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

Title	:	Reporting and Analysis Plan for 201753 A 52-week, Phase III, open-label, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese non-dialysis and peritoneal dialysis subjects with anemia associated with chronic kidney disease
Compound Number	:	GSK1278863
Effective Date	:	19-NOV-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 201753.
- 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.

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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 2015N266248_04.

Revision Chronology:		
Final_V1	08-MAY-2018	Original
Amendment_Final_V1	19-NOV-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 amendment 04 (Dated: 03/JUL/2017) 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 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 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 (α) 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 α=2.5%. Practically, this is equivalent to two-sided significance level of 5%.
9.4.1 Primary Efficacy Analysis Analysis of covariance (ANCOVA) will be conducted as sensitivity analysis to MMRM. This model includes treatment group and baseline Hgb.	7.1.6 Sensitivity and Supportive Analyses Analysis of covariance (ANCOVA); it will be conducted as supplementary analysis to MMRM. This model includes treatment group, baseline Hgb, and **prior ESA use**.	Prior ESA use is considered as important factor impacting Hgb.

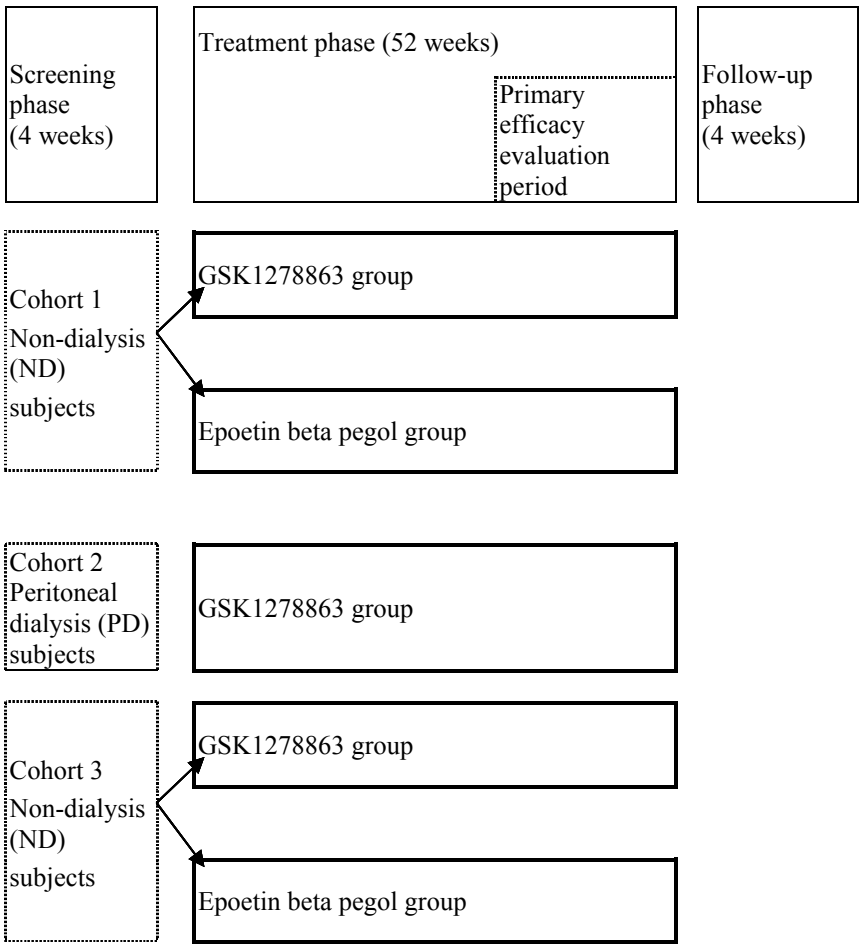
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To demonstrate non-inferiority of GSK1278863 to epoetin beta pegol based on hemoglobin (Hgb) in ND subjects	• Mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52)
Principal Secondary Objectives	**Principal Secondary Endpoints**
• To demonstrate superiority of GSK1278863 to epoetin beta pegol in terms of achievement/maintenance of target Hgb in ND subjects	• Number (%) of subjects with mean Hgb in the target range (11.0-13.0 g/dL) during the primary efficacy evaluation period (Weeks 40 to 52)
Other Secondary Objectives	**Other Secondary Endpoints**
• To evaluate the appropriateness of the starting dose of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the appropriateness of the starting dose of GSK1278863 in PD subjects	• Change in Hgb from baseline to Week 4 (Hgb increase rate) • Number (%) of subjects by Hgb change category in Hgb from baseline to Week 4
• To evaluate dose adjustments of GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate dose adjustments of GSK1278863 in PD subjects	• Distribution of the dose level • Duration of treatment interruption due to Hgb >13 g/dL • Frequency of dose adjustments
• To evaluate the overall Hgb control by GSK1278863 in ND subjects using epoetin beta pegol as control • To evaluate the overall Hgb control by GSK1278863 in PD subjects	• Hgb at each assessment time point and change in Hgb from baseline to each assessment time point • Number (%) of subjects with Hgb within the target range (11.0-13.0 g/dL) at each assessment time point • Proportion (%) of time with Hgb within the target range (11.0-13.0 g/dL) in the primary efficacy evaluation period (Weeks 40 to 52) • Time (number of days) to the lower Hgb target (11.0 g/dL) • Number (%) of subjects who have an Hgb level of less than 7.5 g/dL • Number (%) of subjects who have an Hgb increase of more than 2 g/dL over any 4 weeks before Week 52 • Number (%) of subjects who achieve an Hgb level of more than 13.0 g/dL and number of episodes
• To compare the effect of GSK1278863 versus epoetin beta pegol on iron use in ND subjects • To evaluate effect of GSK1278863 on iron use in PD subjects	• Dose of oral iron in the study period and the primary efficacy evaluation period (Weeks 40 to 52) • Number (%) of subjects who use oral iron during the primary efficacy evaluation period (Weeks 40 to 52)
• To compare the effect of GSK1278863 versus epoetin beta pegol on iron metabolism in ND subjects • To evaluate the effect of GSK1278863 on iron metabolism in PD subjects	• Change in ferritin from baseline • Change in transferrin saturation (TSAT) from baseline • Changes in hepcidin, serum iron, and total iron binding capacity (TIBC) from baseline

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

2.3. Study Design

Overview of Study Design and Key Features



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

Overview of Study Design and Key Features	
	(Cohort 1) • Both ESA non-users and users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4. (Cohort 3) • ESA non-users o Baseline Hgb ≥ 8.0 g/dL and <9.0 g/dL: the subjects will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*. o Baseline Hgb ≥ 9.0 g/dL and <11.0 g/dL: the subjects will start oral treatment with GSK1278863 at the starting dose of 2 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*. • ESA users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4*. *: The HemoCue Hgb value will be measured for safety confirmation at Week 2 in ND subjects. When Hgb > 1.0 g/dL increase over 2 weeks, the dose of GSK1278863 is decreased to the next lower dose. (Cohort 2) • ESA non-users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4. • ESA users will start oral treatment with GSK1278863 at the starting dose of 4 mg once daily (Day 1) and remain on the same regimen until the day of Week 4. ESA users should skip ESA on Day 1 when treatment with GSK1278863 is started. Maintenance Dose • From Weeks 4 to 52, interruption of treatment or dose adjustments will be made within the maintenance dose range of 1-24 mg (Table 6 in the protocol) according to the dose adjustment algorithm (Table 7 in the protocol) to achieve and/or maintain Hgb within the target range (11.0-13.0 g/dL) based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. Epoetin Beta Pegol Starting Dose for ESA Non-users • ESA non-users will start subcutaneous treatment with epoetin beta pegol at a dose of 25 µg once every 2 weeks (Day 1). Dose adjustments will be made within the initial dose range of 25-150 µg (Table 8 in the protocol) according to the dose adjustment criteria (Table 9 in the protocol) to increase Hgb to 11.0 g/dL (lower limit of the target) or more based on the HemoCue Hgb value measured every 4 weeks. Dose changes will be made every 4 weeks. Dose Conversion for ESA Users

Overview of Study Design and Key Features	
	• For ESA users, prior ESA will be replaced with epoetin beta pegol at the equivalent dose once every 4 weeks (Day 1). • At Week 2, HemoCue Hgb value will be measured for subjects' safety confirmation. If the measurement shows an Hgb increase of >1.0 g/dL over 2 weeks, the dose of GSK1278863 will be reduced by one step (or treatment interrupted) at Week 4 (Cohort 3 only). Maintenance Dose • Epoetin beta pegol will be administered once every 4 weeks from dosing interval change (once every 4 weeks) with Hgb ≥11.0 g/dL to Week 52 in ESA non-users and from Weeks 4 to 52 in ESA users • Further details of dosing are provided in the protocol Section 6.4.
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). • In Cohort 1 and Cohort 3 (ND subjects), subjects will be stratified by the current ESA therapy (ESA non-user or ESA user) and the Hgb level on Day 1 and randomized in a 1:1 ratio to one of the two treatment groups according to the randomization schedule. • In Cohort 2 (PD subjects), all eligible subjects will start treatment with GSK1278863 on Day 1.
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 GSK1278863 to epoetin beta pegol based on mean Hgb during the primary efficacy evaluation period (Weeks 40 to 52) in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users).

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

- H_0: Treatment difference (daprodustat – epoetin beta pegol) in mean Hgb during the primary efficacy evaluation period is -1.0 g/dL or less.

- H_1: Treatment difference (daprodustat – epoetin beta pegol) in mean Hgb during the primary efficacy evaluation period is greater than -1.0 g/dL.

Only when the primary endpoint achieves non-inferiority, statistical testing will progress to the principal secondary endpoint with a focus on superiority according to the step-

down procedure. More specifically, the superiority of GSK1278863 to epoetin beta pegol in terms of target Hgb control in ND subjects, including Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users), is to be demonstrated at a 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 (11.0-13.0 g/dL) is equal or less in GSK1278863 than epoetin beta pegol.

- H_1: The proportion of subjects whose mean Hgb during the primary efficacy evaluation period is within the target range (11.0-13.0 g/dL) is greater in GSK1278863 than epoetin beta pegol.

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

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. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screening	• Consists of all subjects who are given subject number and whose data are collected, including demographics 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. • Subjects will be analyzed according to the treatment received.[1] • This population will be used for safety analyses.	• Study Population • Safety
Efficacy Non-dialysis (Efficacy ND)	• Consists of Cohort 1 subjects (both ESA users and ESA non-users) and Cohort 3 subjects (both ESA users and ESA non-users) who are given randomization number with Hgb measurement at both baseline and at least one scheduled visits following the baseline. • Subjects will be analyzed according to randomized treatment.	• Study Population • Efficacy
Efficacy Peritoneal Dialysis (Efficacy PD)	• Consists of Cohort 2 subjects who are given randomization number with Hgb measurement at both baseline and at least one scheduled visits following the baseline.	• Study Population • Efficacy
Intent-To-Treat (ITT)	• Consists of Cohort 1 subjects (only ESA users) and Cohort 3 subjects (both ESA users and ESA non-users) who are given randomization number with Hgb measurement at both baseline and at least one scheduled visits following the baseline.	• Study Population • Efficacy

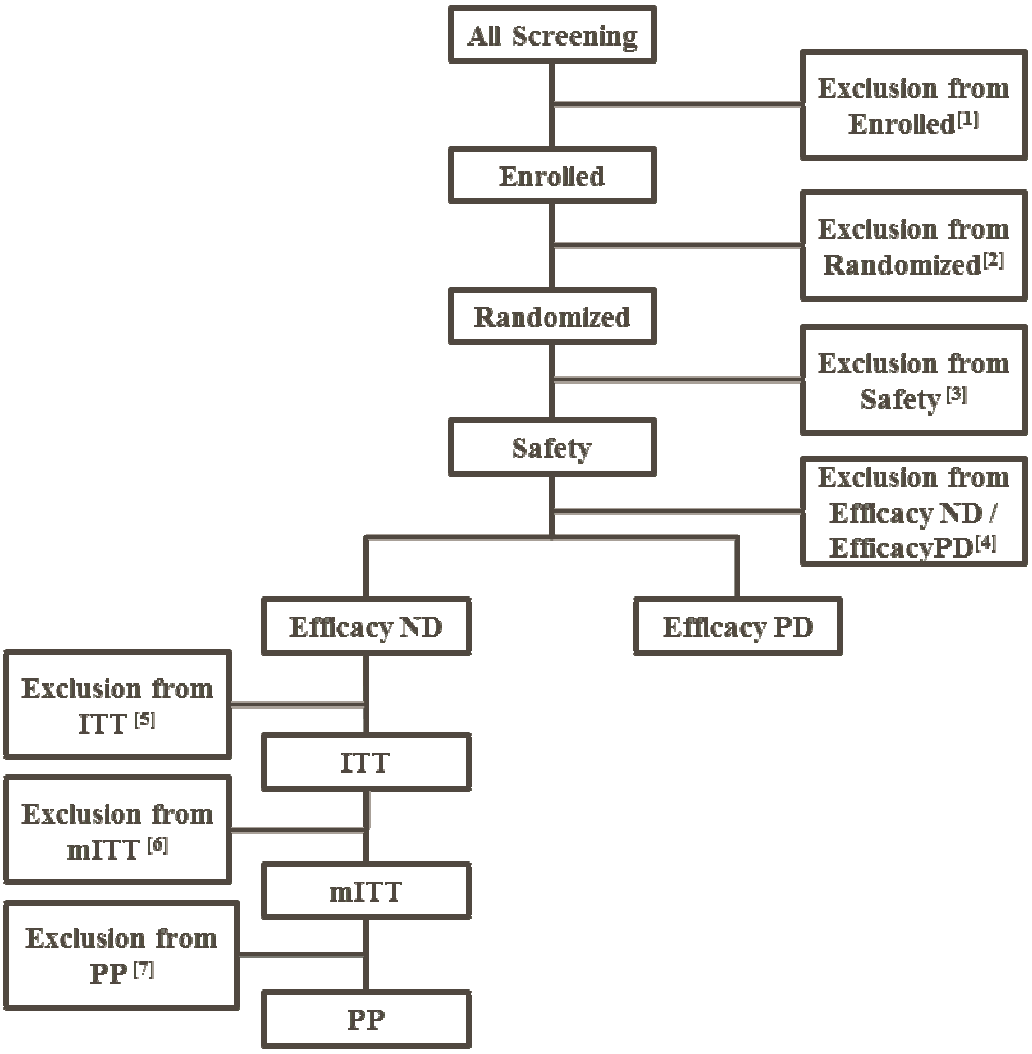
Population	Definition / Criteria	Analyses Evaluated
	• Subjects will be analyzed according to randomized treatment. • This population will be the primary population for an assessment of non-inferiority.	
modified ITT (mITT)	• Consist of all ITT subjects who have at least one Hgb measurement during the efficacy evaluation period. • Subjects will be analyzed according to randomized treatment. • This population will be the primary population for an assessment of superiority.	• Study Population • Efficacy
Per-Protocol (PP)	• Consists of all mITT subjects who are not major protocol violators. • This population will be used for efficacy sensitivity analyses. • 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 GSK1278863-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.
- Refer to 15.6.2 for handling rescreened subjects.

[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.

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]: ESA non-users in Cohort 1 subjects
[6]: Subjects who have no Hgb measurement during the efficacy evaluation period
[7]: Subjects who are major protocol violators (See Section 4.1 and Appendix 1)

4.1. Protocol Deviations

Important protocol deviations (including deviations related to the study 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 summarised 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.

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

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
D1	GSK1278863	Daprodustat	1
D2	Epoetin beta pegol	Epoetin beta pegol	2

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

1. Daprodustat vs Epoetin Beta Pegol

5.2. Baseline Definitions

The baseline Hgb value will be the value from the Day 1 visit. no derivation will be performed and baseline will be set to missing, even if missing at Day 1 visit.

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

5.3. Multicentre 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 pooled for analysis.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata will be used in statistical analyses, the strata will also be used for subgroup analyses.

Randomization is stratified by prior ESA use and baseline Hgb in Cohort 1 and Cohort 3 (ND subjects). Baseline Hgb will be included as a covariate in the primary efficacy analyses. Prior ESA use and baseline Hgb will be included as covariates in the principal secondary efficacy analyses. The reasons why prior ESA use will not be included in the primary analyses are 1) the data for the primary endpoint is longitudinal data and the visit effect and the interaction with visit are important. 2) if including prior ESA use in the analyses the model will be complicate and it will be difficult to interpret the results. While, the data for the principal secondary endpoint is not longitudinal data and it has no visit data. Thus, it will not be complicate even if including prior ESA use in the model.

Category	Details
Strata	ESA use, Baseline Hgb
Covariates	For primary efficacy analyses: • 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. For principal secondary efficacy analyses: • Logistic regression model including treatment group, baseline Hgb, and current ESA therapy (presence or absence) as covariates will be used.

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses.

Subgroup	Categories
Prior ESA Use[1]	Non-user, User
Baseline Hgb (g/dL)[1][2]	ESA non-users: <=9.5, >9.5 ESA users: <11.0, >=11.0
Age (year)	< 65, >=65
Sex	Female, Male
Prior ESA Dose (IU/week)	<4,500, >=4,500[3][4]
Prior ESA Type	Epoetin, Epoetin beta pegol, Darbepoetin alfa
ERI [3]	< median, >= median
Baseline Iron Use[5]	Yes, No

Subgroup	Categories
Baseline Weight (kg)	< 55, >=55
Baseline BMI (kg/m^2)	<20, >=20
History of Diabetes[6]	Yes, No
Dialysis[7]	ND subjects, PD subjects
CKD Stage[8]	Stage 3 (30=<eGFR<60), Stage 4 (15=<eGFR<30), Stage 5 (eGFR<15)

NOTES:

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

[1] Stratum code will be used to determine category. Stratum code=1: ESA non-user, Baseline Hgb <= 9.5, 2: ESA non-user, Baseline Hgb > 9.5, 3: ESA user, Baseline Hgb < 11.0, 4: ESA user, Baseline Hgb >= 11.0.

[2] Hemocue Hgb at Day 1 will be used for categorization.

[3] Additional thresholds might be added in order to divide the population equally as appropriate.

[4] Standardized dose on epoetin i.v. (IU/week) will be used for subgroup.

[5] Subjects who used ferric citrate (trade name: Riona) will also be included in Baseline Iron Use group. This category will be used just for iron analyses. See Section 15.6.3.

[6] Past or current history of diabetes

[7] This subgroup will be used for study population analyses and safety analyses.

[8] CKD Stage will be determined by eGFR (mL/min/1.73m^2) at a screening visit

For prior ESA use, the subgroup of non-users in PD subjects is small. Therefore endpoints summarized for PD subjects (i.e. Safety or Efficacy PD population) by prior ESA use will also be listed for the ESA non-users in PD subjects.

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, change from define in the protocol, see Section 2.1). 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.

Other secondary endpoints, which will be evaluated on a complementary or exploratory basis, will be compared at a two-sided significance level of 5% without multiplicity adjustment.

Since Cohort 2 is a single-arm cohort, no testing will be performed to evaluate the efficacy in PD subjects.

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. For the populations including both ND and PD subjects (All Screening, Enrolled, Randomized, Safety), the summaries will be provided by dialysis (ND and PD separately) unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, population analysed, demographic and baseline characteristics, medical conditions and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Analysis 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		
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		
Exclusions from the Per Protocol Population	mITT	Y		Y
Subjects Excluded from Any Population	Randomized			Y
Composition of Randomized Population	Randomized	Y		
Demographic and Baseline Characteristics				
Demographic Characteristics	ITT/Safety/Efficacy ND/Efficacy PD	Y		Y
Demographic Characteristics by Prior ESA Use	ITT/Safety/Efficacy PD	Y		
Demographic Characteristics by Cohort	Efficacy ND	Y		
Other Baseline Characteristics [1]	Safety			Y
Prior ESA	ITT/Safety/Efficacy PD	Y		Y
Age Ranges	Enrolled	Y		
Race and Racial Combinations	Safety	Y		Y [1]
Family History for CV Risk Factors	Safety	Y		Y

Endpoint / Parameter / Display Type	Population	Data Displays Generated		
		Table	Figure	Listing
Substance Use (History of Tobacco Use, Alcohol Intake)	Safety	Y		Y
Dialysis				
Subjects with Dialysis Initiation during the Study Period	Safety			Y
Subjects with Peritoneal Dialysis at Baseline	Safety			Y
Subjects with Vascular Therapeutic Procedures during the Study Period	Safety			Y
Medical Conditions and Concomitant Medications				
Current/Past Medical Conditions	Safety	Y		Y
Concomitant Medications [2]	Safety	Y		Y
Other Concomitant Medications (ESA, iron, and anti-hypertensive medication)	Safety	Y [3]		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[4]

NOTES :

- Y = Yes display generated.

[1] As a separate listing, include prior ESA type, standardized prior ESA dose, ERI, iron use, diabetes, and CKD stage.
[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. .
[5] For Daprodustat in cohort 3, compliances up to Week 2 and Week 2 to 4 will be including in the listing

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. Reasons for discontinuation of study treatment of subjects will be listed.

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). Reasons for screen failure of subjects will be listed.

Subjects Enrolled by Country and Site ID

The number and percentage of subjects by Country and 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. Important protocol deviations of subjects will be listed.

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. Inclusion/exclusion criteria deviation of subjects will be listed.

- **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 the Per Protocol Population

The number of the exclusions from the PP population and the exclusion categories will be summarized by treatment group and total.

Composition of the Randomized Population

The number and percentage of subjects by dialysis, cohort, and prior ESA use 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, Body Mass Index, and CKD Stage. The period of time on dialysis (years) will also summarized only for PD subjects in Safety population and Efficacy PD population. Age Group (years) will be categorized into 3 ('≤18', '19-64', '≥65'). CKD Stage will be categorized into 3 by eGFR (Stage 3 (30=<eGFR<60), Stage 4 (15=<eGFR<30), Stage 5 (eGFR <15)) at a screening visit. Separate summaries for ITT, Safety, Efficacy ND, and Efficacy PD population will be produced. For Efficacy ND population, summary will also be provided by cohort. For the ITT, Safety, and Efficacy PD populations, summary will also be provided by Prior ESA-use.

Prior ESA

For overall prior ESA medication, the weekly dose (standardized by IU/week) erythropoietin resistance index (ERI), and the number and percentage of subjects' dosing route (intravenous [IV] or subcutaneous [SC]) will be summarized by treatment group and total. For each type of prior ESA medication (epoetin, epoetin beta pegol, and darbepoetin alfa), the weekly dose (IU/week or μg/week), ERI and the number and percentage of subjects' dosing route (IV or SC) will also be summarized by treatment group and total. See Section 15.6.2 for the derivation of 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 for the study phases.

Other Concomitant Medications (On-Therapy ESA, iron, and anti-hypertensive medication)

The similar summary as above will be provided by treatment group and total focusing on on-therapy ESA, on-therapy iron medication (see Section 15.6.2), and on-therapy anti-hypertensive medications. See Section 15.4.1 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.

- **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 monthly dose (for epoetin beta pegol), and cumulative dose will be summarized using the number of subjects exposed, mean, standard deviation, median, minimum, and maximum by treatment groups. 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 groups and total for up to Week 4, Week 40 to 52, and overall. Up to Week 2 and Week 2 to 4 will also be summarized for only cohort 3. The categories will be classified into under compliant, compliant, over compliant.

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				Y			
Observed Case	Efficacy PD				Y			
Observed Case by Subgroup[3]	Efficacy PD				Y			
Model based Mean Hgb during the Primary Efficacy Evaluation Period								
(Primary) MMRM	ITT	Y	Y					
MMRM	mITT/PP /Efficacy ND	Y	Y					
MMRM By Subgroup	ITT	Y	Y[1][2]					
MMRM Excluding ESA Users with Hgb rapid increase at Week 2	ITT	Y	Y					
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
[2] For prior ESA use, Hgb curve over time will also be displayed.
[3] Only for prior ESA use and baseline Hgb.

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 for the mITT and Efficacy PD population. For the Efficacy PD population, summary will also be provided by baseline Hgb.

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 non-inferiority p-value will be provided. Analysis will be repeated by mITT, PP, Efficacy ND populations in the same manner. The subgroup analysis based on the ITT population will be also produced using tables and forest plot (See Section 7.1.5 for the detail).

Sensitivity/Supplementary analysis for Mean Hgb during the Primary Efficacy Evaluation Period

- Excluding ESA Users with Hgb rapid increase at Week 2

  Supplementary analysis excluding the ESA users whose daprodustat dose level was decreased by one step at Week 2 will be performed as the same as primary efficacy analysis using a mixed model for repeated measures.

- 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 as the same 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. Analysis will be repeated for the PP population. The subgroup analysis based on the mITT population will 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, the horizontal and vertical axes indicate values of delta for daprodustat and epoetin beta pegol, will be provided as a heat map that represents non-inferiority p-values obtained from the test conducted for each delta adjustment. The color grids which highlight non-inferiority success or not will 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.
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 (11.0-13.0 g/dL) at first. This confirmation will be established if the lower and upper limit of 95% CI for the mean Hgb based on observed Hgb during the primary efficacy evaluation period in the 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 (Weeks 40 to 52)

Model Specification

- Analyses will be conducted by MMRM as follows:

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

$Hgb_{i,\ week}$: Hgb measurement for subject i at visit k
β_0: Intercept
$\beta_{baseline}$: baseline Hgb effect
$Baseline_i$: Hgb measurement for subject i
β_j: treatment effect (j= daprodustat, epoetin beta pegol)
β_k: visit effect (k = Week 4, Week 8, …, Week 52)
β_{jk}: treatment-by-visit interaction
$\beta_{baseline*k}$: baseline-by-visit interaction
ε_{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 degree 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.

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

μ_{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

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

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

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

δ: 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.
- 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 non-inferiority p-value will be provided.
- Non-inferiority will be established if the lower limit of the 95% CI for the treatment difference (daprodustat - epoetin beta pegol) 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).
- Model based Hgb curve over time with 95% confidence band will be displayed graphically for each treatment.

Subgroup Analyses

- Treatment differences (daprodustat - epoetin beta pegol) of the mean Hgb during the primary efficacy evaluation period, standard error, and the associated 95%CIs will be provided by each subgroup (See Section 5.4.2).
- The subgroup analyses will be based on the ITT population.
- 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.
- 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.
- For prior ESA use, model based Hgb curve over time with 95% confidence band will be displayed graphically for each treatment.

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:

- ***ESA Users with Hgb rapid increase at Week 2***; the primary efficacy analysis will be repeated for the ITT population excluding the ESA users whose daprodustat dose level was decreased by one step at Week 2.

- ***Efficacy ND Population***; the primary efficacy analyses will be repeated for the Efficacy ND population (see Section 4).

- ***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 values considered to be impacted by a red blood cell transfusion, a whole 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, baseline Hgb, and prior ESA use. 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 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 a red blood cell transfusion, a whole 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:

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

$\text{mean}(Hgb_i) = (Hgb_{i,\text{Week 40}} + Hgb_{i,\text{Week 44}} + Hgb_{i,\text{Week 48}} + Hgb_{i,\text{Week 52}})/4$:
mean Hgb during the primary efficacy evaluation period for subject i
β_0: Intercept
$\beta_{baseline}$: baseline Hgb effect
$Baseline_i$: Hgb measurement for subject i
β_j: treatment effect (j= daprodustat, epoetin beta pegol)
β_l: prior ESA use effect (l = ESA user, ESA non user)
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:

$$\mu_j = \beta_0 + \beta_{baseline} * \mu_{baseline} + \beta_j + (\beta_{ESA\ user} + \beta_{ESA\ non\text{-}user})/2$$

μ_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:

$$\mu_{daprodustat} - \mu_{epoetin} = \beta_{daprodustat} - \beta_{epoetin}$$

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

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

δ: 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 the 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 epoetin beta pegol arm will vary independently, and will include scenarios where subjects with missing data on daprodustat have worse outcomes than subjects with missing data on epoetin beta pegol. 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 Yuan 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 201753.

- The analysis will not include subjects who are in the ITT population but who don't have any Hgb measurement on and after Week 4 (i.e., withdrawn at Week 2).
- 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_i (i=1,…,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 covariates and $Y_1,\ldots,Y_{n-1}$.

2. *Delta (Δ) Adjustment Strategy*

- Based on MAR assumption (Δ=0), monotone missing data that occurred before Week 52 will be imputed as shown above. To mimic missing not at random manner, sequentially increasing Δ will be added to imputed values where Δ represents a change in Hgb over 4-week interval. No Δ adjustments will be done for intermittent missing values.
  - Sequentially increasing Δ adjustment is to add n*Δ value on the imputed value of nth monotone missing data. The longer the period of time with monotone missing, the larger Δ 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 Δ is added to an imputed value on Week 44, 2Δ on Week 48, and 3Δ on Week 52.
- Initially, the Δ 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 larger increment (=1.0 g/dL), the exploration will be done with smaller increments to find the more precise tipping points. In order to keep clinically plausible range, if delta adjusted imputed value is lower than 7.0 g/dL or higher than 14.0 g/dL then the value will be replaced by 7.0 g/dL or 14.0 g/dL respectively. To reduce computationally intensive iterations, the further worsening scenarios beyond a range from -4.0 to 4.0 g/dL will not be examined.

3. *Analysis Strategy for Each Imputed Complete Dataset*

- 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 period will be estimated for each imputed complete dataset.

4. *Combine results of m datasets*

- 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.   • 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 mITT and PP population.

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 Efficacy ND Population	Y						
Logistic Regression mITT Population By Subgroup	Y	Y[1]					
Efficacy PD Population				Y			
Efficacy PD Population By Subgroup[2]				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
[2] Only for prior ESA use and baseline Hgb.

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, and non-responders will be summarized. Odds ratio will be estimated by using a logistic regression and provided along with its 95% CI and superiority one-sided p-value. Analysis will be repeated by the ITT, PP, and Efficacy ND populations in the same manner. The subgroup analysis based on the mITT population will be also produced using tables and a forest plot. For the Efficacy PD population, the summary of the number and percentage of responders and non-responders will be produced and the summary by prior ESA use and baseline Hgb will be created.

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-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 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 7.2.1 will be summarised 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 (11.0-13.0 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 target range will be derived from the mean of observed Hgb values during the primary efficacy evaluation period for individuals.
  Analyses will be conducted by a logistic regression model as follows:

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

  π_i: treatment success (mean(Hgb_i) is within the target range or not)
  β_0: Intercept
  $\beta_{baseline}$: baseline Hgb effect
  $Baseline_i$: Hgb measurement for subject i
  β_j: treatment effect (j= daprodustat, epoetin beta pegol)
  β_l: Prior ESA use effect (l = ESA user, ESA non user)
  ε: random error
  i: subject (i = PPD …, N)
  N: number of subjects included in the analysis
- The mean Hgb during the primary efficacy evaluation period will be calculated by individuals 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 efficacy evaluation period due to intercurrent events will be regarded as a non-responder.
- The odds ratio (daprodustat/epoetin beta pegol) will be obtained as follows:
  $OR = \exp(\beta_{daprodustat} - \beta_{epoetin})$
  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.
- If there is a problem with quasi-complete separation, a penalized likelihood method by Firth will be used by specifying the FIRTH option in the MODEL statement.

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 (11.0-13.0 g/dL) will be presented by treatment group. If available, the odds ratio (daprodustat/epoetin beta pegol), 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 for all subgroup specified in Section 5.4.2 and the Efficacy PD population for baseline Hgb. • 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 odd ratios and the associated 95% CIs will be produced using a forest plot for the mITT population. 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 by Prior ESA[1] and baseline Hgb			Y	Y[9]		
Change from baseline in Hgb (g/dL) at each assessment visit			Y	Y		
Change from baseline in Hgb (g/dL) at each assessment visit by Prior ESA[1] and baseline Hgb			Y	Y[9]		
Number (%) of subjects by Hgb change from baseline category at Week 2 and 4 [2]			Y			
Number (%) of subjects by Hgb change from baseline category at Week 2 and 4 by Prior ESA[1][2] and baseline Hgb			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][6]			Y			Y
Time (%) in Hgb target range during the primary efficacy evaluation period by prior ESA use[4][6]			Y			
Time (days) to reach the lower Hgb target (11.0 g/dL) [5][6]			Y	Y		Y
Time (days) to reach the lower Hgb target (11.0 g/dL) by prior ESA use[5][6]			Y	Y		
Number (%) of subjects who have an Hgb level of less than 7.5 g/dL[6]			Y			Y
Number (%) of subjects who have an Hgb level of less than 7.5 g/dL by prior ESA use[6]			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 increase of more than 2.0 g/dL over any 4 weeks by prior ESA use			Y			
Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes[6]			Y			Y
Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes by prior ESA use[6]			Y			

[Endpoint / Parameter/ Display Type]	Absolute					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Hemocue Hgb						Y
Scatter Plot of Hgb Assessments: Central Laboratory vs. HemoCue				Y		
Dose adjustment						
Dose (mg or μg) at each assessment visit / final visit			Y			Y
Dose (mg or μg) at each assessment visit / final visit by prior ESA[1]			Y			
Duration (days) of treatment interruption due to Hgb >13.0 g/dL			Y			Y
Duration (days) of treatment interruption due to Hgb >13.0 g/dL by prior ESA use			Y			
Dose adjustment			Y			
Dose adjustment by prior ESA use			Y			
Number of dose adjustment to reach the lower Hgb target (11.0 g/dL)			Y			
Number of dose adjustment to reach the lower Hgb target (11.0 g/dL) by prior ESA use			Y			
Number (%) of subjects with each dose at each assessment visit			Y	Y		
Number(%) of subjects with each dose at each assessment visit by prior ESA[1]			Y	Y		
Hgb and Dose						
Profiles of Hgb and dose over time					Y	
Iron Use						
Dose of oral iron (mg) during the treatment period and the primary efficacy evaluation period (Week 40 to 52)			Y			
Change from baseline in dose of oral iron (mg) during the treatment period and the primary efficacy evaluation period			Y			
Dose of oral 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			

[Endpoint / Parameter/ Display Type]	Absolute					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Iron Parameters (ferritin, TSAT, hepcidin, serum iron, TIBC)						
Raw observed value at each assessment visit			Y	Y		Y
Raw observed value at each assessment visit by Subgroup[7]			Y	Y		
Change from baseline at each assessment visit	Y	Y	Y			
Change from baseline at each assessment visit by Subgroup[7]	Y	Y[8]	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] prior ESA use, prior ESA dose, prior ESA type, and ERI

[2] <=-1, >-1 to -0.5, >-0.5 to 0, >0 to 0.5, >0.5 to 1, >1 g/dL, within ±0.5 g/dL and over ±1 g/dL for Week 2
<=-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, >2 g/dL, within ±1 g/dL and over ±2 g/dL for Week 4

[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] Kaplan-Meier method will be used to estimate P25, median and P75. Subjects within target range at baseline and subjects who could not reach lower target will be regarded as censored.

[6] 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).

[7] Only baseline iron use, prior ESA use

[8] Only baseline iron use

[9] Only prior ESA use and baseline Hgb

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. The summary will also be provided by prior ESA use, prior ESA dose, prior ESA type, and ERI. Graphical summaries will be provided using mean and 95% CI over time. The graphical summaries will also be provided by prior ESA use. The value at Wk2 (only for Cohort 3) will be provided only in summary (not in graphical summary).

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. The summary will also be provided by prior ESA use, prior ESA dose, prior ESA type, and ERI. Graphical summaries will be provided using mean and 95% CI over time. The graphical summaries will also be provided by prior ESA use. The value at Wk2 (only for Cohort 3) will be provided only in summary (not in graphical summary).

Number (%) of subjects by Hgb change from baseline category at Week 2 and 4

The number and percentage of subjects within each category will be provided by treatment group and the categories will be classified into 6 (i.e., ≤-1, >-1 to -0.5, >-0.5 to 0, >0 to 0.5, >0.5 to 1, >1 g/dL for Week 2, ≤-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, >2 g/dL for Week 4). In addition, 'within ±1 g/dL (i.e., ≤-1 and ≥1)' and 'over ±2 g/dL (i.e., <-2 and >2)' categories for Week 4 and 'within ±0.5 g/dL (i.e., ≤-0.5 and ≥0.5)' and 'over ±1 g/dL (i.e., <-1 and >1)' categories for Week 2 will be provided. The summary will also be provided by prior ESA use, prior ESA dose, prior ESA type, and ERI.

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 Hgb target range during the primary efficacy evaluation period

The time (weeks and percent) within/above/below the target range will be summarized by treatment group using mean, standard deviation, minimum, P25, median, P75, and maximum. For the ITT population, the treatment differences (daprodustat – epoetin beta pegol) 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. The summary will also be provided by prior ESA use.

Time (in days) to reach the lower Hgb target (11.0 g/dL)

The time (days) to reach the lower Hgb target will be summarized by treatment group using P25, median, and P75 by Kaplan-Meier method. Kaplan-Meier plot of time to event will be provided using on-therapy Hgb values including unscheduled visits. Subjects who could not reach lower target will be regarded as censored. Subjects who have baseline central laboratory Hgb >= 11.0 g/dL will be excluded in this analysis. The summary will also be provided by prior ESA use.

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 (excluding Week 2) during the treatment period will be summarized by treatment group. For the ITT population, the odds ratio (daprodustat/epoetin beta pegol) 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 by treatment group using mean, standard deviation, minimum, P25, median, P75, mode, and maximum at each assessment visit. 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. The summary will also be provided by Prior ESA use, prior ESA dose, prior ESA type, and ERI.

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

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

Dose adjustment

The number and percentage of subjects with dose adjustments will be provided. Number of dose adjustments will be summarized by treatment group 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; may be refined) by treatment group during the whole treatment period. For timing of dose adjustments, the

number and percentage of subjects with dose adjustments by each assessment visit will be provided by treatment group. The summary will also be provided by Prior ESA use.

Dose adjustment to reach the lower Hgb target (11.0 g/dL)

The number and percentage of subjects with dose adjustments to reach the lower Hgb target will be provided by treatment group on the basis of on-therapy Hgb. Number of dose adjustment to reach the lower Hgb target will be summarized by treatment group 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) by treatment group. For timing of dose adjustments, the number and percentage of subjects with dose adjustments by each assessment visit will be provided by treatment group. Subjects who do not reach the lower Hgb target during treatment period will be excluded from the summary. The summary will also be provided by Prior ESA use.

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

The number and percentage of subjects with each dose will be provided. Graphical summaries of histogram will be provided with the number of subjects in each dose. Summary and histogram will be produced for each treatment group separately. For daprodustat, dose categories will be classified into 10; N/A (not available), 0 mg (treatment interruption), 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 18 mg, and 24 mg. For epoetin beta pegol, dose categories will be classified into 9, N/A (not available), 0 μg (treatment interruption), 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg. The final visit will be the last visit of treatment exposure for each subject. The summary and histogram will also be provided by Prior ESA use, prior ESA dose, prior ESA type, and ERI.

- **Hgb and Dose**

Profiles over time of Hgb and dose will be plotted for each subject.

- **Iron Use**

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

Monthly Average oral iron dose by quarter (See Section 15.6.3) 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), during the screening period as baseline, and whole treatment period will be used and Quarter 4 represents the primary efficacy evaluation period. This will be also summarized by baseline iron use defined in Section 5.4.2.

Change from baseline in dose of oral iron (mg) during the treatment period and the primary efficacy evaluation period

Change from baseline in average oral iron dose (See Section 15.6.3) 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 Quarter 4 represents the primary efficacy evaluation period. For the ITT population, the treatment differences (daprodustat – epoetin beta pegol) and the associated 95% CIs will also be provided.

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 screening period as baseline, the treatment period, and the primary efficacy evaluation period will be summarized separately. These will be also 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 visits

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. Graphical summaries will also be provided for each iron parameter. These will be also summarized by baseline iron use, prior ESA use.

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 – epoetin beta pegol) and the associated 95% CIs for change from baseline will be provided at each assessment (See Section 7.3.5). 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 the adjusted geometric means percent change from baseline and the associated 95%

CIs over time. For the ITT population, Except for the graphical summaries, these will be also summarized by baseline iron use, prior ESA use, and both them. The graphical summaries will also be provided by only baseline iron use.

7.3.3. Population of Interest

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

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

Any intercurrent events are taken to be irrelevant for secondary endpoints and the secondary 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.

7.3.5. 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.

7.3.5.1. 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: $Iron_{ik} = \beta_0 + \beta_{baseline} * Baseline_i + \beta_j + \beta_k + \beta_{jk} + \beta_{baseline*k} * Baseline_i + \varepsilon_{ik}$ $Iron_{i,\ week}$: change from baseline in iron measurement for subject i at visit k

β_0: Intercept
$\beta_{baseline}$: baseline effect of each iron parameter
$Baseline_i$: the baseline value of each iron parameter for subject i
β_j: treatment effect (j= daprodustat, epoetin beta pegol)
β_k: visit effect (k = Week 4, Week 16, Week 28, Week 40, Week 52)
β_{jk}: treatment-by-visit interaction
$\beta_{baseline*k}$: baseline-by-visit interaction
ε_{ik}: random error for subject i at visit k
i: subject (i = PPD …, 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 mean change from baseline for treatment j at visit k will be calculated as follows for each iron parameter.

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

μ_{jk}: LS mean change from baseline 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

$$\mu_{daprodustat*k} - \mu_{epoetin\ beta\ pegol*k} = \beta_{daprodustat} - \beta_{epoetin\ beta\ pegol} + \beta_{daprodustat*k} - \beta_{epoetin\ beta\ pegol*k}$$

- 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 = $\exp(\mu_{daprodustat*k} - \mu_{epoetin\ beta\ pegol*k})$

Model Checking & Diagnostics

- In case there is a problem with convergence of the unstructured (type=UN) variance-covariance, the following strategy will be examined.
  1. Use Fisher's scoring algorithm for the estimation method.
  2. Set Heterogeneous Toeplitz (type=TOEPH) structure for variance-covariance structure.
  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 – epoetin beta pegol) for change from baseline will also be presented with the associated 95% CI at each assessment visit.

- 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 / epoetin beta pegol) 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 and prior ESA use subgroup (See Section 5.4.2) in the same manner.
- The subgroup analyses will be based on the ITT and Efficacy PD population.
- If there is a problem with convergence for a subgroup, the result of the subgroup will not be displayed.

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
CKD progression (eGFR, serum creatinine, urine creatinine, urine albumin, urine albumin/creatinine ratio)						
Raw observed value at each assessment visit			Y	Y		Y
Change from baseline at each assessment visit			Y	Y		
Number (%) of subjects with eGFR decrease of 30% or more from baseline			Y			
Number (%) of subjects with serum creatinine increase of more than double from baseline			Y			
Other						
Scatter plot of change from baseline in Hgb at Week 4 vs. covariates of interest				Y		
Scatter plot of mean dose during Week 40 to 52 vs. covariates of interest				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

- **CKD progression (eGFR, serum creatinine, urine creatinine, urine albumin, urine albumin/creatinine ratio)**

Raw observed value at each assessment visits

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.

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.

Number (%) of subjects with eGFR decrease of 30% or more from baseline

The number and percentage of subjects with eGFR decrease of 30% or more from baseline will be summarized at each assessment visit by treatment group.

Number (%) of subjects with serum creatinine increase of more than double from baseline

The number and percentage of subjects with serum creatinine increase of more than double from baseline will be summarized at each assessment visit by treatment 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 for the ITT and Efficacy PD populations. 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 for the ITT and Efficacy PD populations. 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. The exploratory endpoints will be summarized based on available and observed data.

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.

8. SAFETY ANALYSES

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

The summary will be provided by dialysis (ND and PD separately) and treatment group.

8.1. Adverse Events Analyses

Adverse event 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 by Prior ESA Use	Y		
On-therapy AEs by SOC and PT by CKD Stage	Y		
On-therapy AEs by SOC and PT and Maximum Intensity	Y		
On-therapy AEs by SOC and PT and Maximum Intensity by Prior ESA Use	Y		
On-therapy AEs up to Week 4 by SOC and PT	Y		
On-therapy AEs up to Week 4 by SOC and PT by Prior ESA Use	Y		
On-therapy AEs up to Week 4 by SOC and PT by Starting Dose of Daprodustat	Y		
On-therapy AEs up to Week 4 by SOC and PT and Maximum Intensity	Y		
On-therapy AEs up to Week 4 by SOC and PT and Maximum Intensity by prior ESA use	Y		
On-therapy Common (>= 2 %) AEs by SOC and PT by onset	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 by Prior ESA Use	Y		
On-therapy Drug-Related AEs by SOC and PT by CKD Stage	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 (>= 2 %) AEs by Overall Frequency by Prior ESA Use	Y		
On-therapy Common (>= 2 %) AEs by Overall Frequency by CKD Stage	Y		

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
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		Y[3]
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 Treatment by SOC and PT	Y		Y
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.
[3] Prior ESA use will also be displayed in the listing.

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 and On-therapy AEs up to Week 4 will also be summarized by prior ESA use. On-therapy AEs will also be summarized by CKD stage. On-therapy AEs up to Week 4 will also be summarized by starting dose of daprodustat (i.e. bycohort, prior ESA use, and baseline Hgb). 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 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. On-therapy AEs and On-therapy AEs up to Week 4 will also be summarized by prior ESA use.

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. On-therapy drug-related AEs will also be summarized by prior ESA use. On-therapy drug-related AEs will also be summarized by CKD stage.

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 AEs, on-therapy AEs 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. The summary will also be provided by prior ESA use and CKD stage.

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

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, 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	Y					

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Post-Baseline Relative to Baseline						
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					
Urinalysis[3] (ND subjects only)						
Urinalysis Values by Visit	Y		Y	Y		
Worst Case Urinalysis Results Relative to Normal Range Post-Baseline Relative to Baseline	Y					
Iron Parameters						
Iron Values by Visit[4]	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 [2]						
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] iPTH and eGFR will be collected as other laboratory tests
[3] Urine creatinine, urine albumin, urine albumin/creatinine ratio
[4] Transferrin and UIBC will be included for this summary and other iron parameters will be provided as efficacy endpoints.

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/Urinalysis/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 values, hematology values, iron parameters, urinalysis values, and other laboratory values will be summarized separately.

Percent change in Lipid Parameters

Lipid parameters 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, hematology, urinalysis, 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 and percentage 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 treatment period	Y		Y			
Other						
Subjects who became pregnant during the study			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 vital signs will be provided for raw values and change from baseline. In a summary of change from baseline, each baseline value 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
SF-36 HR-QoL Scores (PCS, MCS, 8 subscales) by Prior ESA Use			Y			
Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 subscales)	Y		Y			
Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 subscales) by Prior ESA Use	Y		Y			
EQ-5D-5L Scores			Y			Y
EQ-5D-5L Scores by Prior ESA Use			Y			
EQ-5D-5L Index Values			Y			Y
EQ-5D-5L Index Values by Prior ESA Use			Y			
Changes from Baseline in EQ-5D-5L Index Values	Y		Y			
Changes from Baseline in EQ-5D-5L Index Values by Prior ESA Use	Y		Y			
EQ VAS			Y			Y
EQ VAS by Prior ESA Use			Y			
Changes from Baseline in EQ VAS	Y		Y			
Changes from Baseline in EQ VAS by Prior ESA Use	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]), and their changes from baseline 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. The summary will also be provided by prior ESA use.

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 EQ-5D-5L score within each category will be displayed at each assessment visit by treatment group. EQ-5D-5L index values, EQ VAS scores, and their changes from baseline will be provided using mean, standard deviation, median, minimum, and maximum at each assessment visit by treatment group. The summary will also be provided by prior ESA use. For changes from baseline, the adjusted treatment difference and the 95% CIs will also be provided.

9.3. Population of Interest

The analyses will be based on the ITT and Efficacy PD 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 9.1 will be summarized using descriptive statistics 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 7.3.5.1: • 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 – epoetin beta pegol) for change from baseline will also be presented with the associated 95% CI at each assessment visit.
Subgroup Analyses
• Similar to the respective QoL parameters, the above analysis will be repeated by prior ESA use subgroup (See Section 5.4.2) in the same manner. • The subgroup analyses will be based on the ITT and Efficacy PD population. • If there is a problem with convergence for a subgroup, the result of the subgroup will not be displayed.

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, or concentrations obtained in the less interval of last two treatment administrations than 12 hours 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 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. 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, 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 as the same 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 assigned to wrong stratum or 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. gemifibrozil) and strong inducers of CYP2C8 (e.g. rifampin/rifampicin), not include erythropoietin (e.g., epoetin/ darbepoetin alfa/ epoetin beta pegol, excluding epoetin beta pegol supplied by GSK).

[3] See Section 15.6.2; Under 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[9]	Treatment																Follow-up
Week	-4	Day 1	2[10]	4	8	12	16	20	24	28	32	36	40	44	48	52	Early withdrawal[10]	4 weeks after 52 or withdrawal
Permissible range (days)	±7	-	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-	±7
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Medical history, demography, height, weight	X																	
IWRS call	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication dispensing [1,2]		X	X[10]	X	X	X	X	X	X	X	X	X	X	X	X			
Study treatment compliance			X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X		X			X			X			X			X	X	X
Ophthalmology [3]	◄——►					◄——►									◄———	———►		
ECG	X								X							X		
HemoCue Hgb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	Only Hgb	Only Hgb	X	X	X
Clinical chemistry	X	X		X			X			X			X			X	X	X
Urinalysis (ND subjects only)	X	X							X							X		X
Pregnancy test (urine or serum hCG) [4]	X	X		X			X			X			X			X	X	X
Estradiol, FSH [5]	X																	
PK [6]						X			X									
Ferritin, TSAT	X	X		X			X			X			X			X	X	
Serum iron, TIBC, UIBC, serum transferrin, hepcidin		X		X			X			X			X			X	X	
iPTH		X								X						X		
HR-QoL		X				X				X						X	X	
Genetics sample [7]		X																

Phase	Screening[9]	Treatment																Follow-up
Week	-4	Day 1	2[10]	4	8	12	16	20	24	28	32	36	40	44	48	52	Early withdrawal[10]	4 weeks after 52 or withdrawal
Permissible range (days)	±7	-	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	-	±7
Adverse event assessment [8]		◄	►															
Review Concomitant Medications	◄	►																

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

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

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

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.

15.3.1. Definitions of Assessment Windows for Analyses

Analysis Time Point	Definitions
Screening [1]	Data collected in Screening visit If multiple records are present, the latest record will be used for analysis.
Day 1 [1]	Data collected in Day 1 visit If multiple records are present, the latest record will be used for analysis.
Week 2	Data collected in Week 2 visit [2]
Week 4	Data collected in Week 4 visit
Week 8	Data collected in Week 8 visit
Week 12	Data collected in Week 12 visit
Week 16	Data collected in Week 16 visit
Week 20	Data collected in Week 20 visit
Week 24	Data collected in Week 24 visit
Week 28	Data collected in Week 28 visit
Week 32	Data collected in Week 32 visit
Week 36	Data collected in Week 36 visit
Week 40	Data collected in Week 40 visit
Week 44	Data collected in Week 44 visit
Week 48	Data collected in Week 48 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 and Section 15.6.2)
[2] Only ND subjects randomized to Cohort 3

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

NOTES:

- Data of concomitant medication includes anti-hypertensive medication, 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
(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

Randomization Date

Treatment Stop Date + 1 Days

Treatment Stop Date +2 Days

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/mid201753/final_01
QC Spreadsheet	: /arenv/arprod/gsk1278863/mid201753/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):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located 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. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
  • Scheduled visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings, figures, summaries and statistical analyses.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures. • If unscheduled visits are included, details of how summaries will be displayed will be provided in the RAP. • 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. 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. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. 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: • 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). 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. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (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. • For multiple measurements at Screening and/or Day 1 visit, the screening pass visit record will be used for analysis (See Appendix 3: Assessment Windows)
Study Day

• Calculated as the number of days from Randomization Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomization Date → Study Day = Ref Date – Randomization Date
  • 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. • 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) • 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 treatment stop date.
Treatment Stop Date – Epoetin Beta Pegol

• Following definition will be based on "assumed" treatment stop date because the treatment stop date is not captured in eCRF.
Definition:
• 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..
  ○ Week 52 visit date will be based on laboratory Hgb date. HemoCue Hgb date will be used when laboratory Hgb date is unavailable.
• 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 dosing start date + XX days (1 day before the next treatment start date if a subject hadn't withdrawn)
  • Subjects will have every 2 weeks or every 4 weeks injection of epoetin beta pegol, therefore assumed treatment stop date could include "+ 13 or 27 days" to mimic every 2 weeks or every 4 weeks dosing.

Subgroup definition

• For general considerations, see Section 5.4.2
• Regarding prior ESA type, prior ESA dose, and ERI, see Section 15.6.2
• Baseline iron use = use or non-use of pre-therapy iron medications (including ferric citrate (trade name Riona), see Section 15.6.3).
• History of diabetes will be derived from the current history diabetes (Yes/No) in medical history records.
• CKD stage will be derived from the eGFR measurement at a screening visit
• Cohort will be derived from the randomization number.
  ○ Cohort 1 = Randomization Number in PPD
  ○ Cohort 2 = Randomization Number in PPD
  ○ Cohort 3 = Randomization Number in PPD
• Dialysis will be derived from the randomization number.
  ○ ND subjects = Cohort 1 or 3
  ○ PD subjects = Cohort 2

Time Definitions (per GSK standard principles)
• 1 week = 7 days • 1 month = 30.4375 days • 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.
  ○ The screening status of a subject who failed screening but passed rescreening will be 'enrolled', and the reason for failure will not be counted.
  ○ 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.
• 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:
  ○ A date and month will be imputed as PPD as it will not be captured.
• Randomization date will be used as reference date of calculation.
  ○ If randomization date is missing, screening date will be used.

Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]^2

Demographics and Baseline Characteristics

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	CMDRGCOL
Epoetin	00928302 00928303 00928305
Epoetin beta pegol	53876201
Darbepoetin alfa	50520401

- Dosing route (i.v. or s.c.) is captured in eCRF directly.

Prior ESA dose (IU/week) at Baseline

- During screening, subjects may be receiving ESA in multiple ways, including epoetin i.v. or s.c., darbepoeitin alfa i.v. or s.c., or epoetin beta pegol i.v. or s.c. The dose of ESA during the period of 12 weeks prior to randomization will be standardized to obtain a continuous single unit prior ESA dose in terms of epoetin i.v. (IU/week). The standardization will be carried with the following formula based on literature review:
  - For subjects taking epoetin i.v.
    - Standardized mean prior ESA dose (IU/week) = epoetin i.v. dose (IU/week)
  - For subjects taking epoetin s.c.
    - Standardized mean prior ESA dose (IU/week) = (161/113)*epoetin s.c. dose(IU/week): [Besarab 2002]
  - For subjects taking darbepoeitin alfa i.v. or s.c.
    - Standardized mean prior ESA dose (IU/week) = 250*darbepoeitin alfa dose (μg/week)
  - For subjects taking epoetin beta pegol i.v. or s.c.
    - 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)
    $= ([dose]_1 * [frequency]_1 + ... + [dose]_n * [frequency]_n) / \{([duration]_1 + ... + [duration]_n) / 7\}$
    where
    - $[dose]_n$: dose at n th record
    - $[frequency]_n$ = 1 when once daily (QD)
    - $[duration]_n$ = [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.
- Prior ESA dose during the period of 12 weeks prior to randomization will be used for calculation.
  - Let the latest record of earlier records than the date of 12 weeks prior to randomization date be the 1st record. If no earlier record than the date of 12 weeks prior to randomization date, let the earliest record be the 1st record.
  - If prior ESA start date of 1st record is earlier than 12 weeks prior to randomization date then dose and duration of 1st record for calculation of prior ESA dose are defined as follows:
    - $[dose]_1$ = Original dose * $[Duration]_1$ / Original duration
    - Original dose is dose recorded in 1st record

Demographics and Baseline Characteristics

- Original duration = [Prior ESA start date]$_2$ – [prior ESA start date]$_1$
  or
  [Randomization date] – [prior ESA start date]$_1$
  when 1st record is the last prior ESA dose
- [Duration]$_1$ = [Prior ESA start date]$_2$ – [Randomization date – 84]
  or
  84
  when 1st record is the last prior ESA dose

Illustration of Standardized Mean Prior ESA calculation (ex: epoetin i.v.)

i) 1st record is not earlier than 12 weeks prior to randomization date

Record#	Visit	Start Date	Dose (IU)	Duration (days)
1	Screening	10Feb2017	750	24
2	Screening	06Mar2017	750	28
3	Screening	03Apr2017	1500	28
-	Day 1	PPD [Randomization Date]	Total dose = 3000	Total duration = 80

Mean prior ESA dose (IU/week) = 3000/(80/7) = 262.5

ii) 1st record is earlier than 12 weeks prior to randomization date

Record#	Visit	Start Date	Dose (IU)	Duration (days)	Duration for calculation	Dose for calculation
1	Screening	03Feb2017	750	30	27[1]	750*27/30 = 675
2	Screening	05Mar2017	750	29	29	750
3	Screening	03Apr2017	1500	28	28	1500
-	Day 1	PPD [Randomization Date]			Total duration = 84	Total dose = 2925

[1] [Prior ESA start date]$_2$ – [Randomization date – 84] = [05Mar2017] – [06Feb2017] = 27

Mean prior ESA dose (IU/week) = 2925/(84/7) = 243.75

Erythropoietin Resistance Index (ERI) at Baseline

- Calculated as standardized mean prior ESA dose (IU/week) divided by weight (kg) at screening visit and then divided by the achieved Day 1 central laboratory Hgb (g/dL).
- If prior ESA data is missing (e.g. ESA non-user), ERI will not be calculated.

Period of Time on Dialysis at Baseline

- Period of time on dialysis (years) will be defined as follows:
  - (Randomization Date – Date of Dialysis Initiation + 1) / 365.25
  - If Date of Dialysis Initiation is partially missing, follow the same handling as concomitant medications in Section 15.7.2.1.

Exposure

Prescribed Dose and Actual Dose for Daprodustat

- Prescribed dose will be derived from dose level captured in eCRF.
- Actual dose will be derived from dose level associated with a container number in eCRF. Note that unscheduled (additional) bottles will not be taken into account. If a container number is "NA" then actual dose is considered as 0mg.
- 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).

Prescribed Dose and Actual Dose for Epoetin Beta Pegol

- Prescribed dose and actual dose will be derived from dose level captured in eCRF.

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 formula:
  - Time on study treatment (days)
    = [Treatment Stop date] – [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 ([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 Epoetin beta pegol

- 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 formula:
  - Time on study treatment (days)
    = [Treatment Stop date] (see Section 15.6.1)– [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 monthly dose (= Cumulative Dose / Time on study treatment x 30.4375 days) is calculated for each subject using actual dose and the summary statistics are calculated based on the subject average monthly dose.
- Distribution of the dose level

  Dose level will be classified into 8 categories; 0 μg (i.e. treatment interruption), 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg according to actual dose.

Treatment Compliance of Daprodustat

- Treatment compliance of daprodustat will be based on # of tablets and categorized as Under compliance, Compliant, and Over Compliant
  - Calculated compliance < 80% → Under Compliant
  - Calculated compliance ≥ 80% and ≤ 120% → Compliant

Exposure

- Calculated compliance > 120% → Over Compliant

- Treatment compliance will be calculated for daprodustat as following formula:
  - 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 [(Dosing Stop Date – Dosing Start Date + 1 day) x Planned # of tablet / day in Each Visit]

  Planned # of tablet/day is defined as follows according to the protocol:
  - 0 mg → 0 tablet/day (i.e. compliance will not be calculated)
  - 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.
  - Dosing Start Date and Dosing Stop Date will be defined according to the period for compliance calculation as below

Period for Compliance Calculation	Dosing Start Date	Dosing Stop Date[2]
0 – 2 Week[1]	Treatment Start Date	Day 1 Dosing Stop Date
0 – 4 Week (Cohort 1)	Treatment Start Date	Day 1 Dosing Stop Date
0 – 4 Week (Cohort 3)	Treatment Start Date Week 2 Dosing Start Date	Day 1 Dosing Stop Date Week 2 Dosing Stop Date
2 – 4 Week[1]	Week 2 Dosing Start Date	Week 2 Dosing Stop Date
Primary Efficacy Evaluation Period (40 – 52 Week)	Dosing Start Date at each visit from Week 40 to 48	Dosing Stop Date at each visit from Week 40 to 48
Overall	Dosing Start Date at each visit	Dosing Stop Date at each visit

[1] Compliance will not be calculated for Cohort 1.
[2] If Dosing Stop Date is missing Treatment Stop Date will be used.

Treatment Compliance of Epoetin Beta Pegol

- Treatment compliance of epoetin beta pegol will be based on dosing records (dose per every 2 or 4weeks are captured) and categorized as Under compliance, Compliant, and Over Compliant
  - Calculated compliance < 80% → Under Compliant
  - Calculated compliance ≥ 80% and ≤ 120% → Compliant
  - Calculated compliance > 120% → Over Compliant
- Calculated compliance will be provided to derive compliance category only, not provided for any displays. It will be carried using the following formula:
  - Calculated Compliance (%) = [(Total # of dosing) / (Total # of planned dosing)] x 100
  - Total # of dosing = Sum of Numbers of dosing records where Prescribed Dose equals Actual Dose
  - Total # of planned dosing = Sum of # of planned dosing of each dosing records
  - # of planned dosing = Duration / 14 (if Frequency = every 2 weeks and Prescribed dose ≠ 0)
    Duration / 28 (if Frequency = every 4 weeks or Prescribed dose = 0)
  - Duration = Start Date of next dosing record – Start Date
    - If next dosing record is missing, Treatment Stop Date (see Section 15.6.1)+ 1 day will be

Exposure

used. instead of Start Date of next dosing record.

- Dosing records included in compliance calculation for each period are as below.

Period for Compliance Calculation	Dosing Records
0 – 2 Week[1]	First record of Day 1
0 – 4 Week	Day 1 to Week 2 (Day 1 for ESA users in Cohort 1)
2 – 4 Week[1]	Day 1 (ESA users) Week 2 (ESA non-users)
Primary Efficacy Evaluation Period (40 – 52 Week)	Week 40 to 48
Overall	All records

[1] Compliance will not be calculated for Cohort 1.

Medical Conditions and Concomitant Medications

Iron Medication

- Although the following iron-containing drugs are collected as iron medication data, they will not be included in the summary of other concomitant medications.
  - GSK drug code: 54909401 (SUCROFERRIC OXYHYDROXIDE; P-TOL).

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.

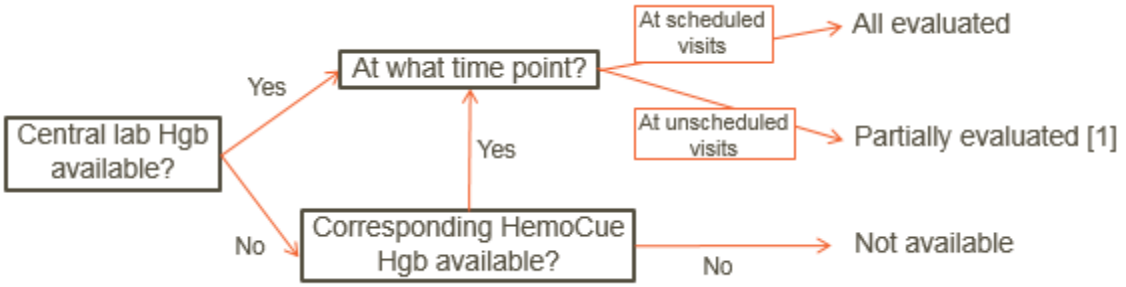
Evaluable Hgb Values

- 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 red blood cell transfusion, a whole blood transfusion, or a non-randomized ESA medication which occurs on or after the randomization date (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 of Hgb data ≤ Blood Product Administration Date + 56 (days)
  - ESA Start Date < Date of Hgb data ≤ ESA Stop Date + 56 (days)

Hgb Values

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
- Time (in days) to reach the lower Hgb target (11.0 g/dL)

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	PPD	1	Day 1	Not calculated
9.8		30	Week 4	0.7
11.9		61	Week 8	2.1
12.6		127	Week 16	Not calculated
12.7		158	Week 20	0.1
12.3		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 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.

Hgb Values

Scatter plot of Change from Baseline in Hgb at Week 4 vs covariates of interest

- The following scatter plot figures will be produced separately:
  - Change from baseline in Hgb (g/dL) at Week 4 vs. Baseline body weight (kg)
  - Change from baseline in Hgb (g/dL) at Week 4 vs. Baseline Hgb (g/dL)
  - Change from baseline in Hgb (g/dL) at Week 4 vs. Prior ESA dose
- Different displays by prior ESA use will be used to differentiate them.
- Vertical axis will indicate the change from baseline in Hgb (g/dL) at Week 4, horizontal axis will indicate the covariates of interest, baseline body weight (kg), 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. Baseline Body Weight (kg)
  - Mean Dose during Week 40 to 52 vs. Baseline Hgb
  - Mean Dose during Week 40 to 52 vs. Prior ESA dose
- Different displays by prior ESA use will be used to differentiate them.
- Vertical axis will indicate the mean dose (mg), horizontal axis will indicate the covariates of interest; baseline body weight (kg), 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 11.0-13.0 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 (Rosendaal1993).

Illustration of calculation

Hgb (g/dL)	Lab Date	Visit	Ref Day	Hgb Shift	Total shift (%) within range	Time in range (weeks)
9.9	PPD	Week 40	0	NC	NC	NC
11.2		Week 44	31	1.3 (=11.2-9.9)	total shift: 0.2 0.2/1.3=15.38%	(31-0)*0.1538/7 =4.77/7 (weeks)
missing		Week 48	61	NA	NA	NC
13.4		Week 52	92	2.2(=13.4-11.2)	total shift: 1.8 1.8/2.2=81.82%	(92-31)*0.8182/7 =49.91/7 (weeks)

Time in Target Range

Overall time in range = (4.77 + 49.91)/7 = 54.68/7 = 7.81 (weeks) Percent time in range = 7.81/(92/7) = 59.42%

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 has withdrawn from the treatment before Week 40 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 has withdrawn before Week 52. In the case of withdraw before Week 52, Treatment Stop Date (see Section 15.6.1) 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 11.2 g/dL on September 1st. The assumption is made that the week, between these scheduled assessments the subjects Hgb increases from 9.9 to 11.2 g/dL in a linear manner, To following steps are taken to calculate the time (days) the subject's Hgb was within target range (11.0 to 13.0 g/dL).
  1. Calculate amount of Hgb shift (9.9 to 11.2 = 1.3 shift) and Hgb shift within range (0.2 out of shift is within range of 11.0 – 13.0)
  2. Calculate percent of total shift (%) within range (0.2/1.3 = 15.38%)
  3. Estimate the number of weeks since last visit within range (15.38% x duration between assessments = 15.38% x 31/7 weeks = 0.68 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,

Time (days) to reach the lower Hgb target (11.0 g/dL)

- Time to reach the lower Hgb target will be determined as follows:
  - Time to reach the lower Hgb target = Date to reach the lower Hgb target – Randomization Date + 1 day
- Subjects who could not reach the lower Hgb target during on-therapy will be regarded as censored. Censored time will be determined as follows:
  - Censored time = Treatment Stop Date – Randomization Date + 1

Dose Adjustment

Dose adjustment algorithm

- 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.
- 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.

Dose Adjustment

- (FL_B): Over 13 g/dL flags will be counted if HemoCue Hgb >13 g/dL is observed.
- (FL_C): Interruption flags will be counted if actual doseis zero.

Treatment durations in each visit will be calculated based on the following formula:

- Daprodustat
  Duration (days) = Treatment Stop Date in the visit – Treatment Start Date in the visit + 1 day
- Epoetin beta pegol group
  Treatment stop date in the visit will be derived from [treatment start date in the next visit – 1 day]. If there is no record of the next scheduled visit, Treatment Stop Date(see Section 15.6.1) will be applied for the record.

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	PPD	29	11.1	4	N	N	N
Week 4		14	11.4	4	N	N	N
Week 8		30	11.8	2	Y	N	N
Week 12		31	13.4	0	Y	Y	Y
Week 16		30	12.6	0	N	N	Y
Week 20		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 g/dL'
- 'Dose adjustment'
- Number of dose adjustment to reach the lower Hgb target (11.0 g/dL)

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 specified 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 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'

Dose Adjustment

Number of dose adjustment to reach the lower Hgb target (11.0 g/dL)

- Reaching the lower Hgb target will be determined on the basis of central laboratory Hgb.
- Subjects who has a baseline central laboratory Hgb value within target range or who does not reach the lower Hgb target during treatment period will be excluded from the summary.
- Number of dose adjustment to reach the lower Hgb target will be counted for each subject as follows
  - Counts of adjustment flag ='Y' at visits before Date to reach the lower Hgb target.

Iron Endpoints

Oral Iron Use

- The following iron-containing drugs will not be included in the analysis of iron use.
  - GSK drug code: 54909401 (SUCROFERRIC OXYHYDROXIDE; P-TOL).

Subjects who used IV and/or oral iron

- Number of subjects who used IV and/or oral iron will be summarized
- Subjects who used IV and/or 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).
  - Regarding oral iron use, the number of subjects who used ferric citrate and other than ferric citrate will also be counted respectively.

Oral Iron Dose by Quarter

- Records of on-therapy iron medication will be used for the following calculations.
- Summary will be created for all subjects (both iron users and iron non-users) and iron users respectively. In a summary containing all subjects, iron dose of subjects who do not use iron medication will be calculated as 0 mg.
- Monthly average oral iron during the treatment period = Total oral iron dose (mg) during the treatment period / (duration in the treatment period (days) / 30.4375 days)
- Monthly average oral iron by quarter = Total oral iron dose during each quarter (mg) / (duration in a quarter (days) / 30.4375 days).
- Total oral 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 oral 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

  Total oral iron dose (mg) during the treatment period will be carried in the same manner.

- Quarters/Duration will be defined as follows:

	Start Date	End Date
baseline	Screening Date	Randomization Date - 1
Treatment	Randomization Date	Treatment Stop Date

period		
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 < screening date, the iron medication start date will be replaced with screening date for the analysis.
- If iron medication stop 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 of divided record and the start date in the latter of divided record will be the former quarter end date and the latter quarter start date, respectively.
- If no start or stop date is recorded on iron medication, the date will be replaced with Screening Date or Treatment Stop Date, respectively.
- For ferric citrate (trade name: Riona, GSK drug code = 00752601), iron dose value for analyses will be converted as follows,
    - Iron dose for analyses (mg) = iron dose (mg) x 62 / 250

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

- The baseline iron use will be defined as a subject takes a pre-therapy iron medication excluding sucroferric oxhydroxide (trade name: P-TOL, GSK drug code = 54909401).

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.SVSTDTC).

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.

AESI categories are classified as follows:

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access
- Cardiomyopathy
- Pulmonary artery hypertension
- Cancer-related mortality and tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

Following events will be programmatically identified as AESIs.

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:

- Any Hgb value > 13 g/dL
- Hgb increase > 2 g/dL over 2 weeks (applied to only Cohort 3)
- Hgb increase > 4 g/dL over 4 weeks

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.
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.
Note: 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.

Any SAE which outcome is fatal will be identified AESI as death.

CV Events

Patient profiles of CV events will be provided according to records captured in eCRF, except for Peripheral Arterial Thrombosis Embolism (PAT) form.

CV events in PAT form will be provided only when a related AE sequence number is not present. This is because several records in PAT form are captured just for AESI information instead of CV events.

Laboratory Parameters
• LDL/HDL cholesterol ratio will be derived from the following equation. ○ LDL/HDL cholesterol ratio = LDL cholesterol (mmol/L)/ HDL cholesterol (mmol/L)

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. ○ Example 1: 2 Significant Digits = '< x' becomes x – 0.01 ○ Example 2: 1 Significant Digit = '> x' becomes x + 0.1 ○ Example 3: 0 Significant Digits = '< x' becomes x – 1 • The following laboratory values will not be applicable for this imputation: ○ Hgb, serum iron, serum ferritin, serum transferrin, TIBC, UIBC, TSAT, and Hepcidin • The default convention for reporting of clinical laboratory units will be the international system of units (SI units).
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: ○Actual dose = 1 mg → 1 mg tablet strength ○Actual dose = 2 mg → 2 mg tablet strength ○Actual dose = 4 mg → 4 mg tablet strength ○Actual dose = 6 mg → 6 mg tablet strength ○Actual dose = 8 mg → 4 mg tablet strength ○Actual dose = 12 mg → 6 mg tablet strength ○Actual dose = 18 mg → 6 mg tablet strength ○Actual dose = 24 mg → 6 mg tablet strength • 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: ○ Treatment Start Date ≤ Date of last dose taken prior to PK sampling ≤ Treatment Stop Date
Others
• Dose normalized PK parameters will be derived from the PK parameters dividing by actual dose (mg). • In aggregated analyses, data collected in Week 12 and Week 24 will be aggregated. • For the PK parameters calculation, the concentration at 0 hr will be set to 0 and assign zero to NQ values. • Individual's PK parameters calculated less than 4-time point concentrations, or any time deviated (beyond ± 30 min of scheduled visits) concentrations, or concentrations obtained in the less interval of last two treatment administrations than 12 hours will be omitted from summaries and figures. but

General
presenting in a listing.

15.6.6. Exploratory Endpoint

CKD Progression
Equation for eGFR
eGFR is estimated by the following Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) equation. Male: eGFR (mL/min/1.73m^2) = 194 * Serum creatinine$^{-1.094}$ * Age$^{-0.287}$ Female: eGFR (mL/min/1.73m^2) = 194 * Serum creatinine$^{-1.094}$ * Age$^{-0.287}$ * 0.739
eGFR decrease of 30% or more from baseline
eGFR decrease of 30% or more from baseline is defined as follows. At each assessment visit, eGFR change (%) = (eGFR – Baseline eGFR) / Baseline eGFR * 100 If eGFR change (%) < -30 then let the eGFR at the visit be decrease of 30% or more from baseline.
Serum creatinine increase of more than double from baseline
Serum creatinine increase of more than double from baseline is defined as follows. At each assessment visit, Serum creatinine change (%) = (Serum creatinine – Baseline serum creatinine) / Baseline serum creatinine * 100 If Serum creatinine change (%) > 200 then let the Serum creatinine at the visit be increase of more than double from baseline.

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).

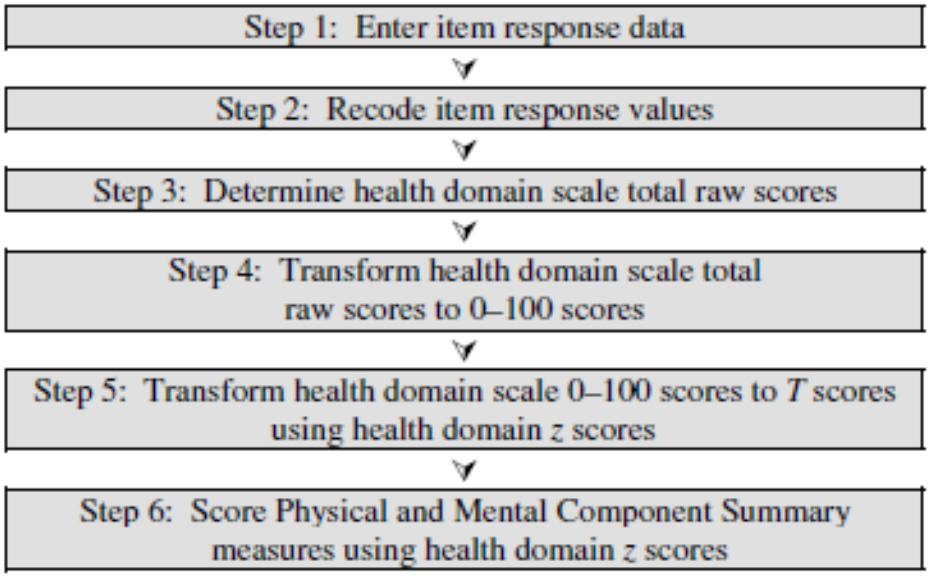
SF-36v2
Overview of Scoring Algorithm

• Scores will be calculated by Optum PRO CoRE (version 1.2). Refer to "User's Manual for the SF-36v2 Health Survey Third Edition" 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
  • 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)

SF-36v2

- 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).



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

- SF-36v2 Acute is being used for this study. [Acute (1 Week)]
- Missing values will be estimated using the *Maximum Data Recovery Mode*.
- 2009 U.S. general population will be set for scoring. [2009 US Norms]

EQ-5D-5L / EQ-VAS

Scoring Algorithm

- EQ-VAS scores will be summarized based on the numbers subjects 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. • Withdrawn subjects were not replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. •

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: o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report, 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: o When only the start year is provided, a '01' will be used for the day and 'Jan' will be used for the month o When only the start month and year is provided, a ‘01’ will be used for the day. 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. 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) • The recorded partial date will be displayed in listings.
Adverse Events	• The eCRF 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 %

Urinalysis Parameters			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
Urine albumin/creatinine ratio	g/mol		> 3.4 g/mol

Other Parameters			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
iPTH	ng/L	N/A	> 9x ULRR
eGFR	mL/min/1.73m^2	≥ 40% decrease from baseline	

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	White Blood Cell

15.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
HemoCue
OptumOptum PRO CoRE
P-TOL
Riona
SAS
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 1.59	Not Applicable
Efficacy	2.1 to 2.133	2.1 to 2.91
Safety	3.1 to 3.126	3.1 to 3.3
Patient Reported Outcome	4.1 to 4.34	Not Applicable
Pharmacokinetic	5.1 to 5.8	5.1 to 5.15
Section	**Listings**	
ICH Listings	1 to 49	
Other Listings	50 to 90	
Patient Profile Listings	91 to 100	

15.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up display provided: 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 – ND Subjects	
1.19	ITT	DM1	Summary of Demographic Characteristics - ITT	
Efficacy				
2.1	ITT	EFF_T1	Summary of Hgb (g/dL) by Visit – ITT	
2.3	ITT	EFF_T1	Summary of Hgb (g/dL) by Visit by Prior ESA and baseline Hgb– ITT	
2.7	ITT	EFF_T1	Summary of Change from Baseline in Hgb (g/dL) by Visit by Prior ESA and baseline Hgb- ITT	
2.9	mITT	EFF_T2	Summary of Mean Hgb (g/dL) Based on Observed Cases During the Primary Efficacy Evaluation Period – mITT	
2.10	Efficacy PD	EFF_T2	Summary of Mean Hgb (g/dL) Based on Observed Cases During the Primary Efficacy Evaluation Period - Efficacy PD	
2.12	ITT	EFF_T3	Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – ITT	
2.16	ITT	EFF_T3	Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – Subgroup	Only subgroup of prior ESA use
2.25	mITT	EFF_T5	Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period - mITT	
2.58	ITT	EFF_T11	Summary of Dose by Visit – ITT	

Headline Results Analysis				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Safety				
3.1	Safety	AE1	Summary of On-Therapy AEs by SOC and PT – ND Subjects	
3.2	Safety	AE1	Summary of On-Therapy AEs by SOC and PT – PD Subjects	ICH E3
3.55	Safety	AE1	Summary of On-Therapy Serious AEs – ND Subjects	
3.65	Safety	SAFE_T2	Summary of On-Therapy AEs of Special Interest – ND Subjects	
3.66	Safety	SAFE_T2	Summary of On-Therapy AEs of Special Interest – PD Subjects	
3.121	Safety	SAFE_T6	Summary of Ophthalmologic Exams at Screening – ND Subjects	
3.122	Safety	SAFE_T6	Summary of Ophthalmologic Exams at Screening – PD Subjects	
3.123	Safety	SAFE_T7	Summary of On-Therapy Ophthalmologic Exams – ND Subjects	
3.124	Safety	SAFE_T7	Summary of On-Therapy Ophthalmologic Exams – PD Subjects	
44	Safety	SAFE_L1	Listing of Adverse Events of Special Interest	ICH E3 Displays will be produced with AESI category in addition of AE8 template.
82	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 – ND Subjects	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.2.	Randomized	ES8	Summary of Subject Status and Reason for Study Withdrawal – PD Subjects	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.3.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment – ND Subjects	ICH E3	Y
1.4.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment – PD Subjects	ICH E3	Y
1.5.	All Screening	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	Y
1.6.	Enrolled	NS1	Summary of Subjects Enrolled by Country and Site ID – ND Subjects	EudraCT/clinical operations	Y
1.7.	Enrolled	NS1	Summary of Subjects Enrolled by Country and Site ID – PD Subjects	EudraCT/clinical operations	Y
Protocol Deviations					
1.8.	Randomized	DV1	Summary of Important Protocol Deviations – ND Subjects	ICH E3	Y
1.9.	Randomized	DV1	Summary of Important Protocol Deviations – PD Subjects	ICH E3	Y
1.10.	Randomized	IE1	Summary of Inclusion/Exclusion Criteria Deviations – ND Subjects	ICH E3	Y
1.11.	Randomized	IE1	Summary of Inclusion/Exclusion Criteria Deviations – PD Subjects	ICH E3	Y

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Population Analyzed					
1.12.	Randomized	SP1	Summary of Study Populations – ND Subjects	IDSL	Y
1.13.	Randomized	SP1	Summary of Study Populations – ND Subjects, Cohort 1	IDSL	Y
1.14.	Randomized	SP1	Summary of Study Populations – ND Subjects, Cohort 3	IDSL	Y
1.15.	Randomized	SP1	Summary of Study Populations – PD Subjects	IDSL	Y
1.16.	mITT	SP2	Summary of Exclusions from the Per Protocol Population	IDSL	Y
1.17.	Randomized	POP_T1	Summary of Composition of the Randomized Population		Y
Demographic and Baseline Characteristics					
1.18.	ITT	DM1	Summary of Demographic Characteristics - ITT	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.19.	ITT	DM1	Summary of Demographic Characteristics by Prior ESA Use – ITT		Y
1.20.	Safety	DM1	Summary of Demographic Characteristics – Safety, ND Subjects	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.21.	Safety	DM1	Summary of Demographic Characteristics by Prior ESA Use – Safety, ND Subjects		Y
1.22.	Safety	DM1	Summary of Demographic Characteristics – Safety, PD Subjects	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.23.	Safety	DM1	Summary of Demographic Characteristics by Prior ESA Use – Safety, PD Subjects		Y
1.24.	Efficacy ND	DM1	Summary of Demographic Characteristics – Efficacy ND	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.25.	Efficacy PD	DM1	Summary of Demographic Characteristics – Efficacy PD	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.26.	Efficacy PD	DM1	Summary of Demographic Characteristics by Prior ESA Use – Efficacy PD		Y
1.27.	Efficacy ND	DM1	Summary of Demographic Characteristics – Efficacy ND, Cohort 1	ICH E3, GSK CTR, FDAAA, EudraCT	Y

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
1.28.	Efficacy ND	DM1	Summary of Demographic Characteristics – Efficacy ND, Cohort 3	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.29.	Safety	POP_T1	Summary of Prior ESA Medication – Safety, ND Subjects		Y
1.30.	Safety	POP_T1	Summary of Prior ESA Medication – Safety, PD Subjects		Y
1.31.	ITT	POP_T1	Summary of Prior ESA Medication – ITT		Y
1.32.	Efficacy PD	POP_T1	Summary of Prior ESA Medication – Efficacy PD		Y
1.33.	Enrolled	DM11	Summary of Age Ranges – ND Subjects	EudraCT	Y
1.34.	Enrolled	DM11	Summary of Age Ranges – PD Subjects	EudraCT	Y
1.35.	Safety	DM5	Summary of Race and Racial Combinations – Safety, ND Subjects	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.36.	Safety	DM5	Summary of Race and Racial Combinations – Safety, PD Subjects	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.37.	Safety	FH1	Summary of Family History for CV Risk Factors – ND Subjects	IDSL	Y
1.38.	Safety	FH1	Summary of Family History for CV Risk Factors – PD Subjects	IDSL	Y
1.39.	Safety	SU1	Summary of Substance Use (History of Tobacco Use, Alcohol Intake) – ND Subjects	IDSL	Y
1.40.	Safety	SU1	Summary of Substance Use (History of Tobacco Use, Alcohol Intake) – PD Subjects	IDSL	Y
Medical Conditions and Concomitant Medications					
1.41.	Safety	MH4	Summary of Current Medical Conditions – ND Subjects	ICH E3	Y
1.42.	Safety	MH4	Summary of Current Medical Conditions – PD Subjects	ICH E3	Y
1.43.	Safety	MH4	Summary of Past Medical Conditions – ND Subjects	ICH E3	Y
1.44.	Safety	MH4	Summary of Past Medical Conditions – PD Subjects	ICH E3	Y

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
1.45.	Safety	CM1	Summary of Concomitant Medications (Pre-Therapy) – ND Subjects	ICH E3	Y
1.46.	Safety	CM1	Summary of Concomitant Medications (Pre-Therapy) – PD Subjects	ICH E3	Y
1.47.	Safety	CM1	Summary of Concomitant Medications (On-Therapy) – ND Subjects	ICH E3	Y
1.48.	Safety	CM1	Summary of Concomitant Medications (On-Therapy) – PD Subjects	ICH E3	Y
1.49.	Safety	CM1	Summary of Concomitant Medications (Post-Therapy) – ND Subjects	ICH E3	Y
1.50.	Safety	CM1	Summary of Concomitant Medications (Post-Therapy) – PD Subjects	ICH E3	Y
1.51.	Safety	CM1	Summary of Other Concomitant Medications (On-Therapy) – ND Subjects		Y
1.52.	Safety	CM1	Summary of Other Concomitant Medications (On-Therapy) – PD Subjects		Y
1.53.	Safety	POP_T2	Summary of Blood Products and Blood Supportive Care Products – ND Subjects		Y
1.54.	Safety	POP_T2	Summary of Blood Products and Blood Supportive Care Products – PD Subjects		Y
Exposure and Treatment Compliance					
1.55.	Safety	EX1	Summary of Exposure to Study Treatment – ND Subjects		Y
1.56.	Safety	EX1	Summary of Exposure to Study Treatment – PD Subjects		Y
1.57.	Safety	POP_T4	Summary of Treatment Compliance – ND Subjects		Y

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
1.58.	Safety	POP_T4	Summary of Treatment Compliance – PD Subjects		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 - ITT		Y
2.2.	Efficacy PD	EFF_T1	Summary of Hgb (g/dL) by Visit – Efficacy PD		Y
2.3.	ITT	EFF_T1	Summary of Hgb (g/dL) by Visit by Prior ESA and baseline Hgb– ITT		Y
2.4.	Efficacy PD	EFF_T1	Summary of Hgb (g/dL) by Visit by Prior ESA and baseline Hgb– Efficacy PD		Y
2.5.	ITT	EFF_T1	Summary of Change from Baseline in Hgb (g/dL) by Visit - ITT		Y
2.6.	Efficacy PD	EFF_T1	Summary of Change from Baseline in Hgb (g/dL) by Visit – Efficacy PD		Y
2.7.	ITT	EFF_T1	Summary of Change from Baseline in Hgb (g/dL) by Visit by Prior ESA and baseline Hgb- ITT		Y
2.8.	Efficacy PD	EFF_T2	Summary of Change from Baseline in Hgb (g/dL) by Visit by Prior ESA and baseline Hgb – Efficacy PD		Y
Mean Hgb Based on Observed Hgb During the Primary Efficacy Evaluation Period					
2.9.	mITT	EFF_T2	Summary of Mean Hgb (g/dL) Based on Observed Cases During the Primary Efficacy Evaluation Period – mITT		Y
2.10.	Efficacy PD	EFF_T2	Summary of Mean Hgb (g/dL) Based on Observed Cases During the Primary Efficacy Evaluation Period - Efficacy PD		Y
2.11.	Efficacy PD	EFF_T2	Summary of Mean Hgb (g/dL) Based on Observed Cases During the Primary Efficacy Evaluation Period by prior ESA use and by Baseline Hgb – Efficacy PD		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
Primary Efficacy Analyses: Model based Mean Hgb During the Primary Efficacy Evaluation Period					
2.12.	ITT	EFF_T3	Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period - ITT		Y
2.13.	mITT	EFF_T3	Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – mITT		Y
2.14.	PP	EFF_T3	Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – PP		Y
2.15.	Efficacy ND	EFF_T3	Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – Efficacy ND		Y
2.16.	ITT	EFF_T3	Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period – Subgroup		Y
Sensitivity Analyses					
2.17.	ITT	EFF_T3	Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Excluding ESA Users with Hgb Rapid Increase at Week 2		Y
2.18.	ITT	EFF_T3	Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using Evaluable Hgb		Y
2.19.	mITT	EFF_T3	Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using ANCOVA - mITT		Y
2.20.	PP	EFF_T3	Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using ANCOVA – PP		Y
2.21.	mITT	EFF_T3	Sensitivity Analysis of Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period Using ANCOVA - Subgroup		Y
2.22.	ITT	EFF_T4	Tipping Point Summary for Non-Inferiority Test (Daprodustat vs Epoetin Beta Pegol) – ITT		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.23.	mITT	EFF_T4	Tipping Point Summary for Non-Inferiority Test (Daprodustat vs Epoetin Beta Pegol) – mITT		Y
2.24.	PP	EFF_T4	Tipping Point Summary for Non-Inferiority Test (Daprodustat vs Epoetin Beta Pegol) - PP		Y
Number (%) of Subjects with Mean Hgb in Target Range during the Primary Efficacy Evaluation Period					
2.25.	mITT	EFF_T5	Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period - mITT		Y
2.26.	ITT	EFF_T5	Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period – ITT		Y
2.27.	PP	EFF_T5	Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period - PP		Y
2.28.	Efficacy ND	EFF_T5	Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period – Efficacy ND		Y
2.29.	mITT	EFF_T5	Analysis of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period - Subgroup		Y
2.30.	Efficacy PD	EFF_T5	Summary of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period – Efficacy PD		Y
2.31.	Efficacy PD	EFF_T5	Summary of Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period by Baseline Hgb – Efficacy PD		Y
Hgb					
2.32.	ITT	EFF_T6	Summary of Number (%) of Subjects by Hgb Change from Baseline Category at Week 2 and 4 - ITT		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.33.	Efficacy PD	EFF_T6	Summary of Number (%) of Subjects by Hgb Change from Baseline Category at Week 4 – Efficacy PD		Y
2.34.	ITT	EFF_T6	Summary of Number (%) of Subjects by Hgb Change from Baseline Category at Week 2 and 4 by Prior ESA – ITT		Y
2.35.	Efficacy PD	EFF_T6	Summary of Number (%) of Subjects by Hgb Change from Baseline Category at Week 4 by Prior ESA – Efficacy PD		Y
2.36.	ITT	EFF_T7	Summary of Number (%) of Subjects with Hgb within the Target Range by Visit - ITT		Y
2.37.	Efficacy PD	EFF_T7	Summary of Number (%) of Subjects with Hgb within the Target Range by Visit – Efficacy PD		Y
2.38.	ITT	EFF_T8	Summary of Time (%) in Hgb Target Range During the Primary Efficacy Evaluation Period – ITT		Y
2.39.	Efficacy PD	EFF_T8	Summary of Time (%) in Hgb Target Range During the Primary Efficacy Evaluation Period – Efficacy PD		Y
2.40.	ITT	EFF_T8	Summary of Time (%) in Hgb Target Range During the Primary Efficacy Evaluation Period by Prior ESA Use - ITT		Y
2.41.	Efficacy PD	EFF_T8	Summary of Time (%) in Hgb Target Range During the Primary Efficacy Evaluation Period by Prior ESA Use – Efficacy PD		Y
2.42.	ITT	EFF_T8A	Summary of Time (days) to Reach the Lower Hgb Target (11.0 g/dL) – ITT		Y
2.43.	Efficacy PD	EFF_T8A	Summary of Time (days) to Reach the Lower Hgb Target (11.0 g/dL) – Efficacy PD		Y
2.44.	ITT	EFF_T8A	Summary of Time (days) to Reach the Lower Hgb Target (11.0 g/dL) by Prior ESA Use - ITT		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.45.	Efficacy PD	EFF_T8A	Summary of Time (days) to reach the Lower Hgb Target (11.0 g/dL) by Prior ESA Use – Efficacy PD		Y
2.46.	ITT	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Level of Less than 7.5 g/dL - ITT		Y
2.47.	Efficacy PD	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Level of Less than 7.5 g/dL – Efficacy PD		Y
2.48.	ITT	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Level of Less than 7.5 g/dL by Prior ESA Use - ITT		Y
2.49.	Efficacy PD	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Level of Less than 7.5 g/dL by Prior ESA Use – Efficacy PD		Y
2.50.	ITT	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 weeks - ITT		Y
2.51.	Efficacy PD	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 weeks – Efficacy PD		Y
2.52.	ITT	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 weeks by Prior ESA Use - ITT		Y
2.53.	Efficacy PD	EFF_T9	Summary of Number (%) of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 weeks by Prior ESA Use – Efficacy PD		Y
2.54.	ITT	EFF_T10	Summary of Number (%) of Subjects Who Have Hgb Level of More than 13.0 g/dL and Number of Episodes - ITT		Y
2.55.	Efficacy PD	EFF_T10	Summary of Number (%) of Subjects Who Have Hgb Level of More than 13.0 g/dL and Number of Episodes – Efficacy PD		Y
2.56.	ITT	EFF_T10	Summary of Number (%) of Subjects Who Have Hgb Level of More than 13.0 g/dL and Number of Episodes by Prior ESA Use - ITT		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.57.	Efficacy PD	EFF_T10	Summary of Number (%) of Subjects Who Have Hgb Level of More than 13.0 g/dL and Number of Episodes by Prior ESA Use – Efficacy PD		Y
Dose Adjustment					
2.58.	ITT	EFF_T11	Summary of Dose by Visit – ITT		Y
2.59.	Efficacy PD	EFF_T11	Summary of Dose by Visit – Efficacy PD		Y
2.60.	ITT	EFF_T11	Summary of Dose by Visit by Prior ESA- ITT		Y
2.61.	Efficacy PD	EFF_T11	Summary of Dose by Visit by Prior ESA– Efficacy PD		Y
2.62.	ITT	EFF_T14	Summary of Duration (days) of Treatment Interruption due to Hgb >13.0 g/dL - ITT		Y
2.63.	Efficacy PD	EFF_T14	Summary of Duration (days) of Treatment Interruption due to Hgb >13.0 g/dL – Efficacy PD		Y
2.64.	ITT	EFF_T14	Summary of Duration (days) of Treatment Interruption due to Hgb >13.0 g/dL by Prior ESA Use - ITT		Y
2.65.	Efficacy PD	EFF_T14	Summary of Duration (days) of Treatment Interruption due to Hgb >13.0 g/dL by Prior ESA Use – Efficacy PD		Y
2.66.	ITT	EFF_T15	Summary of Dose Adjustment - ITT		Y
2.67.	Efficacy PD	EFF_T15	Summary of Dose Adjustment – Efficacy PD		Y
2.68.	ITT	EFF_T15	Summary of Dose Adjustment by Prior ESA Use - ITT		Y
2.69.	Efficacy PD	EFF_T15	Summary of Dose Adjustment by Prior ESA Use – Efficacy PD		Y
2.70.	ITT	EFF_T15	Summary of Dose Adjustment to Reach the Lower Hgb Target (11.0 g/dL) – ITT		Y
2.71.	Efficacy PD	EFF_T15	Summary of Dose Adjustment to Reach the Lower Hgb Target (11.0 g/dL) – Efficacy PD		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.72.	ITT	EFF_T15	Summary of Dose Adjustment to Reach the Lower Hgb Target (11.0 g/dL) by Prior ESA Use - ITT		Y
2.73.	Efficacy PD	EFF_T15	Summary of Dose Adjustment to Reach the Lower Hgb Target (11.0 g/dL) by Prior ESA Use – Efficacy PD		Y
2.74.	ITT	EFF_T12	Summary of Number (%) of Subjects with Each Dose for Daprodustat by Visit - ITT		Y
2.75.	ITT	EFF_T13	Summary of Number (%) of Subjects with Each Dose for Epoetin Beta Pegol by Visit - ITT		Y
2.76.	Efficacy PD	EFF_T12	Summary of Number (%) of Subjects with Each Dose for Daprodustat by Visit – Efficacy PD		Y
2.77.	ITT	EFF_T12	Summary of Number (%) of Subjects with Each Dose for Daprodustat by Visit by Prior ESA- ITT		Y
2.78.	ITT	EFF_T13	Summary of Number (%) of Subjects with Each Dose for Epoetin Beta Pegol by Visit by Prior ESA- ITT		Y
2.79.	Efficacy PD	EFF_T12	Summary of Number (%) of Subjects with Each Dose for Daprodustat by Visit by Prior ESA– Efficacy PD		Y
Iron Use					
2.80.	ITT	EFF_T16	Summary of Dose of Oral Iron (mg) During the Treatment Period – ITT		Y
2.81.	Efficacy PD	EFF_T16	Summary of Dose of Oral Iron (mg) During the Treatment Period – Efficacy PD		Y
2.82.	ITT	EFF_T16	Summary of Dose of Oral Iron (mg) Change from Baseline During the Treatment Period - ITT		Y
2.83.	Efficacy PD	EFF_T16	Summary of Dose of Oral Iron (mg) Change from Baseline During the Treatment Period – Efficacy PD		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.84.	ITT	EFF_T16	Summary of Dose of Oral Iron (mg) During the Treatment Period by Baseline Iron Use – ITT		Y
2.85.	Efficacy PD	EFF_T16	Summary of Dose of Oral Iron (mg) During the Treatment Period by Baseline Iron Use – Efficacy PD		Y
2.86.	ITT	EFF_T17	Summary of Number (%) of Subjects with Iron Use During the Treatment Period – ITT		Y
2.87.	Efficacy PD	EFF_T17	Summary of Number (%) of Subjects with Iron Use During the Treatment Period – Efficacy PD		Y
2.88.	ITT	EFF_T17	Summary of Number (%) of Subjects with Iron Use During the Treatment Period by Baseline Iron Use – ITT		Y
2.89.	Efficacy PD	EFF_T17	Summary of Number (%) of Subjects with Iron Use During the Treatment Period by Baseline Iron Use – Efficacy PD		Y
Iron Parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC)					
2.90.	ITT	LB1	Summary of Ferritin (ug/L) by Visit – ITT		Y
2.91.	Efficacy PD	LB1	Summary of Ferritin (ug/L) by Visit – Efficacy PD		Y
2.92.	ITT	LB1	Summary of Ferritin (ug/L) Change from Baseline by Visit - ITT		Y
2.93.	Efficacy PD	LB1	Summary of Ferritin (ug/L) Change from Baseline by Visit – Efficacy PD		Y
2.94.	ITT	EFF_T18	Summary of Transferrin Saturation (%) by Visit - ITT		Y
2.95.	Efficacy PD	EFF_T18	Summary of Transferrin Saturation (%) by Visit – Efficacy PD		Y
2.96.	ITT	EFF_T19	Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit - ITT		Y
2.97.	Efficacy PD	EFF_T19	Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit – Efficacy PD		Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.98.	ITT	EFF_T18	Summary of Hepcidin (nmol/L) by Visit - ITT		Y
2.99.	Efficacy PD	EFF_T18	Summary of Hepcidin (nmol/L) by Visit – Efficacy PD		Y
2.100.	ITT	EFF_T19	Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit – ITT		Y
2.101.	Efficacy PD	EFF_T19	Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit – Efficacy PD		Y
2.102.	ITT	LB1	Summary of Serum Iron (umol/L) by Visit - ITT		Y
2.103.	Efficacy PD	LB1	Summary of Serum Iron (umol/L) by Visit – Efficacy PD		Y
2.104.	ITT	LB1	Summary of Serum Iron (umol/L) Change from Baseline by Visit - ITT		Y
2.105.	Efficacy PD	LB1	Summary of Serum Iron (umol/L) Change from Baseline by Visit – Efficacy PD		Y
2.106.	ITT	LB1	Summary of Total Iron Binding Capacity (umol/L) by Visit - ITT		Y
2.107.	Efficacy PD	LB1	Summary of Total Iron Binding Capacity (umol/L) by Visit – Efficacy PD		Y
2.108.	ITT	LB1	Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit - ITT		Y
2.109.	Efficacy PD	LB1	Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit – Efficacy PD		Y
2.110.	ITT	LB1	Summary of Ferritin (ug/L) by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.111.	Efficacy PD	LB1	Summary of Ferritin (ug/L) by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.112.	ITT	LB1	Summary of Ferritin (ug/L) Change from Baseline by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.113.	Efficacy PD	LB1	Summary of Ferritin (ug/L) Change from Baseline by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.114.	ITT	EFF_T18	Summary of Transferrin Saturation (%) by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.115.	Efficacy PD	EFF_T18	Summary of Transferrin Saturation (%) by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.116.	ITT	EFF_T19	Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.117.	Efficacy PD	EFF_T19	Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.118.	ITT	EFF_T18	Summary of Hepcidin (nmol/L) by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.119.	Efficacy PD	EFF_T18	Summary of Hepcidin (nmol/L) by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.120.	ITT	EFF_T19	Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit by Subgroup — ITT	baseline iron use, prior ESA use	Y
2.121.	Efficacy PD	EFF_T19	Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.122.	ITT	LB1	Summary of Serum Iron (umol/L) by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.123.	Efficacy PD	LB1	Summary of Serum Iron (umol/L) by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.124.	ITT	LB1	Summary of Serum Iron (umol/L) Change from Baseline by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.125.	Efficacy PD	LB1	Summary of Serum Iron (umol/L) Change from Baseline by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.126.	ITT	LB1	Summary of Total Iron Binding Capacity (umol/L) by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.127.	Efficacy PD	LB1	Summary of Total Iron Binding Capacity (umol/L) by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
2.128.	ITT	LB1	Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit by Subgroup - ITT	baseline iron use, prior ESA use	Y
2.129.	Efficacy PD	LB1	Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit by Subgroup – Efficacy PD	baseline iron use, prior ESA use	Y
CKD Progression					
2.130.	ITT	LB1	Summary of CKD Progression by Visit		Y
2.131.	ITT	LB1	Summary of CKD Progression Change from Baseline by Visit		Y
2.132.	ITT	EFF_T20T20	Summary of Number (%) of Subjects with eGFR Decrease of 30% or More from Baseline		Y
2.133.	ITT	EFF_T20T20	Summary of Number (%) of Subjects with Serum Creatinine Increase of More Than Double from Baseline		Y

15.10.4.3. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Raw Mean Hgb During the Primary Efficacy Evaluation Period					
2.1.	ITT	EFF_F1	Plot of Mean Change from Baseline in Hgb (g/dL) and 95% CIs over Time by Treatment – ITT		Y
2.2.	Efficacy PD	EFF_F1	Plot of Mean Change from Baseline in Hgb (g/dL) and 95% CIs over Time by Treatment – Efficacy PD		Y
2.3.	ITT	EFF_F1	Plot of Mean Change from Baseline in Hgb (g/dL) and 95% CIs over Time by Treatment by Prior ESA Use and Baseline Hgb – ITT		Y
2.4.	Efficacy PD	EFF_F1	Plot of Mean Change from Baseline in Hgb (g/dL) and 95% CIs over Time by Treatment by Prior ESA Use and Baseline Hgb– Efficacy PD		Y
2.5.	ITT	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CIs over Time by Treatment – ITT		Y
2.6.	Efficacy PD	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CIs over Time by Treatment – Efficacy PD		Y
2.7.	ITT	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CIs over Time by Treatment by Prior ESA Use and Baseline Hgb – ITT		Y
2.8.	Efficacy PD	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CIs over Time by Treatment by Prior ESA Use and Baseline Hgb – Efficacy PD		Y
Model-Based Mean Hgb During the Primary Efficacy Evaluation Period					
2.9.	ITT	EFF_F2	Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment – ITT		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.10.	mITT	EFF_F2	Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment - mITT		Y
2.11.	PP	EFF_F2	Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment - PP		Y
2.12.	Efficacy ND	EFF_F2	Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment – Efficacy ND		Y
2.13.	ITT	EFF_F2	Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment – Excluding ESA Users with Hgb Rapid Increase at Week 2		Y
2.14.	ITT	EFF_F2	Sensitivity Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment – Evaluable Hgb		Y
2.15.	ITT	EFF_F3	Forest Plot of Model-Adjusted Treatment Difference (Daprodustat vs Epoetin Beta Pegol) for Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period by Subgroup - MMRM		Y
2.16.	ITT	EFF_F2	Hgb Curve over Time (with 95% Confidence Band) by Mixed Model for Repeated Measures by Treatment by Prior ESA Use – ITT		Y
2.17.	mITT	EFF_F3	Sensitivity Forest Plot of Model-Adjusted Treatment Difference (Daprodustat vs Epoetin Beta Pegol) for Mean Hgb (g/dL) During the Primary Efficacy Evaluation Period by Subgroup - ANCOVA		Y
2.18.	ITT	EFF_F4	Tipping Point Display for Non-Inferiority Test (Daprodustat vs Epoetin Beta Pegol) – ITT		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.19.	mITT	EFF_F4	Tipping Point Display for Non-Inferiority Test (Daprodustat vs Epoetin Beta Pegol) – mITT		Y
2.20.	PP	EFF_F4	Tipping Point Display for Non-Inferiority Test (Daprodustat vs Epoetin Beta Pegol) - PP		Y
Number (%) of Subjects with Mean Hgb in Target Range During the Primary Efficacy Evaluation Period					
2.21.	mITT	EFF_F5	Forest Plot of Model-Adjusted Odds Ratio (Daprodustat / Epoetin Beta Pegol) for Proportion of Subjects with Mean Hgb in the Target Range During the Primary Efficacy Evaluation Period by Subgroup		Y
Hgb					
2.22.	ITT	EFF_F6	Figure of Number (%) of Subjects with Hgb within the Target Range over Time - ITT	Like Fig. 2.7.6.2.3.1-2 in NESP CTD 2.7.6	Y
2.23.	Efficacy PD	EFF_F6	Figure of Number (%) of Subjects with Hgb within the Target Range over Time – Efficacy PD	Like Fig. 2.7.6.2.3.1-2 in NESP CTD 2.7.6	Y
2.24.	ITT	AE11	Cumulative Distribution of Time (days) to Reach the Lower Hgb Target (11.0 g/dL) - ITT		Y
2.25.	Efficacy PD	AE11	Cumulative Distribution of Time (days) to Reach the Lower Hgb Target (11.0 g/dL) – Efficacy PD		Y
2.26.	ITT	AE11	Cumulative Distribution of Time (days) to Reach the Lower Hgb Target (11.0 g/dL) by Prior ESA Use - ITT		Y
2.27.	Efficacy PD	AE11	Cumulative Distribution of Time (days) to Reach the Lower Hgb Target (11.0 g/dL) by Prior ESA Use – Efficacy PD		Y
2.28.	ITT	EFF_F7	Scatter Plot of Hgb Assessments: Central Laboratory vs. HemoCue - ITT		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.29.	Efficacy PD	EFF_F7	Scatter Plot of Hgb Assessments: Central Laboratory vs. HemoCue – Efficacy PD		Y
Dose Adjustment					
2.30.	ITT	EFF_F8	Histogram of Daprodustat Dose (mg) by Visit - ITT		Y
2.31.	ITT	EFF_F8	Histogram of Epoetin Beta Pegol Dose (ug) by Visit - ITT		Y
2.32.	Efficacy PD	EFF_F8	Histogram of Daprodustat Dose (mg) by Visit – Efficacy PD		Y
2.33.	ITT	EFF_F8	Histogram of Daprodustat Dose (mg) by Visit by Prior ESA – ITT		Y
2.34.	ITT	EFF_F8	Histogram of Epoetin Beta Pegol Dose (mg) by Visit by Prior ESA – ITT		Y
2.35.	Efficacy PD	EFF_F8	Histogram of Daprodustat Dose (ug) by Visit by Prior ESA – Efficacy PD		Y
Subject Listing					
2.36.	ITT	EFF_F9	Subject Profiles of Hgb and Dose over Time - ITT		Y
2.37.	Efficacy PD	EFF_F9	Subject Profiles of Hgb and Dose over Time – Efficacy PD		Y
Iron Parameters					
2.38.	ITT	EFF_F1	Plot of Mean Ferritin (ug/L) Change from Baseline and 95% CIover Time – ITT		Y
2.39.	Efficacy PD	EFF_F1	Plot of Mean Ferritin (ug/L) Change from Baseline and 95% CI over Time – Efficacy PD		Y
2.40.	ITT	EFF_F1	Plot of Geometric Mean Transferrin Saturation Percent Change from Baseline and 95% CI over Time – ITT		Y
2.41.	Efficacy PD	EFF_F1	Plot of Geometric Mean Transferrin Saturation Percent Change from Baseline and 95% CI over Time – Efficacy PD		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.42.	ITT	EFF_F1	Plot of Geometric Mean Hepcidin Percent Change from Baseline and 95% CI over Time – ITT		Y
2.43.	Efficacy PD	EFF_F1	Plot of Geometric Mean Hepcidin Percent Change from Baseline and 95% CI over Time – Efficacy PD		Y
2.44.	ITT	EFF_F1	Plot of Mean Serum Iron (umol/L) Change from Baseline and 95% CI over Time - ITT		Y
2.45.	Efficacy PD	EFF_F1	Plot of Mean Serum Iron (umol/L) Change from Baseline and 95% CI over Time – Efficacy PD		Y
2.46.	ITT	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) Change from Baseline and 95% CI over Time – ITT		Y
2.47.	Efficacy PD	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) Change from Baseline and 95% CI over Time – Efficacy PD		Y
2.48.	ITT	EFF_F1	Plot of Mean Ferritin (ug/L) Change from Baseline and 95% CI over Time by Baseline Iron Use – ITT		Y
2.49.	Efficacy PD	EFF_F1	Plot of Mean Ferritin (ug/L) Change from Baseline and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
2.50.	ITT	EFF_F1	Plot of Geometric Mean Transferrin Saturation Percent Change from Baseline and 95% CI over Time by Baseline Iron Use – ITT		Y
2.51.	Efficacy PD	EFF_F1	Plot of Geometric Mean Transferrin Saturation Percent Change from Baseline and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
2.52.	ITT	EFF_F1	Plot of Geometric Mean Hepcidin Percent Change from Baseline over Time and 95% CI by Baseline Iron Use - ITT		Y
2.53.	Efficacy PD	EFF_F1	Plot of Geometric Mean Hepcidin Percent Change from Baseline over Time and 95% CI by Baseline Iron Use – Efficacy PD		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.54.	ITT	EFF_F1	Plot of Mean Serum Iron (umol/L) Change from Baseline and 95% CI over Time by Baseline Iron Use – ITT		Y
2.55.	Efficacy PD	EFF_F1	Plot of Mean Serum Iron (umol/L) Change from Baseline and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
2.56.	ITT	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) Change from Baseline and 95% CI over Time by Baseline Iron Use – ITT		Y
2.57.	Efficacy PD	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) Change from Baseline and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
2.58.	ITT	EFF_F1	Plot of Mean Ferritin (ug/L) and 95% CI over Time - ITT		Y
2.59.	Efficacy PD	EFF_F1	Plot of Mean Ferritin (ug/L) and 95% CI over Time - Efficacy PD		Y
2.60.	ITT	EFF_F1	Plot of Geometric Mean Transferrin Saturation (%) and 95% CI over Time – ITT		Y
2.61.	Efficacy PD	EFF_F1	Plot of Geometric Mean Transferrin Saturation (%) and 95% CI over Time – Efficacy PD		Y
2.62.	ITT	EFF_F1	Plot of Geometric Mean Hepcidin (nmol/L) and 95% CI over Time – ITT		Y
2.63.	Efficacy PD	EFF_F1	Plot of Geometric Mean Hepcidin (nmol/L) and 95% CI over Time – Efficacy PD		Y
2.64.	ITT	EFF_F1	Plot of Mean Serum Iron (umol/L) and 95% CI over Time – ITT		Y
2.65.	Efficacy PD	EFF_F1	Plot of Mean Serum Iron (umol/L) and 95% CI over Time – Efficacy PD		Y
2.66.	ITT	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) and 95% CI over Time – ITT		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.67.	Efficacy PD	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) and 95% CI over Time – Efficacy PD		Y
2.68.	ITT	EFF_F1	Plot of Mean Ferritin (ug/L) and 95% CI over Time by Baseline Iron Use – ITT		Y
2.69.	Efficacy PD	EFF_F1	Plot of Mean Ferritin (ug/L) and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
2.70.	ITT	EFF_F1	Plot of Geometric Mean Transferrin Saturation (%) and 95% CI over time by Baseline Iron Use – ITT		Y
2.71.	Efficacy PD	EFF_F1	Plot of Geometric Mean Transferrin Saturation (%) and 95% CI over time by Baseline Iron Use – Efficacy PD		Y
2.72.	ITT	EFF_F1	Plot of Geometric Mean Hepcidin (nmol/L) and 95% CI over Time by Baseline Iron Use – ITT		Y
2.73.	Efficacy PD	EFF_F1	Plot of Geometric Mean Hepcidin (nmol/L) and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
2.74.	ITT	EFF_F1	Plot of Mean Serum Iron (umol/L) and 95% CI over Time by Baseline Iron Use – ITT		Y
2.75.	Efficacy PD	EFF_F1	Plot of Mean Serum Iron (umol/L) and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
2.76.	ITT	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) and 95% CI over Time by Baseline Iron Use – ITT		Y
2.77.	Efficacy PD	EFF_F1	Plot of Mean Total Iron Binding Capacity (umol/L) and 95% CI over Time by Baseline Iron Use – Efficacy PD		Y
Other					
2.78.	ITT	EFF_F1	Plot of Mean and 95% CI for CKD Progression by Visit		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.79.	ITT	EFF_F1	Plot of Mean and 95% CI for CKD Progression Change from Baseline over Time		Y
2.80.	ITT	EFF_F10	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Body Weight - ITT		Y
2.81.	ITT	EFF_F10	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Baseline Hgb - ITT		Y
2.82.	ITT	EFF_F10	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Prior ESA Dose - ITT		Y
2.83.	ITT	EFF_F10	Scatter Plot of Mean Dose During Week 40 to 52 vs. Body Weight – ITT		Y
2.84.	ITT	EFF_F10	Scatter Plot of Mean Dose During Week 40 to 52 vs. Baseline Hgb – ITT		Y
2.85.	ITT	EFF_F10	Scatter Plot of Mean Dose During Week 40 to 52 vs. Prior ESA Dose - ITT		Y
2.86.	Efficacy PD	EFF_F10	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Body Weight – Efficacy PD		Y
2.87.	Efficacy PD	EFF_F10	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Baseline Hgb – Efficacy PD		Y
2.88.	Efficacy PD	EFF_F10	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Prior ESA Dose – Efficacy PD		Y
2.89.	Efficacy PD	EFF_F10	Scatter Plot of Mean Dose During Week 40 to 52 vs. Body Weight – Efficacy PD		Y
2.90.	Efficacy PD	EFF_F10	Scatter Plot of Mean Dose During Week 40 to 52 vs. Baseline Hgb – Efficacy PD		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.91.	Efficacy PD	EFF_F10	Scatter Plot of Mean Dose During Week 40 to 52 vs. Prior ESA Dose – Efficacy PD		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 – ND Subjects	ICH E3	Y
3.2.	Safety	AE1	Summary of On-Therapy AEs by SOC and PT – PD Subjects	ICH E3	Y
3.3.	Safety	AE1	Summary of On-Therapy AEs by SOC and PT by Prior ESA Use – ND Subjects		Y
3.4.	Safety	AE1	Summary of On-Therapy AEs by SOC and PT by Prior ESA Use – PD Subjects		Y
3.5.	Safety	AE1	Summary of On-Therapy AEs by SOC and PT by CKD Stage – ND Subjects		Y
3.6.	Safety	AE1	Summary of On-Therapy AEs by SOC and PT by CKD Stage – PD Subjects		Y
3.7.	Safety	AE5	Summary of On-Therapy AEs by SOC and PT and Maximum Intensity – ND Subjects	ICH E3	Y
3.8.	Safety	AE5	Summary of On-Therapy AEs by SOC and PT and Maximum Intensity – PD Subjects	ICH E3	Y
3.9.	Safety	AE5	Summary of On-Therapy AEs by SOC and PT and Maximum Intensity by Prior ESA Use – ND Subjects		Y
3.10.	Safety	AE5	Summary of On-Therapy AEs by SOC and PT and Maximum Intensity by Prior ESA Use – PD Subjects		Y
3.11.	Safety	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT – ND Subjects		Y
3.12.	Safety	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT – PD Subjects		Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.13.	Safety	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT by Prior ESA Use – ND Subjects		Y
3.14.	Safety	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT by Prior ESA Use – PD Subjects		Y
3.15.	Safety	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT by Starting Dose of Daprodustat – ND Subjects		Y
3.16.	Safety	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT by Starting Dose of Daprodustat – PD Subjects		Y
3.17.	Safety	AE5	Summary of On-Therapy AEs up to Week 4 by SOC and PT and Maximum Intensity – ND Subjects		Y
3.18.	Safety	AE5	Summary of On-Therapy AEs up to Week 4 by SOC and PT and Maximum Intensity – PD Subjects		Y
3.19.	Safety	AE5	Summary of On-Therapy AEs up to Week 4 by SOC and PT and Maximum Intensity by Prior ESA Use – ND Subjects		Y
3.20.	Safety	AE5	Summary of On-Therapy AEs up to Week 4 by SOC and PT and Maximum Intensity by Prior ESA Use – PD Subjects		Y
3.21.	Safety	SAFE_T1	Summary of On-Therapy Common (>= 2 %) AEs by SOC and PT by Onset – ND Subjects	Not cumulative summary	Y
3.22.	Safety	SAFE_T1	Summary of On-Therapy Common (>= 2 %) AEs by SOC and PT by Onset – PD Subjects	Not cumulative summary	Y
3.23.	Safety	AE1	Summary of Post-Therapy AEs by SOC and PT – ND Subjects	ICH E3	Y
3.24.	Safety	AE1	Summary of Post-Therapy AEs by SOC and PT – PD Subjects	ICH E3	Y
3.25.	Safety	AE5	Summary of Post-Therapy AEs by SOC and PT and Maximum Intensity – ND Subjects	ICH E3	Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.26.	Safety	AE5	Summary of Post-Therapy AEs by SOC and PT and Maximum Intensity – PD Subjects	ICH E3	Y
3.27.	Safety	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT – ND Subjects	ICH E3	Y
3.28.	Safety	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT – PD Subjects	ICH E3	Y
3.29.	Safety	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT by Prior ESA Use – ND Subjects		Y
3.30.	Safety	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT by Prior ESA Use – PD Subjects		Y
3.31.	Safety	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT by CKD Stage – ND Subjects		Y
3.32.	Safety	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT by CKD Stage – PD Subjects		Y
3.33.	Safety	AE5	Summary of On-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity – ND Subjects	ICH E3	Y
3.34.	Safety	AE5	Summary of On-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity – PD Subjects	ICH E3	Y
3.35.	Safety	AE1	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT – ND Subjects		Y
3.36.	Safety	AE1	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT – PD Subjects		Y
3.37.	Safety	AE1	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT by Prior ESA Use – ND Subjects		Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.38.	Safety	AE1	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT by Prior ESA Use – PD Subjects		Y
3.39.	Safety	AE5	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT and Maximum Intensity – ND Subjects		Y
3.40.	Safety	AE5	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT and Maximum Intensity – PD Subjects		Y
3.41.	Safety	AE1	Summary of Post-Therapy Drug-Related AEs by SOC and PT – ND Subjects		Y
3.42.	Safety	AE1	Summary of Post-Therapy Drug-Related AEs by SOC and PT – PD Subjects		Y
3.43.	Safety	AE5	Summary of Post-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity – ND Subjects		Y
3.44.	Safety	AE5	Summary of Post-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity – PD Subjects		Y
3.45.	Safety	AE3	Summary of On-Therapy Non-Serious Drug-Related AEs – ND Subjects	Required for Plain Language Summary	Y
3.46.	Safety	AE3	Summary of On-Therapy Non-Serious Drug-Related AEs – PD Subjects	Required for Plain Language Summary	Y
3.47.	Safety	AE3	Summary of On-Therapy Common (>= 2 %) AEs by Overall Frequency – ND Subjects	ICH E3	Y
3.48.	Safety	AE3	Summary of On-Therapy Common (>= 2 %) AEs by Overall Frequency – PD Subjects	ICH E3	Y
3.49.	Safety	AE3	Summary of On-Therapy Common (>= 2 %) AEs by Overall Frequency by Prior ESA Use – ND Subjects		Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.50.	Safety	AE3	Summary of On-Therapy Common (>= 2 %) AEs by Overall Frequency by Prior ESA Use – PD Subjects		Y
3.51.	Safety	AE3	Summary of On-Therapy Common (>= 2 %) AEs by Overall Frequency by CKD Stage – ND Subjects		Y
3.52.	Safety	AE3	Summary of On-Therapy Common (>= 2 %) AEs by Overall Frequency by CKD Stage – PD Subjects		Y
3.53.	Safety	AE15	Summary of On-Therapy Common (>=5%) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences) – ND Subjects	FDAAA, EudraCT	Y
3.54.	Safety	AE15	Summary of On-Therapy Common (>=5%) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences) – PD Subjects	FDAAA, EudraCT	Y
Serious and Other Significant AEs					
3.55.	Safety	AE1	Summary of On-Therapy Serious AEs – ND Subjects	GSK CTR	Y
3.56.	Safety	AE1	Summary of On-Therapy Serious AEs – PD Subjects	GSK CTR	Y
3.57.	Safety	AE1	Summary of Post-Therapy Serious AEs – ND Subjects	GSK CTR	Y
3.58.	Safety	AE1	Summary of Post-Therapy Serious AEs – PD Subjects	GSK CTR	Y
3.59.	Safety	AE3	Summary of On-Therapy Serious Drug-Related AEs – ND Subjects	Required for Plain Language Summary	Y
3.60.	Safety	AE3	Summary of On-Therapy Serious Drug-Related AEs – PD Subjects	Required for Plain Language Summary	Y
3.61.	Safety	AE16	Summary of On-Therapy Serious AEs by SOC and PT (Subjects & No. of Occurrences) – ND Subjects	FDAAA, EudraCT	Y
3.62.	Safety	AE16	Summary of On-Therapy Serious AEs by SOC and PT (Subjects & No. of Occurrences) – PD Subjects	FDAAA, EudraCT	Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.63.	Safety	AE1	Summary of AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT – ND Subjects	IDSL	Y
3.64.	Safety	AE1	Summary of AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT – PD Subjects	IDSL	Y
AEs of Special Interest					
3.65.	Safety	SAFE_T2	Summary of On-Therapy AEs of Special Interest – ND Subjects		Y
3.66.	Safety	SAFE_T2	Summary of On-Therapy AEs of Special Interest – PD Subjects		Y
3.67.	Safety	SAFE_T2	Summary of Post-Therapy AEs of Special Interest – ND Subjects		Y
3.68.	Safety	SAFE_T2	Summary of Post-Therapy AEs of Special Interest – PD Subjects		Y
Laboratory: Chemistry					
3.69.	Safety	LB1	Summary of Chemistry Values by Visit – ND Subjects	ICH E3 Includes Baseline values	Y
3.70.	Safety	LB1	Summary of Chemistry Values by Visit – PD Subjects	ICH E3 Includes Baseline values	Y
3.71.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit – ND Subjects	ICH E3	Y
3.72.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit – PD Subjects	ICH E3	Y
3.73.	Safety	SAFE_T3	Summary of Percent Change from Baseline in Lipid Parameters (Total Cholesterol, LDL Cholesterol, HDL Cholesterol, and LDL/HDL Cholesterol Ratio) by Visit – ND Subjects		Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.74.	Safety	SAFE_T3	Summary of Percent Change from Baseline in Lipid Parameters (Total Cholesterol, LDL Cholesterol, HDL Cholesterol, LDL/HDL Cholesterol Ratio) by Visit – PD Subjects		Y
3.75.	Safety	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.76.	Safety	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y
3.77.	Safety	LB17	Summary of Worst Case Chemistry Results Relative to PCI Criteria Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.78.	Safety	LB17	Summary of Worst Case Chemistry Results Relative to PCI Criteria Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y
Hematology					
3.79.	Safety	LB1	Summary of Hematology Values by Visit – ND Subjects	ICH E3 Includes Baseline values	Y
3.80.	Safety	LB1	Summary of Hematology Values by Visit – PD Subjects	ICH E3 Includes Baseline values	Y
3.81.	Safety	LB1	Summary of Hematology Changes from Baseline by Visit – ND Subjects	ICH E3	Y
3.82.	Safety	LB1	Summary of Hematology Changes from Baseline by Visit – PD Subjects	ICH E3	Y
3.83.	Safety	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.84.	Safety	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.85.	Safety	LB17	Summary of Worst Case Hematology Results Relative to PCI Criteria Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.86.	Safety	LB17	Summary of Worst Case Hematology Results Relative to PCI Criteria Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y
Urinalysis					
3.87.	Safety	LB1	Summary of Urinalysis Values by Visit – ND Subjects	ICH E3 Includes Baseline values	Y
3.88.	Safety	LB1	Summary of Urinalysis Changes from Baseline by Visit – ND Subjects	ICH E3	Y
3.89.	Safety	LB15	Summary of Worst Case Urinalysis Results Relative to Normal Range Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.90.	Safety	LB17	Summary of Worst Case Urinalysis Results Relative to PCI Criteria Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
Iron Parameters					
3.91.	Safety	LB1	Summary of Iron Values by Visit – ND Subjects	ICH E3 Includes Baseline values	Y
3.92.	Safety	LB1	Summary of Iron Values by Visit – PD Subjects	ICH E3 Includes Baseline values	Y
3.93.	Safety	LB1	Summary of Iron Changes from Baseline by Visit – ND Subjects	ICH E3	Y
3.94.	Safety	LB1	Summary of Iron Changes from Baseline by Visit – PD Subjects	ICH E3	Y
3.95.	Safety	LB15	Summary of Worst Case Iron Results Relative to Normal Range Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.96.	Safety	LB15	Summary of Worst Case Iron Results Relative to Normal Range Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.97.	Safety	LB17	Summary of Worst Case Iron Results Relative to PCI Criteria Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.98.	Safety	LB17	Summary of Worst Case Iron Results Relative to PCI Criteria Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y
Other Laboratory Tests					
3.99.	Safety	LB1	Summary of Other Laboratory Values by Visit – ND Subjects	ICH E3 Includes Baseline values	Y
3.100.	Safety	LB1	Summary of Other Laboratory Values by Visit – PD Subjects	ICH E3 Includes Baseline values	Y
3.101.	Safety	LB1	Summary of Other Laboratory Changes from Baseline by Visit – ND Subjects	ICH E3	Y
3.102.	Safety	LB1	Summary of Other Laboratory Changes from Baseline by Visit – PD Subjects	ICH E3	Y
3.103.	Safety	LB15	Summary of Worst Case Other Laboratory Results Relative to Normal Range Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.104.	Safety	LB15	Summary of Worst Case Other Laboratory Results Relative to Normal Range Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y
3.105.	Safety	LB17	Summary of Worst Case Other Laboratory Results Relative to PCI Criteria Post-Baseline Relative to Baseline – ND Subjects	ICH E3	Y
3.106.	Safety	LB17	Summary of Worst Case Other Laboratory Results Relative to PCI Criteria Post-Baseline Relative to Baseline – PD Subjects	ICH E3	Y
Hepatobiliary (Liver)					
3.107.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting – ND Subjects	IDSL	Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.108.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting – PD Subjects	IDSL	Y
3.109.	Safety	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria – ND Subjects	IDSL	Y
3.110.	Safety	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria – PD Subjects	IDSL	Y
ECG					
3.111.	Safety	EG1	Summary of ECG Findings – ND Subjects	IDSL	Y
3.112.	Safety	EG1	Summary of ECG Findings – PD Subjects	IDSL	Y
3.113.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit – ND Subjects	IDSL	Y
3.114.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit – PD Subjects	IDSL	Y
Vital Signs					
3.115.	Safety	VS1	Summary of Vital Signs by Visit – ND Subjects		Y
3.116.	Safety	VS1	Summary of Vital Signs by Visit – PD Subjects		Y
3.117.	Safety	VS1	Summary Change from Baseline in Vital Signs by Visit – ND Subjects		Y
3.118.	Safety	VS1	Summary Change from Baseline in Vital Signs by Visit – PD Subjects		Y
3.119.	Safety	VS7	Summary of Worst Case Vital Sign Results Relative to PCI Criteria Post-Baseline Relative to Baseline – ND Subjects		Y
3.120.	Safety	VS7	Summary of Worst Case Vital Sign Results Relative to PCI Criteria Post-Baseline Relative to Baseline – PD Subjects		Y

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Ophthalmology					
3.121.	Safety	SAFE_T6	Summary of Ophthalmologic Exams at Screening – ND Subjects		Y
3.122.	Safety	SAFE_T6	Summary of Ophthalmologic Exams at Screening – PD Subjects		Y
3.123.	Safety	SAFE_T7	Summary of On-Therapy Ophthalmologic Exams – ND Subjects		Y
3.124.	Safety	SAFE_T7	Summary of On-Therapy Ophthalmologic Exams – PD Subjects		Y
Change in Anti-Hypertensive Medications					
3.125.	Safety	SAFE_T8	Summary of Change in Anti-Hypertensive Medications Due to Increased Blood Pressure – ND Subjects		Y
3.126.	Safety	SAFE_T8	Summary of Change in Anti-Hypertensive Medications Due to Increased Blood Pressure – PD Subjects		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 – ND Subjects	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, and LDL/HDL Cholesterol Ratio) over Time – ND Subjects		Y
3.3.	Safety	SAFE_F1	Plot of Percent Change from Baseline in Lipid Parameters (Total cholesterol, LDL Cholesterol, HDL Cholesterol, and LDL/HDL Cholesterol Ratio) over Time – PD Subjects		Y

15.10.4.6. Patient Reported Outcome Tables

Patient Reported Outcome: 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) – ITT	including PCS and MCS	Y
4.2.	Efficacy PD	SF2	Summary of SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) - Efficacy PD	including PCS and MCS	Y
4.3.	ITT	SF2	Summary of SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) by Prior ESA Use – ITT	including PCS and MCS	Y
4.4.	Efficacy PD	SF2	Summary of SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) by Prior ESA Use - Efficacy PD	including PCS and MCS	Y
4.5.	ITT	SF4	Summary of Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) – ITT	including PCS and MCS	Y
4.6.	Efficacy PD	SF4	Summary of Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) - Efficacy PD	including PCS and MCS	Y
4.7.	ITT	SF4	Summary of Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) by Prior ESA Use – ITT	including PCS and MCS	Y
4.8.	Efficacy PD	SF4	Summary of Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) by Prior ESA Use - Efficacy PD	including PCS and MCS	Y
4.9.	ITT	PRO_T1	Summary of EQ-5D-5L Score - ITT		Y
4.10.	Efficacy PD	PRO_T1	Summary of EQ-5D-5L Score - Efficacy PD		Y
4.11.	ITT	PRO_T1	Summary of EQ-5D-5L Score by Prior ESA Use - ITT		Y
4.12.	Efficacy PD	PRO_T1	Summary of EQ-5D-5L Score by Prior ESA Use - Efficacy PD		Y
4.13.	ITT	PRO_T2	Summary of EQ-5D-5L Index Value - ITT		Y

Patient Reported Outcome: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
4.14.	Efficacy PD	PRO_T2	Summary of EQ-5D-5L Index Value - Efficacy PD		Y
4.15.	ITT	PRO_T2	Summary of EQ-5D-5L Index Value by Prior ESA Use - ITT		Y
4.16.	Efficacy PD	PRO_T2	Summary of EQ-5D-5L Index Value by Prior ESA Use - Efficacy PD		Y
4.17.	ITT	PRO_T2	Summary of Changes from Baseline in EQ-5D-5L Index Value – ITT		Y
4.18.	Efficacy PD	PRO_T2	Summary of Changes from Baseline in EQ-5D-5L Index Value - Efficacy PD		Y
4.19.	ITT	PRO_T2	Summary of Changes from Baseline in EQ-5D-5L Index Value by Prior ESA Use – ITT		Y
4.20.	Efficacy PD	PRO_T2	Summary of Changes from Baseline in EQ-5D-5L Index Value by Prior ESA Use - Efficacy PD		Y
4.21.	ITT	PRO_T3	Summary of EQ Visual Analog Scale (VAS) - ITT		Y
4.22.	Efficacy PD	PRO_T3	Summary of EQ Visual Analog Scale (VAS) - Efficacy PD		Y
4.23.	ITT	PRO_T3	Summary of EQ Visual Analog Scale (VAS) by Prior ESA Use - ITT		Y
4.24.	Efficacy PD	PRO_T3	Summary of EQ Visual Analog Scale (VAS) by Prior ESA Use - Efficacy PD		Y
4.25.	ITT	PRO_T3	Summary of Changes from Baseline in EQ Visual Analog Scale (VAS) – ITT		Y
4.26.	Efficacy PD	PRO_T3	Summary of Changes from Baseline in EQ Visual Analog Scale (VAS) - Efficacy PD		Y
4.27.	ITT	PRO_T3	Summary of Changes from Baseline in EQ Visual Analog Scale (VAS) by Prior ESA Use – ITT		Y
4.28.	Efficacy PD	PRO_T3	Summary of Changes from Baseline in EQ Visual Analog Scale		Y

Patient Reported Outcome: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**SAC**
			(VAS) by Prior ESA Use - Efficacy PD		
4.29.	ITT	PRO_T4	Analysis of Changes from Baseline in Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) - ITT		Y
4.30.	ITT	PRO_T4	Analysis of Changes from Baseline in Changes from Baseline in SF-36 HR-QoL Scores (PCS, MCS, 8 Subscales) by Prior ESA Use - ITT		Y
4.31.	ITT	PRO_T5	Analysis of Changes from Baseline in EQ-5D-5L Index Value - ITT		Y
4.32.	ITT	PRO_T5	Analysis of Changes from Baseline in EQ-5D-5L Index Value by Prior ESA Use - ITT		Y
4.33.	ITT	PRO_T5	Analysis of Changes from Baseline in EQ Visual Analog Scale (VAS) - ITT		Y
4.34.	ITT	PRO_T5	Analysis of Changes from Baseline in EQ Visual Analog Scale (VAS) by Prior ESA Use - ITT		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 Subject 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.	Safety	TA1	Listing of Planned and Actual Treatments	GSK CSR	Y
Protocol Deviations					
5.	Randomized	DV2	Listing of Important Protocol Deviations		Y
6.	Randomized	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		Y
Population Analyzed					
7.	Randomized	SP3	Listing of Subjects Excluded from Any Population		Y
8.	mITT	SP3	Listing of Subjects Excluded from Per Protocol Population	Include the exclusion categories	Y
Demographic and Baseline Characteristics					
9.	Safety	DM2	Listing of Demographic Characteristics	ICH E3	Y
10.	Safety	POP_L1	Listing of Other Baseline Characteristics		Y
11.	Safety	CM2	Listing of Prior ESA		Y
12.	Safety	DM9	Listing of Race	ICH E3	Y
Exposure and Treatment Compliance					
13.	Safety	POP_L2	Listing of Exposure Data - Daprodustat	ICH E3	Y

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
14.	Safety	POP_L3	Listing of Exposure Data - Epoetin Beta Pegol	ICH E3	Y
15.	Safety	POP_L4	Listing of Study Medication Compliance	ICH E3	Y
Efficacy					
Hgb					
16.	ITT	EFF_L1	Listing of Hgb Data – ITT		Y
17.	Efficacy PD	EFF_L1	Listing of Hgb Data – Efficacy PD		Y
18.	Efficacy PD	EFF_L1	Listing of Hgb Data – PD, ESA Non-Users	ESA non-users only	Y
19.	ITT	EFF_L2	Listing of Subjects Who Have Hgb Level of Less than 7.5 g/dL – ITT		Y
20.	Efficacy PD	EFF_L2	Listing of Subjects Who Have Hgb level of Less than 7.5 g/dL – Efficacy PD		Y
21.	Efficacy PD	EFF_L2	Listing of Subjects Who Have Hgb level of Less than 7.5 g/dL – PD, ESA Non-Users	ESA non-users only	Y
22.	ITT	EFF_L2	Listing of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 Weeks – ITT		Y
23.	Efficacy PD	EFF_L2	Listing of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 Weeks – Efficacy PD		Y
24.	Efficacy PD	EFF_L2	Listing of Subjects Who Have Hgb Increase of More than 2.0 g/dL over Any 4 Weeks – PD, ESA Non-Users	ESA non-users only	Y
25.	ITT	EFF_L2	Listing of Subjects Who Have Hgb Level of More than 13.0 g/dL – ITT		Y
26.	Efficacy PD	EFF_L2	Listing of Subjects Who Have Hgb Level of More than 13.0 g/dL – Efficacy PD		Y

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
27.	Efficacy PD	EFF_L2	Listing of Subjects Who Have Hgb Level of More than 13.0 g/dL – PD, ESA Non-Users	ESA non-users only	Y
28.	ITT	EFF_L3	Listing of Subjects with Treatment Interruption due to Hgb > 13 g/dL – ITT		Y
29.	Efficacy PD	EFF_L3	Listing of Subjects with Treatment Interruption due to Hgb > 13 g/dL- Efficacy PD		Y
30.	Efficacy PD	EFF_L3	Listing of Subjects with Treatment Interruption due to Hgb > 13 g/dL- PD, ESA Non-Users	ESA non-users only	Y
31.	ITT	EFF_L7	Listing of Subjects Who Reach the Lower Hgb Target - ITT		Y
32.	Efficacy PD	EFF_L7	Listing of Subjects Who Reach the Lower Hgb Target – Efficacy PD		Y
33.	Efficacy PD	EFF_L7	Listing of Subjects Who Reach the Lower Hgb Target – PD, ESA Non-Users	ESA non-users only	Y
Dose Adjustment					
34.	Efficacy PD	EFF_L4	Listing of Dose Level – PD, ESA Non-Users	ESA non-users only	Y
35.	Efficacy PD	EFF_L5	Listing of Dose Adjustment – PD, ESA Non-Users	ESA non-users only	Y
Safety					
Adverse Events					
36.	Safety	AE8	Listing of All Adverse Events	ICH E3	Y
37.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	Y
38.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	Y
Serious and Other Significant Adverse Events					
39.	Safety	AE8	Listing of Fatal Serious Adverse Events	ICH E3	Y

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
40.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	Y
41.	All Screening	AE8	Listing of Serious AEs in Screening Period		Y
42.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	Y
43.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	Y
44.	Safety	SAFE_L1	Listing of Adverse Events of Special Interest	ICH E3 Displays will be produced with AESI category in addition of AE8 template.	Y
All Laboratory					
45.	Safety	LB5	Listing of All Chemistry Data for Subjects with Any Value Outside of Normal Range/of PCI	ICH E3	Y
46.	Safety	LB5	Listing of All Hematology Data for Subjects with Any Value Outside of Normal Range/of PCI	ICH E3	Y
47.	Safety	LB5	Listing of All Urinalysis Laboratory Data for Subjects with Any Value Outside of Normal Range	ICH E3	Y
48.	Safety	LB5	Listing of All Iron Parameters Laboratory Data for Subjects with Any Value Outside of Normal Range/of PCI	ICH E3	Y
49.	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					
50.	Safety	FH4	Listing of Family Members with History of Cardiovascular Risk Factors		Y
51.	Safety	SU2	Listing of Substance Use History		Y
Dialysis					
52.	Safety	POP_L8	Listing of Dialysis Initiation During the Study Period		Y
53.	Safety	POP_L8	Listing of Peritoneal Dialysis at Baseline		Y
54.	Safety	POP_L9	Listing of Subjects with Vascular Therapeutic Procedures During the Study Period		Y
Medical Conditions and Concomitant Medication					
55.	Safety	MH2	Listing of Medical Conditions		Y
56.	Safety	CM2	Listing of Concomitant Medications		Y
57.	Safety	POP_L5	Listing of ESA Concomitant Medications		Y
58.	Safety	POP_L6	Listing of Iron Concomitant Medications		Y
59.	Safety	POP_L7	Listing of Anti-Hypertensive Concomitant Medications		Y
60.	Safety	POP_L8	Listing of Blood Products and Blood Supportive Care Products		Y
Efficacy					
Iron Parameters					
61.	ITT	LB5	Listing of Iron Parameter Data - ITT	All iron parameters will be included.	Y
62.	Efficacy PD	LB5	Listing of Iron Parameter Data – Efficacy PD	All iron parameters will be included.	Y

Other Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
CKD Progression					
63.	ITT	EFF_L6	Listing of CKD Progression		Y
Safety					
Suicidality-Related Adverse Event					
64.	Safety	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1-Section 2)		Y
65.	Safety	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)		Y
66.	Safety	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: (Section 4)		Y
67.	Safety	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: (Section 5 - Section 8)		Y
Clinical Laboratory, ECG, Vital Sign, and Ophthalmology Exam					
68.	Safety	LB5	Listing of Chemistry Data		Y
69.	Safety	LB5	Listing of Hematology Data		Y
70.	Safety	LB5	Listing of Other Laboratory Data		Y
71.	Safety	LB5	Listing of Urinalysis Data		Y
72.	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
73.	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
74.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		Y
75.	Safety	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score		Y

Other Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
76.	Safety	LIVER7	Listing of Liver Biopsy Details		Y
77.	Safety	LIVER8	Listing of Liver Imaging Details		Y
78.	Safety	EG3	Listing of ECG Values		Y
79.	Safety	EG5	Listing of ECG Findings	Delete column of 'Clinically Significant Change from Baseline?' from EG5 template	Y
80.	Safety	VS4	Listing of Vital Signs		Y
81.	Safety	VS4	Listing of All Vital Signs for Subjects with Values of PCI		Y
82.	Safety	SAFE_L2	Listing of Ophthalmologic Exams		Y
83.	Safety	SAFE_L3	Listing of Subjects Who Have Any Change in Anti-Hypertensive Medications Due to Increased Blood Pressure		Y
Other					
84.	Safety	PREG1a	Listing of Subjects Who Became Pregnant During the Study		Y
Patient Reported Outcome					
85.	ITT	PRO_L1	Listing of SF-36v2 Summary Scores and Domain Scores – ITT	Including PCS and MCS	Y
86.	Efficacy PD	PRO_L1	Listing of SF-36v2 Summary Scores and Domain Scores – Efficacy PD	Including PCS and MCS	Y
87.	ITT	PRO_L2	Listing of Individual Scores of EQ-5D-5L VAS – ITT	Including index value	Y
88.	Efficacy PD	PRO_L2	Listing of Individual Scores of EQ-5D-5L VAS – Efficacy PD	Including index value	Y
Pharmacokinetic Parameters					
89.	PK	PK07	Listing of Daprodustat Pharmacokinetic Concentration-Time Data by Dose Level		Y
90.	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					
91.	Safety	IDSL standard	Patient Profile Listing of Arrhythmias		Y
92.	Safety	IDSL standard	Patient Profile Listing of Congestive Heart Failure		Y
93.	Safety	IDSL standard	Patient Profile Listing of Cerebrovascular Events/Stroke/ Transient Ischemic Attack		Y
94.	Safety	IDSL standard	Patient Profile Listing of Deep Venous Thrombosis/ Pulmonary Embolism		Y
95.	Safety	IDSL standard	Patient Profile Listing of Myocardial Infarction /Unstable Angina		Y
96.	Safety	IDSL standard	Patient Profile Listing of Peripheral Arterial Thrombosis Embolism		Y
97.	Safety	IDSL standard	Patient Profile Listing of Pulmonary Hypertension		Y
98.	Safety	IDSL standard	Patient Profile Listing of Revascularization		Y
99.	Safety	IDSL standard	Patient Profile Listing of Valvulopathy		Y
100.	Safety	IDSL standard	Patient Profile Listing of Deaths		Y

15.11. Appendix 11: Example Mock Shells for Data Displays

Example 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_201753_Amendment 1 [19-NOV-2018]		
Section # and Name	**Description of Change**	**Brief Rationale**
Cover page	Approvers were changed.	Changed according to INS_689064 (1.0)
5.4.2 Examination of Subgroups	Cutoff values of baseline Hgb for ESA non-users and ERI were changed.	Cutoff value of baseline Hgb is aligned with stratification factor in randomization. Cutoff value of ERI was reconsidered.
6.1 Overview of Planned Study Population Analyses 15.10.4 Table of Contents for SAC Deliverable	Listing of Other Baseline Characteristics including prior ESA type, standardized prior ESA dose, ERI, iron use, diabetes, and CKD stage was added.	Required information was added.
6.2 Planned Summary Display Details 15.6.2 Study Population	Added the period of time on dialysis for PD subjects in demographic characteristics.	PD subjects are on peritoneal dialysis.
6.2 Planned Summary Display Details	Added compliance up to week 2 and week 2 to 4 for only cohort 3	Subjects in cohort 3 have week 2 visit.
7.1 Primary Efficacy Analyses 15.10.4 Table of Contents for SAC Deliverable	Added tables of the tipping point analysis	It would facilitate review of tipping point results.
7.1.6.1 Evaluable Hgb	Blood transfusion impacting Hgb values was clarified as red blood cell transfusion and whole blood transfusion.	Clarification
7.1.6.3 Tipping Point Analysis	Added statement of subjects who do not have Hgb on and after week 4 will be excluded in the tipping point analysis	The subjects are not included in the primary analysis.
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 one-sided p-value for odds ratio has been specified in Section 7.2.5.1 Statistical Methodology Specification	Clarification
7.2.5.1 Statistical Methodology Specification	Added handling to a problem with quasi-complete separation.	The problem with quasi-complete separation may occur.

Reporting and Analysis Plan_201753_Amendment 1 [19-NOV-2018]		
Section # and Name	**Description of Change**	**Brief Rationale**
7.3.1 Endpoint / Variables	Subgroup analyses by baseline Hgb for Hgb raw value, change from baseline in Hgb, number of subjects with Hgb within target range were added.	Analyses required from PMDA consultation
7.3.1 Endpoint / Variables 7.3.2 Summary Measure 15.10.4 Table of Contents for SAC Delivrable	Figures of the raw observed values for each iron parameter were added.	It would facilitate review of iron parameters results
7.3.2 Summary Measure	Added categories for Hgb change from baseline at week 2	Change we would like to confirm at week 2 is half of change at week 4.
7.3.2 Summary Measure	Added subgroup analyses by prior ESA dose, prior ESA type, and ERI for following analyses. Dose at each assessment visit / final visit Duration of treatment interruption due to Hgb > 13.0 g/dL Number of subjects with each dose at each assessment visit	Reconsidered required subgroup analysis
7.3.2 Summary Measure	Added summarizing oral iron dose in screening period as baseline.	Some subjects use oral iron at screening. It is useful for comparing change from baseline.
7.3.2 Summary Measure	Treatment difference and 95% CI for change from baseline of iron parameters were added.	It would facilitate review of iron parameters results
7.3.4 Strategy for Intercurrent (Post-Randomization) Events	The strategy for analysis of change from baseline in iron parameters was added.	The analysis was added.
7.3.5.1 Statistical Methodology Specification	The statistical methodology specification for analysis of change from baseline in iron parameters was added.	The analysis was added.
7.4.2 Summary Measure 15.10.4 Table of Contents for SAC Delivrable	Figures of the raw observed value for CKD progression were added.	It would facilitate review of CKD progression results.
8.1.1 Planned Adverse Events Analyses Displays	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.	Clarification according to PMDA requirement
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	A model-based approach would be effectively estimate the results of the QoL parameters more

Reporting and Analysis Plan_201753_Amendment 1 [19-NOV-2018]		
Section # and Name	**Description of Change**	**Brief Rationale**
	Statistical Methodology Specification. Also, the strategy for intercurrent events was added as appropriate.	effectively
15.1.1 Exclusions from Per Protocol Population	It has been clarified that the exclusion criteria 07 does not include ESA medications.	Clarification
15.6.2 Study Population	Clarification has been made to prior ESA dose at baseline.	Clarification
15.6.2 Study Population	Clarification has been made to treatment compliance of daprodustat and epoetin beta pegol	Clarification
15.6.2 Study Population	Excluded P-TOL in iron medication summary although P-TOL is collected as iron medication.	Clarification
15.6.2 Study Population	Added a linear regression line with 95% CI band and R-squared for scatter plot of Hgb assessment	Clarification
15.6.3 Efficacy	Added statement of using different displays by prior ESA use for the following scatter plots. Change from baseline in Hgb at week 4 vs covariates of interest Mean dose during week 40 to 52 vs covariates of interest	Clarification
15.6.3 Efficacy	Clarification has been made to dose adjustment algorithm.	Clarification
15.6.3 Efficacy	Clarification has been made to duration of treatment interruption due to Hgb > 13.0 g/dL.	Clarification
15.6.3 Efficacy	Clarification has been made to oral iron dose by quarter.	Clarification
15.6.3 Efficacy	Excluded P-TOL for Iron use subgroup.	Clarification
15.6.4 Safety	Specified AESIs to be programmatically identified.	Some AESIs are not manually-selected by SRT.
15.6.5 Pharmacokinetic	Added a following condition omitted from summaries. concentrations obtained in the less interval of last two treatment administrations than 12 hours	Added according to the protocol.
15.6.6 Exploratory Endpoint	Added equation of eGFR.	Clarification
15.6.7 Patient Reported Outcome	Changed overview of scoring algorithm in SF-36v2.	Removed inaccurate information
15.8 Appendix 8: Values of Potential Clinical Importance	Added PCI value of eGFR	Addition