Daprodustat Pharmacokinetic Concentration-Time Data by Dose Level | | Y |
| 71. | PK | PK13 | Listing of Derived Daprodustat Pharmacokinetic Parameters by Dose Level | | Y |

### 15.10.4.11. Patient Profile Listings

| Patient Profile Listings | | | | | |
|---|---|---|---|---|---|
| **No.** | **Population** | **IDSL / TST ID / Example Shell** | **Title** | **Programming Notes** | **SAC** |
| **Safety** | | | | | |
| 72. | Safety | IDSL standard | Patient Profile Listing of Arrhythmias | | Y |
| 73. | Safety | IDSL standard | Patient Profile Listing of Congestive Heart Failure | | Y |
| 74. | Safety | IDSL standard | Patient Profile Listing of Cerebrovascular Events/Stroke/ Transient Ischemic Attack | | Y |
| 75. | Safety | IDSL standard | Patient Profile Listing of Deep Venous Thrombosis/ Pulmonary Embolism | | Y |
| 76. | Safety | IDSL standard | Patient Profile Listing of Myocardial Infarction /Unstable Angina | | Y |
| 77. | Safety | IDSL standard | Patient Profile Listing of Peripheral Arterial Thrombosis Embolism | | Y |
| 78. | Safety | IDSL standard | Patient Profile Listing of Pulmonary Hypertension | | Y |
| 79. | Safety | IDSL standard | Patient Profile Listing of Revascularization | | Y |
| 80. | Safety | IDSL standard | Patient Profile Listing of Valvulopathy | | Y |
| 81. | Safety | IDSL standard | Patient Profile Listing of Deaths | | Y |

## 15.11. Appendix 11: Example Mock Shells for Data Displays

Full mock shells for data displays are developed as separate documents.

# 16. REVISION HISTORY

Note that minor wording changes are not included in below.

| Reporting and Analysis Plan_201754_Amendment_Final_V1.1 [06-Aug-2018] | | |
|---|---|---|
| **Section # and Name** | **Description of Change** | **Brief Rationale** |
| 4 Analysis Populations<br>15.3 Appendix 3: Assessment Windows | It has been clarified that Hgb assessments at HemoCue visits (Week 2, 6, 10, …) will not be included in the analysis. | Clarification |
| 5.4.2 Examination of Subgroups | Subgroup definitions for ERI and period of time on dialysis were refined. | It would facilitate review of subgroup results |
| 6 Study Population Analyses<br>15.10.4 Table of Contents for SAC Deliverable | Some modifications were made for study population displays as below:<br>1. Added 2 listings; subjects excluded from any population and subjects excluded from per-protocol population<br>2. Removed a summary of race and racial combination based on ITT population.<br>3. Added a separate listing of study specific baseline characteristics | 1. It would facilitate review of results of populations analyzed.<br>2. Safety population would be sufficient to be assessed<br>3. It would facilitate review of results of baseline characteristics. |
| 6.2 Planned Summary Display Details | Clarifications has been made to the way to display of exposure and treatment compliance. | Clarification |
| 7.1 Primary Efficacy Analyses<br>15.10.4 Table of Contents for SAC Deliverable | Added tables of the tipping point analysis | It would facilitate review of tipping point results. |
| 7.1.6.3 Tipping Point Analysis | The number of imputations was reconsidered and a text was updated. | Modifications |
| 7.2 Principal Secondary Efficacy Analyses | A method to construct 95% CI and a one-sided p-value for odds ratio has been specified in Section 7.2.5.1 Statistical Methodology Specification | Clarification |
| 7.3 Secondary Efficacy Analyses<br>15.10.4 Table of Contents for SAC Deliverable | Added several Hgb summaries by prior ESA dose, prior ESA type, and ERI and a listing of subjects with treatment interruption due to Hgb > 13 g/dL. | It would facilitate review of switching from ESA to daprodustat and treatment interruption due to Hgb > 13 g/dL |
| 7.3 Secondary Efficacy Analyses | Text added to a summary of dose to be provided for both treatment group. | To ensure the dose results for both treatment group |

| Reporting and Analysis Plan_201754_Amendment_Final_V1.1 [06-Aug-2018] | | |
|---|---|---|
| **Section # and Name** | **Description of Change** | **Brief Rationale** |
| 7.4 Exploratory Efficacy Analyses<br>15.10.4 Table of Contents for SAC Deliverable | Figures of the raw observed values for each iron parameter were added. | It would facilitate review of iron parameters results |
| 7.4 Exploratory Efficacy Analyses | It has been clarified that the scatter plot figures will be created for only daprodustat group. | Clarification |
| 7.4 Exploratory Efficacy Analyses | Analysis using a mixed model for repeated measures has been added for change from baseline in the respective iron parameter in Section 7.4.5.1 Statistical Methodology Specification. Also, the strategy for intercurrent events was added as appropriate. | A model-based approach would be effectively estimate the results of the iron parameters more effectively |
| 8.1.1 Planned Adverse Events Analyses Displays | 1. Clarification has been made to a summary of AEs by onset, i.e., the first occurrences for each subject will be used for the summary.<br>2. Text added to description of a summary of SAEs (subjects & No. of occurrences) | 1. Clarification according to PMDA requirement<br>2. Correction |
| 8.3 Clinical Laboratory Analyses | LDL/HDL cholesterol ratio was added as one of lipid parameters of interest. | It would facilitate review of lipid parameters results |
| 8.4.1 Planned Other Safety Analyses Displays | Update has been made to the ophthalmology exam to add the response (Y/N) to any questions. | Clarification |
| 9 Patient Reported Outcome Analyses | Clarification has been made to the terminology of EQ-5D-5L scores and the index value. | Clarification |
| 9 Patient Reported Outcome Analyses | Statistical methodology specification using a mixed model for repeated measures has been added for the change from baseline in the respective QoL parameter in Section 9.5.1 Statistical Methodology Specification. Also, the strategy for intercurrent events was added as appropriate. | A model-based approach would be effectively estimate the results of the QoL parameters more effectively |
| 15.1.1 Exclusions from Per Protocol Population | It has been clarified that the exclusion criteria 07 does not include ESA medications. | Clarification |
| 15.5.2 Reporting Standards | Text modified for a detailed description of rules to present summary statistics for continuous data. | To avoid internal inconsistency: the details of displays were also described in each analysis section |
| 15.6.1 Subgroup Definition | Correction was made to the definition of period of time on dialysis. | Correction |
| 15.6.2 Prior ESA Dose | Correction was made to a numeric character in an illustration table. | Correction |
| 15.6.2 Exposure | 1. Update was made to consider that additional bottles may occur in an unscheduled | 1. Changed definitions to consider all |

| Reporting and Analysis Plan_201754_Amendment_Final_V1.1 [06-Aug-2018] | | |
|---|---|---|
| **Section # and Name** | **Description of Change** | **Brief Rationale** |
| | visit. Text added to clarify that the container number(s) in an unscheduled visit will be counted for treatment compliance, however not counted for the actual dose.<br>2. Clarification has been made to categorization of treatment compliance of daprodustat and a display for darbepoetin alfa. | possible records of drug accountability.<br>2. Clarification |
| 15.6.3 Evaluable Hgb Values | Text in evaluable Hgb values corrected. | Correction |
| 15.6.3 Scatter Plot of Hgb Assessments | Clarification has been made to a display including the linear regression line with 95% CI band, R-squared, and Pearson's correlation coefficient.<br>Regarding description of other exploratory scatter plot figures, text corrected appropriately. | Clarification and correction |
| 15.6.3 Time in Target Range | Text added to clarify the general Hgb rule for the whole analysis. | Clarification |
| 15.6.3 Dose Adjustment | 1. Modification has been made to the dose adjustment definition to use the actual dose instead of the prescribed dose<br>2. Updates were made to the derivation for duration of treatment interruption due to Hgb >13.0 g/dL to follow the protocol-defined treatment interruption. | 1. Dose adjustment summaries should be focused on actual use in clinical practice.<br>2. Treatment interruption based on dose adjustment algorithm defined in the protocol should be provided. |
| 15.6.4 Safety | Text added to identify thrombosis and/or tissue ischemia events secondary to excessive erythropoiesis using Hgb criteria. | Hgb criteria would be useful to identify the secondary to excessive erythropoiesis events in an unbiased way. |
| 15.6.6 Iron Endpoints | Text modified to clarify the handling of Riona and P-TOL in iron endpoints and text related to Riona and P-TOL removed from IV iron dose section since they are oral tablets and not used for IV iron. | Clinical review; Riona will be absorbed and affect iron evaluation so be counted as iron use. P-TOL contains nonabsorbable iron so not be counted. |
| 15.6.7 Patient Reported Outcome | Product name of SF-36 scoring software was updated and the detail of scoring algorithm was removed. Also, text added to specify the scoring conditions. | Scoring software is currently updated and a newer scoring algorithm is not available at present therefore removed. |
| 15.10.3 Table of Contents for Headline Results Deliverable | Ophthalmology and AESI results were added to the headline results deliverable. | It would facilitate review of headline results. |
| 15.10.4 Table of Contents for SAC Deliverable | Some titles and programming notes were updated for clarifications. Also, the numbering of displays has been updated as appropriate. | Based on study team's review of dry-run deliverables, team's input has been reflected. |