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

Title	:	Reporting and Analysis Plan for A Phase 3 randomized, double-blind, active-controlled, parallel-group, multi-center study in hemodialysis participants with anemia of chronic kidney disease to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of daprodustat compared to recombinant human erythropoietin, following a switch from recombinant human erythropoietin or its analogs.
Compound Number	:	GSK1278863
Effective Date	:	02-SEP-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204837 (GSK Document Number 2016N279035_00)

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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: 204837 (GSK Document Number 2016N279035_00)

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

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

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• None	• New displays related to COVID-19 pandemic have been added	• Assessing the impact of the COVID-19 pandemic
• Only include randomized subjects who have both baseline and at least one Hgb assessment during the EP in the primary Hgb analysis	• All randomized subjects will be included in the primary Hgb analysis by imputing missing post-baseline Hgb data using pre-specified multiple imputation approach	• Addressing the feedback from FDA
• None	• Worsening of Hypertension has been added to the list of AESI and is included in the summary and analysis of AESI	• Worsening of Hypertension added to the listing of AESI across the daprodustat program following review of data supporting Japan NDA
• None	• Number of RBC transfusions, whole blood transfusions, and transfusion events are included in the exploratory efficacy analysis of RBC and Whole Blood Transfusions	• Number of RBC transfusions, whole blood transfusions, and transfusion events have been defined and included in the exploratory endpoints
• None	• Time to first RBC transfusion and/or whole blood transfusion is included in the exploratory efficacy analysis of RBC and Whole Blood Transfusions	• Time to first RBC transfusion and/or whole blood transfusion has been included in the exploratory endpoints
• Subgroup: Weight: < 75kg, ≥75kg	• Baseline post-dialysis weight quartiles	• Subgroup update prior to unblinding the trial
• Baseline hsCRP: ≤3 mg/L, >3 mg/L	• Baseline hsCRP quartiles	• Subgroup update prior to unblinding the trial

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• PK endpoint: pre-dose trough (Ctau)	• "Pre-dose trough (Ctau)" has been replaced with "Pre-dose trough (Ctrough)	• Ctrough is more accurate for TIW dosing regimen
• None	• New PK-related parameters (Dapro Efficacy Dose Parameters, Dapro Efficacy Special Parameters, Dapro Safety Dose Parameters, Dapro Safety Special Parameters)	• Provides transparency to the intermediate endpoints required for figure creation at individual and population level.
• Explore the graphical relationship between Dapro exposure and Mean Hgb	• Explore the graphical relationship between Dapro exposure and Mean Hgb change from baseline	• Mean Hgb change from baseline is a better assessment of daprodustat efficacy than absolute Hgb.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare the effect of daprodustat to epoetin alfa on Hgb efficacy when administered three-times weekly to hemodialysis-dependent participants (non-inferiority)	• Mean change in Hgb between baseline and over the evaluation period (EP, mean over Weeks 28 to 52)
Principal Secondary Objectives	**Principal Secondary Endpoints** (tested for superiority, adjusted for multiplicity)
• To compare daprodustat administered three-times weekly to epoetin alfa on the use of intravenous (IV) iron	• Average monthly IV iron dose (mg)/participant to Week 52
Safety Objectives	**Safety Endpoints**
• To compare the safety and tolerability of daprodustat administered three-times weekly to epoetin alfa	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest and MACE • Reasons for discontinuation of study treatment • Absolute values and changes from baseline in laboratory parameters, BP and heart rate (HR)
Secondary Objectives	**Secondary Endpoints** (Non-PK endpoints tested for superiority[1], with no multiplicity adjustment)
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on Hgb variability	• Hgb change from baseline to Week 52 [1] • % time Hgb in analysis range (10 to 11.5 g/dL) during the EP [1] • N (%) responders, defined as mean Hgb within the Hgb analysis range 10 to 11.5 g/dL during the EP
• To compare daprodustat administered three-times weekly to epoetin alfa on the time to rescue	• Time to stopping study treatment due to meeting rescue criteria

Objectives	Endpoints
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on BP	• Change from baseline in SBP, DBP and mean arterial pressure (MAP) at Week 52 and at the end of study treatment • Number of BP exacerbation events per 100 patient years • N (%) with at least one BP exacerbation event during study
• To generate pharmacokinetic parameters of daprodustat and predominant metabolites following three-times weekly dosing	• Plasma daprodustat, M2, M3, M4, M5, M6 and M13 PK parameters pre-dose trough (Ctau) and Cmax
• To compare daprodustat administered three-times weekly to epoetin alfa on global symptom severity and change	• Change from Baseline at Weeks 8,12, 28, and 52 in PGI-S
Exploratory Objectives (no statistical testing planned)	**Exploratory Endpoints**
• To evaluate graphical relationships between exposure parameters and selected efficacy endpoints of daprodustat administered three-times weekly	• Extrapolated Cmax of daprodustat vs. the percent time within the Hgb target range during the EP • Extrapolated Cmax of daprodustat vs. mean Hgb over the 52-week treatment period • Mean weekly daprodustat dose over 52 weeks vs. the percent time within the Hgb target range during the EP • Mean weekly daprodustat dose over 52 weeks vs. mean Hgb over the 52-week treatment period
• To evaluate graphical relationships between daprodustat administered three-times weekly against MACE and the combined safety endpoint of MACE + thromboembolic event + hospitalization for Congestive Heart Failure (CHF)	• Extrapolated Cmax of daprodustat in participants without MACE compared to those with MACE (as well as for the combined safety endpoint of MACE + thromboembolic event + hospitalization for CHF) • Mean weekly daprodustat dose in participants without MACE compared to those with MACE (as well as for the combined safety endpoint of MACE + thromboembolic event + hospitalization for CHF)
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on BP and BP medication changes	• Observed and change from baseline in SBP, DBP and MAP by visit • Number of BP medications per participant by visit • Change from baseline in the number or dose of BP medications per participant by visit • N (%) of participants who had no change in the number or dose of BP medications from baseline by visit • N (%) of participants who had an increase in the number or dose of BP medications from baseline by visit • N (%) of participants who had a decrease in the number or dose of BP medications from baseline by visit
• To further compare the effect of daprodustat administered three-times weekly to epoetin alfa on Hgb variability	• Hgb observed and change from baseline across all visits • % of time Hgb is above, within and below the analysis range of 10 to 11.5 g/dL during the EP • Number (%) of participants with mean Hgb above, within and below the Hgb analysis range during the EP • Number (%) of participants with a Hgb <7.5 g/dL during the EP • Number of times Hgb <7.5 g/dL during the EP

Objectives	Endpoints
	• Number (%) of participants with a >1 g/dL increase in Hgb within any 2-week period (assessed at Week 2 through Week 8), or with a >2 g/dL increase in Hgb within any 4-week period up to Week 52 • Number (%) of participants with a >1 g/dL decrease in Hgb within any 2-week period (assessed at Week 2 through Week 8), or with a >2 g/dL decrease in Hgb within any 4-week period up to Week 52 • N (%) of participants with a Hgb value ≥12 g/dL during the EP • Number of times Hgb ≥12 g/dL during the EP • % of time Hgb ≥12 g/dL during the EP
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, transferrin saturation (TSAT), total iron, total iron binding capacity (TIBC) across all visits • Average quarterly ferritin • Average quarterly TSAT • Average quarterly IV iron dose/participant • N (%) of participants who met iron management criteria • N (%) of participants who reduced IV iron supplementation relative to baseline [defined as total iron (mg) over 4 weeks prior to randomization] during EP [defined as average monthly IV iron dose (mg) over Weeks 28 to 52]
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on the need for red blood cell (RBC) and whole blood transfusions	• Number (%) of participants who receive at least one RBC or whole blood transfusion by Week 52 • Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years
• Characterize the pharmacodynamic (PD) effect of daprodustat administered three-times weekly on EPO, vascular endothelial growth factor (VEGF) and RBC	• Maximum observed change from baseline in EPO • Maximum observed % change from baseline in VEGF • Change from baseline in hematocrit, RBC count, and reticulocyte count
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on lipid parameters.	• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)]

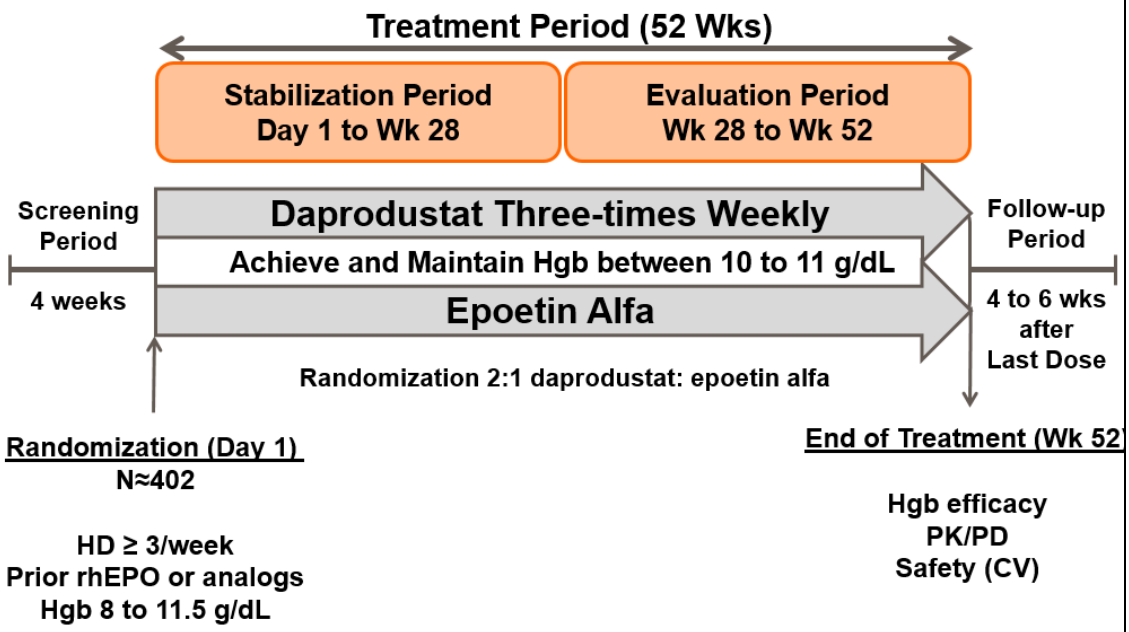
• To evaluate the dose adjustment scheme	• Assigned dose by visit and at Day 1, Week 28, and Week 52
	• Most recent dose prior to Week 28, Week 52 and end of study treatment
	• Number (%) of participants with 0, 1, 2, or >2 dose adjustments during the following periods:
	  o Day 1 to < Week 28
	  o Week 28 to < Week 52
	  o Day 1 to < Week 52
	• Number of dose adjustments during the following periods:
	  o Day 1 to < Week 28

Objectives	Endpoints
	○ Week 28 to < Week 52 ○ Day 1 to < Week 52 • Number of dose adjustments per year during Day 1 to < Week 52 • Time dose held for Hgb ≥12 g/dL
• To further compare daprodustat administered three-times weekly to epoetin alfa on global symptom severity and change	• Shift tables (Baseline to Weeks 8, 12, 28, and 52) in PGI-S • N (%) of participants within each PGI-C symptom change level at Weeks 8, 12, 28, and 52

1. Hgb change from baseline to Week 52 is tested for non-inferiority, using the -0.75 g/dL margin used in the primary analysis. % time in range is tested first for non-inferiority, then for superiority. The non-inferiority margin for % time in range is defined in Section 7.3.1.

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a randomized, double-blind, active-controlled, parallel-group, multi-center study in hemodialysis-dependent participants, including combination methods such as hemodiafiltration or hemofiltration with HD, who have anemia of CKD and are currently treated with rhEPO or its analogs.
	• This study includes a 4-week Screening Period, a 52-week Treatment Period and a Follow-up Period
	• The 52-week Treatment Period consists of:
	  ○ The Stabilization Period (SP), defined as the period from Day 1 to Week 28 (up to but excluding the Week 28 visit), during which study treatment will be dose-titrated to achieve and maintain Hgb in the target range.
	  ○ The Evaluation Period (EP), defined as the period from Week 28 to Week 52, to assess long-term efficacy and safety. The study treatment may be dose-titrated, if needed, during this period to achieve or maintain Hgb level in the target range.
	• Each participant will remain in the study for up to 62 weeks, including screening through the follow-up period. Participants who permanently discontinue study treatment will remain in the study.

Treatment Assignment	• The randomization schedule will be computer generated by Pharmaceutical Product Development, LLC (PPD) prior to the start of the study, using the validated randomization system Prism. Participants will be randomized centrally using an Interactive Response Technology (IRT) system. • Randomization will be stratified by region. Following stratification, participants will be randomized 2:1 to daprodustat or epoetin alfa. Daprodustat will be administered three-times weekly and epoetin alfa will be administered once weekly or three-times weekly, depending on dose level. • Due to the difference in formulations between the investigational product and the active control (tablets versus IV injection), and in order to maintain the study blind,

Overview of Study Design and Key Features	
	each participant will receive a tablet and an IV study treatment; one will be active and one will be inactive. Participants randomized to receive daprodustat will also receive saline IV injection. Participants randomized to receive epoetin alfa will also receive placebo tablets.
Dosing	• The dose of both study treatments will be adjusted in order to maintain Hgb concentration in the target range (10.0 to 11.0 g/dL). Adjustment of both study treatments (tablets and IV injection formulation) will follow a protocol-specified study treatment dose adjustment algorithm to achieve and maintain Hgb within the target range of 10.0 to 11.0 g/dL, inclusive. Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both study treatment arms. Please refer to the protocol for starting doses, dose steps, dose adjustment algorithm, and temporary study treatment interruption.
Time & Events	• Refer to Section 14.2. Appendix 2: Schedule of Activities
Interim Analysis	• There are no plans to evaluate interim data for the purposes of stopping based on Hgb efficacy data. • The IDMC will periodically receive unblinded safety reports containing clinical endpoints (whether adjudicated or pending adjudication) and SAEs, from an independent Statistical Data Analysis Center (SDAC) while Phase 3 studies with daprodustat are ongoing. The IDMC may recommend stopping this study for safety at any time.

2.4. Statistical Hypotheses

The primary Hgb efficacy objective will assess the estimand defined as the effect of daprodustat treatment relative to rhEPO on the change in Hgb from baseline to the average of all values in the EP, regardless of adherence to treatment including interruptions and discontinuations, the use of non-randomized ESA medication for any reason including rescue therapy, or the use of blood transfusions, in subjects on dialysis currently treated with an ESA with anemia secondary to CKD and assuming subjects do not die before the end of the EP. The analysis will test whether daprodustat is non-inferior to rhEPO according to the following statistical hypotheses:

- Null: The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-epoetin alfa), is less than or equal to -0.75 g/dL.

- Alternative: The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-epoetin alfa), is greater than -0.75 g/dL

The non-inferiority margin is pre-defined as -0.75 g/dL. This margin was selected to be consistent across all clinical trials in the daprodustat Phase 3 clinical development program in participants with anemia of chronic kidney disease, and it was determined based upon a combination of clinical judgment, statistical reasoning and regulatory guidance for designing non-inferiority trials.

Statistical significance of non-inferiority will be assessed at the one-sided 2.5% level. An analysis of covariance (ANCOVA) model including randomization stratification factor, baseline hemoglobin and treatment will be used to obtain a point estimate and the two-

sided 95% confidence interval (CI) for the treatment difference (daprodustat-rhEPO) and generate the p-value for the non-inferiority test. The non-inferiority p-value will show strength of evidence against the null hypothesis. Non-inferiority will be established if the lower limit of the two-sided 95% CI for the treatment difference is greater than -0.75 g/dL.

3. PLANNED ANALYSES

3.1. Interim Analyses

The IDMC will periodically receive unblinded safety reports containing, at a minimum, clinical endpoints (whether adjudicated or pending adjudication) and SAEs, from an independent Statistical Data Analysis Center (SDAC) while the study is ongoing. The IDMC may recommend stopping the study for safety at any time. (See IDMC charter for further details).

There are no plans to evaluate interim data for the purposes of stopping based on Hgb efficacy data.

3.2. Final Analyses

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

1. The end of the study has been reached, as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes generated by the Pharmaceutical Product Development, LLC (PPD) have been distributed according to GSK and PPD procedures.

4. ANALYSIS POPULATIONS

Inclusion in any analysis population is contingent on a subject signing informed consent.

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who sign the ICF	• Study Population
All Randomized (ITT)	• All randomized participants. This is the primary population for Hgb efficacy analyses. Participants will be analysed according to the treatment to which they were randomized. • Any participant who receives a treatment randomization number will be considered to have been randomized.	• Study Population • Efficacy • Selected Safety
Enrolled	• All participants who passed screening and entered the study. For this study, the Enrolled and All Randomized (ITT) populations will be identical. (Note: Use of enrolled population is required for some displays.) • Subjects will be analysed according to the treatment to which they were randomized.	• Study Population
Safety	• All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.[1]	• Safety
Per-Protocol (PP)	• All ITT participants who do not have PP population exclusions. This population will be the basis for a supportive analysis of the primary efficacy parameter.	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
	Participants will be analyzed according to the treatment to which they were randomized. • Protocol deviations that would exclude participants from the PP population are defined in Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population. • The PP set will not be analyzed if this population comprises more than 80% of the All Randomized (ITT) population.	
Pharmacokinetic (PK)	• All randomized participants for whom a post-baseline PK sample was obtained and analyzed. This will be the population used for all the PK displays.	• PK

[1]: Only subjects receiving incorrect study treatment for the duration of their study participation will be analyzed according to the treatment received. Otherwise, subjects will be analyzed according to the treatment to which they were randomized.

Refer to Appendix 10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to eligibility criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Exclusions from the main study populations described above will also be summarised. (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 [31OCT2019, Version 3.0] using the Protocol Deviation Management System (PDMS)

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured. Protocol deviations related to incorrect treatment will be managed as described below.
- This dataset will be the basis for the summaries and listings of protocol deviations.

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

Handling of recording of treatment dispensing errors as protocol deviation:

- Dispensing of incorrect container will be logged as an important PD and included in the PD dataset.
- If it is recorded that the incorrect container was dispensed, it will NOT be flagged as a reason for exclusion from the Per Protocol population, since it is not known

before DBF/Unblinding if the incorrect container contained the incorrect treatment.

- Decisions on whether or not the participant took incorrect treatment because of treatment dispensing errors have to be made after unblinding (i.e. post DBF). For Daprodustat/Placebo, this can be done after unblinding using the corresponding container number. For rhEPO/saline, to which no container numbers are assigned, if the incorrect treatment was given, it would be reported as an unblinded protocol deviation in the PDMS and be entered into the unblinded eCRF, which is designed specifically for capturing the wrong rhEPO dose.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
PPD Randomization System		Data Displays for Reporting	
Code	Description	Description	Order in TLF
1	daprodustat	Dapro	1
2	rhEPO	rhEPO	2
		Total	3

NOTE: "No Treatment" and "All Treated" will be included in selected tables, when needed, and will be displayed in the order shown in the table shell.

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

1. daprodustat vs rhEPO

5.2. Baseline Definitions and Derivations

5.2.1. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest non-missing pre-dose assessment on or before the randomization date, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline (except as noted in the baseline definitions for post-dialysis SBP, DBP, MAP, HR and weight).

Parameter	Study Assessments Intended as Baseline		Baseline Used in Data Display
	Screening (Week -4)	Day 1 (Pre-Dose)	
Efficacy			
Hgb		X	Day 1
Monthly IV iron[1]		X	Day 1
Iron parameters		X	Day 1
Safety			
Pre-dialysis SBP, DBP, MAP, HR, Weight		X	Day 1
Estimated dry weight		X	Day 1
Post-dialysis[2] SBP, DBP, MAP, HR, Weight	X		Week -4
Lipid parameters, clinical chemistry,		X	Day 1

Parameter	Study Assessments Intended as Baseline		Baseline Used in Data Display
	Screening (Week -4)	Day 1 (Pre-Dose)	
hematology, other laboratory and hepatobiliary (liver) tests			
ECG[3]	X		Week -4
PRO			
PGI-S		X	Day 1

NOTE: Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
[1]: Baseline monthly IV iron dose will be defined as total IV iron (mg) over the 12 weeks prior to randomization. See Section 14.6.3.
[2]: Post-dialysis baseline values for SBP, DBP, MAP, HR, and weight will be defined as the latest non-missing pre-dose assessment before the randomization date. This will most often be the value recorded at the Week -4 visit. However, for cases where the treatment start date falls after the randomization date, the randomization date will be used as the baseline measurement.
[3]: The Week -4 (screening) ECG must be performed pre-dialysis, and may be performed on any dialysis day from the Week -4 visit to the Day 1 visit, except during the first dialysis session of the week. Two additional ECGs are required if the screening ECG indicates prolonged QTc. In this case, the average QTcB value of all three ECGs will be used as the baseline QTcB.

5.2.2. Derivations and Handling of Missing Baseline Data

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Change from Baseline

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and the change from baseline value will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

Percent Change from Baseline

Lipid parameters will be log-transformed and the percent change from baseline will be reported. Other endpoints may also be log-transformed if deemed appropriate.

To calculate a geometric mean for baseline measurement or at a specified timepoint, the following steps are used:

1. Log-transform the data points
2. Calculate the mean and standard error (SE) of the log-transformed data

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

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

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

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

So, geometric mean for percent change from baseline =

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

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

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

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

So, minimum percent change from baseline =

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

Where i = subject.

Unless otherwise specified, the baseline definitions specified in Section 5.2.1 will be used for derivations for endpoints/parameters and indicated on summaries and listings. Unless otherwise specified, if baseline data is missing, no derivation will be performed and the % change from baseline value will be set to missing. The baseline definition will be footnoted on all change from baseline displays.

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by investigative site, country, and the regions.

Region	Countries
Region 1: Asia Pacific	Republic of Korea
Region 2: Eastern Europe	Poland, Romania, Russian Federation
Region 3: Western Europe/Canada/Australia	Australia, Canada, France, Italy, Spain, United Kingdom
Region 4: Latin America	Argentina, Brazil
Region:5: USA	USA

For any summaries that include information related to a subject's center or investigator, the most recent center and investigator at the time that the database is final will be used.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Strata	Regions listed in Section 5.3.
Covariates	Baseline Hgb (For the analysis of the primary endpoint and other analyses of Hgb-related endpoints) For subgroup analyses, statistical models will be adjusted for the covariates used in the original analysis (randomization stratification factor and baseline hemoglobin), subgroup, treatment and treatment by subgroup interaction (see Section 5.4.2 for the subgroup variables.).

Randomization is stratified by the prognostic factor, region, which will be taken into account within the analysis models.

5.4.2. Examination of Subgroups

- The following is a non-exhaustive list of covariates that may be used in summaries of demographics, descriptive summaries and statistical analyses.
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.

- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup. If there are less than 25 subjects in one of the subgroup categories with two levels (e.g., history of stroke (Yes/No)), then statistical comparison will not be performed for that subgroup. Due to small sample sizes in American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, and Mixed Race categories, statistical comparison for race group will include Asian, Black or African American, and White categories only. For baseline Hgb subgroup, if there are fewer than 25 subjects in the category <9 g/dL, the categories <9 g/dL and 9 - <10 g/dL will be combined to < 10 g/dL.
- A pre-specified strategy for prioritizing subgroups/covariates is defined below (as recommended in the 2015 draft Committee for Medicinal Products for Human Use (CHMP) guidance on the investigation of subgroups in confirmatory clinical trials)

- The primary and principal secondary endpoints will be evaluated for the subgroups below. Although subgroup analyses are aimed to assess for consistency with the overall results, they may have low power, especially if the subgroup is small or has a low number of events. Statistical models (ANCOVA) will be adjusted for the covariates used in the original analysis, subgroup, treatment and treatment by subgroup interaction. For the subgroup Regions combined (USA vs. non-USA), the randomization stratification factor Region (with 5 levels, Regions 1- 5) will not be included in the statistical model.

- For subgroup analyses of time-to-event endpoints, point estimates and confidence intervals for the rate per 100 person-years will be reported for each treatment group within a subgroup, as well as the point estimate and two-sided 95% CI for the difference in rates between treatments within a subgroup. For within-group rates, the two-sided 95% CI will be obtained using an exact Poisson method. For difference in rates between treatments, the two-sided 95% CI will be constructed with a Normal approximation using Wald's method [Liu, 2006].

- For Hgb using mixed model repeated measures (MMRM) approach in the original analysis, the statistical model for the corresponding subgroup analyses will have the following factors: region, baseline value, baseline value by time, and subgroup by treatment by time interaction terms. The model will be run without main effects (treatment, visit, and subgroup) and two-way interaction terms (subgroup by time, treatment by time, and subgroup by treatment) for computational ease since in SAS, the main effects and two-way interaction terms are included within the three-way interaction term, thus giving equivalent result. If the model encounters convergence issues, then the following steps will be performed in this sequence:
  - Step 1: Use Fisher scoring method
    - Scoring=0 will be used as the first option, which is equivalent to no scoring, and if the model fails to converge, the scoring will be updated to scoring=1
    - The scoring will be updated each time the model fails to converge until a maximum of scoring=4 is reached. At this point, if the model fails to converge, Step 2 will be utilized.

- Step 2: If the model fails to converge, instead of unstructured, TOEPH variance-covariance matrix will be used in conjunction with Step 1
- Step 3: If the model fails to converge, denominator degrees of freedom will be changed from Kenward-Roger to Residual in conjunction with Steps 1 and 2.

Please note that if the model still fails to converge after Step 3, model-adjusted subgroup analysis will not be performed. The associated descriptive statistics will be displayed. If the original model fails to converge, but it converges after one of the three steps, the output will display the changes made to the original model in a footnote.

- When a subgroup category assesses the same or a similar parameter (e.g., country is similar to region) as the prognostic stratification variable, the randomization stratification variable will be removed from the model.
- Point estimates and two-sided 95% CIs will be estimated within subgroups, the subgroup by treatment interaction p-value will be calculated and subgroup results will be graphically presented (e.g. Forest Plots). Directional consistency in subgroup treatment effects and a non-significant interaction p-value (two-sided 10% level) would support that the overall treatment effect is broadly applicable to the full study population. Subgroup analyses will not be adjusted for multiplicity.

    - In addition, a nominal one-sided non-inferiority p-value using a non-inferiority margin of -0.75 g/dL and a nominal one-sided superiority p-value will be generated for the difference between treatment groups for each level of the hyporesponder subgroup analyses of the primary Hgb endpoint.

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
Key Covariates/Subgroups of Regulatory/Clinical Interest or Potential Biological Plausibility for Different Subgroup Effects			
Age (years)	Summary statistics of continuous values	Yes	No
Age at randomization (Grouping 1)	<65 years, 65-<75 years, ≥75 years	Yes	Yes
Age at randomization (Grouping 2)	≤18 years, 19-64 years, ≥65 years	Yes	No
Age at randomization (Grouping 3)	18-64 years, 65 - 84 years, ≥ 85 years	No (included in stand-alone age ranges table)	No
Gender	Female, Male	Yes	Yes
Ethnicity	Hispanic or Latino, Not Hispanic or Latino	Yes	Yes
High level race	American Indian or Alaskan Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Mixed Race	Yes	Yes
Race detail	Black or African American (African American/African Heritage) American Indian or Alaskan Native Asian - Central/South Asian Heritage Asian - East Asian Heritage Asian - Japanese Heritage Asian - South East Asian Heritage Native Hawaiian or Other Pacific Islander White – Arabic/North African Heritage White – White/Caucasian/European Heritage	Yes	No

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
	Mixed Asian Race Mixed White Race Mixed Race		
Region	See Regions categories defined in Section 5.3	Yes	Yes
Region combined	US, Non-US	Yes	Yes
Country	See Countries listed in Section 5.3	Yes	No
Dialysis Type at Screening	In-center Hemodialysis Hemofiltration/Hemodiafiltration Missing	Yes	No
Prior ESA type at Randomization	Darbepoetin alfa only Epoetin only Pegzerepoetin alfa only Combination	Yes	No
Standardized prior ESA dose (U/week) [1]	Summary statistics of continuous values	Yes	No
Standardized Prior ESA dose group[1]	<7,000 U/week, ≥7,000 U/week, Missing	Yes	Yes

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
Baseline erythropoietin resistance index (ERI) (U/kg/wk/g/L)	Summary statistics of continuous values	Yes	No
Baseline ERI quartiles	Overall ITT Population Quartile 1: <xx U/kg/wk/g/L Overall ITT Population Quartile 2: xx - <xx U/kg/wk/g/L Overall ITT Population Quartile 3: xx - <xx U/kg/wk/g/L Overall ITT Population Quartile 4: >= xx U/kg/wk/g/L Missing	Yes	No
rhEPO hyporesponder[1]	No, Yes, Missing	Yes	Yes
Standardized Prior ESA Dose (U/week) for rhEPO Hyporesponders	Summary statistics of continuous values	Yes	No
Standardized Prior ESA Dose (U/week) for rhEPO Non-hyporesponders	Summary statistics of continuous values	Yes	No
Alternate definition of rhEPO hyporesponder Definition 2[1]	No, Yes, Missing	Yes	No
Alternate definition of rhEPO hyporesponder Definition 3[1]	No, Yes, Missing	Yes	No
Baseline Hgb (g/dL)	Continuous covariate for Hgb primary analysis; summary statistics of continuous values	Yes	No
Baseline Hgb group	<9 g/dL, 9 - <10 g/dL, 10 - 11 g/dL, >11 g/dL, Missing	Yes	Yes
Baseline post-dialysis body mass index (kg/m^2)	Summary statistics of continuous values	Yes	No
Baseline post-dialysis body mass index group	<30 kg/m^2, ≥30 kg/m^2, Missing	Yes	Yes

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
Baseline post-dialysis Weight (kg)	Summary statistics of continuous values	Yes	No
Baseline post-dialysis Weight group	< 75kg, ≥75kg, Missing	Yes	No
Baseline post-dialysis weight quartiles	Overall ITT Population Quartile 1: < xx kg Overall ITT Population Quartile 2: xx kg - < xx kg Overall ITT Population Quartile 3: xx kg - < xx kg Overall ITT Population Quartile 4: >= xx kg Missing	Yes	Yes
Baseline hsCRP (mg/L)	Summary statistics of continuous values	Yes	No
Baseline hsCRP group	≤3 mg/L, >3 mg/L, Missing	Yes	No
Baseline hsCRP quartiles	Overall ITT Population Quartile 1: < xx mg/L Overall ITT Population Quartile 2: xx mg/L - < xx mg/L Overall ITT Population Quartile 3: xx mg/L - < xx mg/L Overall ITT Population Quartile 4: >= xx mg/L Missing	Yes	Yes
Standardized prior ESA dose (U/week) for baseline hsCRP Overall ITT Population Quartile 1: < xx mg/L	Summary statistics of continuous values	Yes	No
Standardized prior ESA dose (U/week) for baseline hsCRP Overall ITT Population Quartile 2: xx -< xx mg/L	Summary statistics of continuous values	Yes	No

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
Standardized prior ESA dose (U/week) for baseline hsCRP Overall ITT Population Quartile 3:xx - < xx mg/L	Summary statistics of continuous values	Yes	No
Standardized prior ESA dose (U/week) for baseline hsCRP Overall ITT Population Quartile 4: >= xx mg/L	Summary statistics of continuous values	Yes	No
Smoking History	Never smoked, Current smoker, Former smoker	No (included in stand-alone substance use table)	Yes
Other Exploratory Covariates/Subgroups where Biological Plausibility for Heterogeneous Effects Are Not Known or Anticipated			
CV risk score for hemodialysis patients	Low risk (Overall ITT Population tertile 1: < xx), Medium risk (Overall ITT Population tertile 2: xx - < xx), High risk (Overall ITT Population tertile 3: ≥ xx)	Yes	No
Dialysis vintage at screening	0 - <2 years, 2 - <5 years, ≥5 years, Missing	Yes	Yes
History of diabetes	No, Yes, Missing	Yes	Yes
History of stroke	No, Yes, Missing	Yes	Yes
History of MI	No, Yes, Missing	Yes	Yes
History of cancer	No, Yes, Missing	Yes	Yes
History of heart failure	No, Yes, Missing	Yes	Yes
History of thromboembolic events	No, Yes, Missing	Yes	Yes
Hospitalization within 6 months prior to screening	No, yes, Missing	Yes	Yes

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
Transfusion within 6 months prior to screening	No, Yes, Missing	Yes	Yes
Baseline iron use	No iron use IV iron use only Oral iron use only Other iron use only IV and oral iron use only IV and other iron use only Oral and other iron use only IV, oral and other iron use	Yes	No
Standardized Baseline IV Iron dose (mg/month)	Continuous covariate for monthly IV iron dose analysis, summary statistics of continuous values	Yes	No
Standardized baseline IV iron dose (mg/month) for subjects using IV iron at baseline	Continuous covariate for monthly IV iron dose analysis, summary statistics of continuous values	Yes	No
Baseline Pre-dialysis SBP (mmHg)	Continuous covariate for change from baseline in SBP analysis, summary statistics of continuous values	Yes	No
Baseline Post-dialysis SBP (mmHg)	Continuous covariate for change from baseline in SBP analysis, summary statistics of continuous values	Yes	No
Baseline Pre-dialysis DBP (mmHg)	Continuous covariate for change from baseline in DBP analysis, summary statistics of continuous values	Yes	No
Baseline Post-dialysis DBP (mmHg)	Continuous covariate for change from baseline in DBP analysis, summary statistics of continuous values	Yes	No
Baseline Pre-dialysis MAP (mmHg)	Continuous covariate for change from baseline in MAP analysis, summary statistics of continuous values	Yes	No
Baseline Post-dialysis MAP (mmHg)	Continuous covariate for change from baseline in MAP analysis, summary statistics of continuous values	Yes	No

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
Dialysis access type used at baseline	Arteriovenous fistula Arteriovenous graft Central venous catheter – tunneled Central venous catheter – non-tunneled Other Missing	Yes	No
ACEI/ARB use at randomization	No, yes	Yes	Yes
Phosphate binders use at randomization	No, yes	Yes	No
Vitamin D use at randomization	No, yes	Yes	No
Baseline Kt/V urea for HD subjects	Summary statistics of continuous values	Yes	No
Baseline URR for HD subjects (%)	Summary statistics of continuous values	Yes	No
History of cardiovascular disease	No, Yes	Yes	No
Beta blockers use at randomization	No, Yes	Yes	No
SGLT2i use at randomization	No, Yes	Yes	No
Statin use at randomization	No, Yes	Yes	No
Aspirin use at randomization	No, Yes	Yes	No
Vitamin K antagonist use at randomization	No, Yes	Yes	No
Insulin use at randomization	No, Yes	Yes	No
Calcimimetics use at randomization	No, Yes	Yes	No

Category	Categories and/or Subgroups	Summary of Demographics & Baseline Characteristics	Subgroup Analysis for Primary Hgb & Principal Secondary Endpoints
Diabetic medication use at randomization	No, Yes	Yes	No
Baseline estimated dry weight (kg)	Summary statistics of continuous values	Yes	No

[1]: Prior ESA dose standardization and rhEPO hyporesponders are defined in Section 14.6.2. Supportive definitions of hyporesponders will be included in the summary of demographics and baseline characteristics, but will not be used in subgroup analyses

Further details of subgroup analysis are provided in the corresponding analysis sections.

5.5. Multiple Comparisons and Multiplicity

The primary endpoint will be tested first for non-inferiority, using the lower limit of the 2-sided 95% confidence interval. Conditional on achieving statistical significance (i.e., passing the primary gate by establishing non-inferiority) the single principal secondary endpoint will be tested for superiority using a one-sided 2.5% significance level. This two-step hierarchical strategy will preserve the study-wise Type I error rate at a one-sided 2.5% level.

The additional secondary/exploratory endpoints, if tested, will not be adjusted for multiplicity. A nominal one-sided 2.5% significance level will be applied per test.

Subgroup analyses will not be adjusted for multiplicity.

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
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
14.8	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 All Randomized (ITT) population, unless otherwise specified. All summary tables will include a Total column, unless otherwise specified.

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

6.2. Display Details

6.2.1. Subject Disposition

The number and percentage of subjects who completed the study as well as subjects who withdrew from the study will be summarized by subject status and reason for withdrawal. For purpose of the disposition table, the number of subjects who completed the study will consist of all randomized subjects who, as documented in the eCRF, Study Conclusion form, have completed all study periods through the Week 52 visit. This summary table will be repeated by region and by country. [NOTE: Per study protocol Section 5.3, "A participant who dies while on study is also considered to have completed the study."] The summary of subject status and reasons for study withdrawal will also be repeated by relationship to the COVID-19 pandemic.

A listing of reasons for study withdrawal will be provided for all subjects who were withdrawn from the study. This listing will include treatment, site ID, unique subject ID, subject ID, date of withdrawal, study day of withdrawal, primary reason for withdrawal from study, was a follow-up phone contact attempted 3 times, and was a follow-up certified letter mailed.

The number and percentage of subjects who passed screening (i.e. enrolled) and who failed screening and therefore were not entered into the study will be summarized along with the reasons for failure will be summarized for those subjects who failed screening. (Note that the reasons for rescreen subjects who initially failed but subsequently enrolled are not included in the display.)

A summary of all screening attempts and associated reasons for screen failure will be provided for the screened population. This summary will count each screening attempt individually, regardless of whether or not there was a subsequent re-screen.

A listing of the screen failure record for all subjects who failed screening and were not enrolled in the study will be produced. This listing will include Country, site ID, unique subject ID, Subject ID, date of screen failure, reason term(s) for screen failure (including the specify text, if any).

A listing of screening status will be provided for all subjects who were rescreened for the study. The listing will include unique subject ID, subject ID, screening status, date of screen failure, and reason for screen failure.

Treatment status and reasons for discontinuation of study treatment will be summarized, which will include the overall number and percentage of subjects who never received study treatment, the overall number and percentage of subjects who prematurely discontinued study treatment during the study, including the breakdown of the number and percentage of subjects who died while taking study treatment and those that did not die while taking study treatment, and a summary of the reasons and subreasons for study treatment discontinuation overall and separately for subjects who died while taking study treatment and for subjects who did not die while taking study treatment, and the overall number and percentage of subjects who did not prematurely discontinue study treatment during the study summarized by treatment group and overall.(NOTE: Deaths with death date > Treatment End Date + 3 Days are considered “Did Not Die While Taking Study Treatment”. Deaths with death date ≤ Treatment End Date + 3 Days are considered “Died While Taking Study Treatment”)

This summary table will be repeated by region and by country. The overall only summary of subject status and reasons for discontinuation of study treatment will be repeated by relationship to the COVID-19 pandemic.

A listing of the study treatment discontinuation record will be provided for all subjects who prematurely discontinued study treatment. This listing will include treatment, site ID, unique subject ID, Subject ID, date of last dose, study day of discontinuation, primary reason for discontinuation, subreasons for discontinuation, and related to study treatment.

A Kaplan-Meier plot of time to early withdrawal from the study will be produced by treatment group.

Two Kaplan-Meier plots of time to permanent study treatment discontinuation by treatment group will be produced. The first plot will include all subjects who discontinued study treatment, and the second plot will only include subjects who discontinued study treatment but did not die while on study treatment.

The number and percentage of subjects by Region, Country, Site ID and Investigator name will be summarized by treatment group and overall for the Enrolled population.

A listing of participants for whom the treatment blind was broken during the study will be provided.

A listing of planned and actual treatments will be provided. This listing will include country, site ID, investigator name, unique subject ID, Subject ID, randomization number, randomization date, randomized treatment, actual treatment and deviation.

The type of subject contact at the Week 52 visit will be provided by treatment group and overall.

A summary of the subject survival status by study completion status will be provided by treatment group and overall.

6.2.2. Protocol Deviations

The number and percentage of subjects who had important protocol deviations (as defined in the protocol deviation management plan) will be summarized by category and by treatment group and overall. This summary table will be repeated by relationship to the COVID-19 pandemic.

A listing of important protocol deviations will be provided. The listing will include treatment, site ID, unique subject ID, Subject ID, date of deviation, study day of deviation, protocol deviation category, protocol deviation coded term, and protocol deviation description.

The number and percentage of subjects who had inclusion/exclusion criteria deviations will be summarized by inclusion/exclusion type, criteria description and by treatment group and overall.

A listing of subjects with inclusion/exclusion criteria deviations will be provided. The listing will include treatment, site ID, unique subject ID, Subject ID, inclusion/exclusion type, and criteria description.

6.2.3. Population Analysed

The number and percentage of screened subjects in the Screened, Safety, All Randomized (ITT), Enrolled, Per Protocol and PK populations will be summarized by treatment group and overall.

The number and percentage of subjects excluded from the Safety and PP populations will be summarized by reason, treatment group and overall in individual displays for each study population.

A listing of subjects excluded from the Safety and PP populations will be provided. The listing will include the treatment arm, site ID, unique subject ID, Subject ID, date of deviation, study day of deviation, category, coded term, criteria which lead to exclusion, and the populations from which the subject was excluded.

6.2.4. Demographic and Baseline Characteristics

Demographic and baseline data will include all covariates/subgroup variables listed in Section 5.4.2. for summary of demographics and baseline characteristics.

All the above demographic and baseline data will be summarized by treatment group and overall for All Randomized (ITT) and Safety populations. This table will be repeated for the primary definition of a hyporesponder outlined in Section 14.6.2.in the All Randomized (ITT) population.

A by-subject listing of selected demographic and baseline characteristics will also be produced. This listing will include treatment, site ID, unique subject ID, subject ID, year of birth, age, sex, ethnicity, height, weight, and BMI.

A summary of age ranges will be produced based on the Enrolled population

Summaries of race and racial combinations will be produced for each treatment group and overall.

A listing of race and race detail by subject will also be produced, which will include treatment, site ID, unique subject ID, Subject ID, race, and race detail.

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

A summary of dialysis modality and frequency at baseline, Week 28 and Week 52 will be provided by treatment group and overall. This summary will include the number and percentage of subjects who have temporarily or permanently stopped dialysis at these time points, as well as summary statistics for total residual urine volume.

The number and percentage of subjects with dialysis modality changes at any point in the study will be provided by treatment group and overall.

6.2.5. Medical Conditions, Prior and Concomitant Medications

A summary of medical conditions will be provided by treatment group and overall.

For reporting purposes, medications will be classified as prior (pre-treatment), concomitant (on-treatment), and/or post-treatment using the associated start and stop dates recorded in the eCRF and relative to the first and last dose dates of IP (see Section 14.4.1). Medications will be coded using the GSK Drug coding dictionary (current version at the time of DBR).

The number and percentage of subjects reporting the use of each concomitant medication will be summarized by treatment group and overall, anatomical therapeutic chemical (ATC) Level 1, 2, 3, and Ingredient. Summaries of pre-treatment, on-treatment, and posttreatment medication will be provided separately. See Section 14.4.1 for a summary of study phases for concomitant medications.

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

The number and percentage of subjects with any non-randomized ESA use in addition to study treatment during the treatment period (see Section 14.6.2) will be provided by treatment group and overall. Similarly, the number and percentage of subjects with any non-randomized ESA used instead of study treatment during the treatment period (see Section 14.6.2) will be provided by treatment group and overall. Additionally, the duration of the non-randomized ESA use during the treatment period will be summarized

using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group and overall, as well as by the number and percentage of subjects in the following duration categories: < 5 days, ≥ 5 days - < 14 days, ≥ 14 days - < 28 days, ≥ 28 days.

A listing of prior and concomitant ESA use will be provided with details of the ESA use.

6.2.6. Exposure and Treatment Compliance

Months of exposure (see Section 14.6.2.4) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group and overall. Additionally, the number and percentage of subjects with exposure ≤ 6-month and > 6-month will be provided by treatment group and overall.

A listing of exposure data will be provided. This listing will include treatment, site ID, unique subject ID, Subject ID, dose start date, dose stop date, duration of time on dose, dose, dose units, dose form, route of administration, and flags for missed dose, zero dose and dose hold. Exposure data from the unblinded eCRF will be listed separately.

Percent compliance will be estimated by 100*(Total Cumulative Dose/Planned Dose for a specific time period). The number and percentage of subjects in each study treatment compliance category (see Section 14.6.2.4) during the study will be summarized by treatment group for the following time periods: Day 1 < Week 28, Week 28 - <= Week 52, and Day 1 - <= Week 52 (Overall Compliance).

The percentage of time that subjects spend in each of the three compliance categories, (i.e., under compliant, compliant and over compliant) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group for the following time periods: Day 1 < Week 28, Week 28 - <= Week 52, and Day 1 - <= Week 52 (Overall Compliance).

6.2.7. COVID-19 Impacted Visits

A summary of the number and percentage of subjects with any visit impacted by the COVID-19 pandemic and each visit impacted by the COVID-19 pandemic may be produced. The summary will include the impact and the reason for impact overall (any visit) and at each impacted visit.

A listing of all subjects with visits and assessments impacted by the pandemic will be produced.

A figure of COVID-19 pandemic visit impacts may be produced. The figure is a stacked bar chart for each impacted visit. The stack bar is color coded by impact.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

The primary efficacy estimand is the effect of daprodustat treatment relative to rhEPO on the change in Hgb from baseline to the average of all values in the EP, regardless of adherence to treatment including interruptions and discontinuations, the use of non-randomized ESA medication for any reason including rescue therapy, or the use of blood transfusions, in patients defined by the inclusion/exclusion criteria and assuming patients do not die before the end of the EP.

7.1.1. Endpoint / Variables

Mean change in Hgb between baseline and over the evaluation period (EP, mean over Week 28 and 52).

7.1.2. Summary Measure

Model-adjusted mean treatment difference (LS mean difference) in Hgb change between baseline and over the evaluation period.

7.1.3. Population of Interest

The target population is defined by the study's inclusion and exclusion criteria.

The analysis population included in the primary efficacy analyses will be based on the All Randomized (ITT) population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The following are the intercurrent events for the primary efficacy analyses:

- Death prior to the end of the EP (i.e. before Week 52 visit)
- Study treatment interruption or discontinuation prior to the end of the EP
- Use of non-randomized ESA medications for any reason including rescue prior to the end of the EP
- Receipt of blood transfusions prior to the end of the EP

Except for the intercurrent event of deaths prior to the end of the EP, a treatment policy strategy will be used in which all Hgb data recorded during the EP (Weeks 28-52) will be included in the primary efficacy analysis, regardless of discontinuation or interruption of study medication due to any reasons, and regardless of receipt of non-randomized ESA medications for any reason including rescue, or blood transfusions. For deaths, a hypothetical strategy will be used as described in Section 7.1.5.1.

The following are causes of missing Hgb data affecting the primary efficacy endpoint that are not due to intercurrent events:

- Study withdrawal prior to the end of the EP

- Permanent switching from clinic visits to remote visits prior to end to EP
- Intermittent missing Hgb values at one or more visits with the EP

Missing data will be imputed as described in Section 7.1.5.1.

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, endpoint / variable defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Mean change in Hgb between baseline and over the evaluation period (EP, mean over Weeks 28 to 52)
Model Specification

• Hgb during the EP will be defined as the mean of all available post-randomization Hgb values (on and off-treatment) during the EP (Week 28-52).
• The ANCOVA model used to quantify the difference in mean Hgb change will adjust for the following baseline values:
  ○ Treatment
  ○ Baseline Hgb (see Section 5.2.1)
  ○ Region (as randomized, see Section 5.3 & Section 5.4.1)

Multiple Imputation Analysis

• Multiple imputation analysis will be performed using all available Hgb values (on and off-treatment) and conducted under a set of assumptions about missing Hgb values (see Section 14.6.3).
  ○ Intermittent missing post-baseline scheduled Hgb data in both arms through Week 52 will be imputed using PROC MI procedure with NIMPUTE = 200 and MCMC IMPUTE = monotone to generate 200 datasets with only monotone missing patterns. Burn in iterations (NBITER) and maximum iteration (MAXITER) will both be set to 500. The seed for reproducibility is set to 204837. The imputations will be done by study treatment, and region.
  ○ For each of the monotone missing dataset (out of the 200 imputed as indicated above), the missing scheduled Hgb values through Week 52 will be imputed based on the MAR assumption and will be performed using PROC MI by treatment, and region. The monotone regression will have baseline Hgb, prior scheduled (possibly imputed) Hgb values, and may include region, as covariates (see Model Checking & Diagnostics, below). The seed for reproducibility is set to 204837.
  ○ The low and high cutoffs at Hgb values of 6 g/dL and 15 g/dL will be applied to all imputed Hgb values.

- EP Hgb values will be computed and compared across treatment groups using the primary ANCOVA model described above. Rubin's rules [Rubin, 1987] will be used to combine results of the imputed datasets using SAS PROC MIANALYZE procedure. As a result, a single estimated treatment difference and its standard error will be produced, with which a 95% CI will be calculated.

Model Checking & Diagnostics

- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data, if justified.
- Models will be examined for treatment interactions with baseline Hgb and stratification factor.
- For multiple imputation model checking and diagnostics, refer to Model Checking & Diagnostics for Tipping Point Analysis

Model Results Presentation

- All available observed Hgb values (on and off-treatment) will be summarized using mean, standard deviation, minimum, P25, median, P75 and maximum at each visit by treatment group. In addition to scheduled visits, the baseline value and mean EP, mean Alt. EP, and end of treatment will be included (see Section 14.6.3).
    - This summary of Hgb by visit will be repeated for central laboratory Hgb values only and for HemoCue Hgb values only.
    - This display will also be repeated for visits up to and including Week 52, using the data used for the primary Hgb analysis (i.e., including imputed values).
- All available observed Hgb change from baseline values (on and off-treatment) will also be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each post-baseline visit, including the mean EP, mean Alt EP and end of treatment values (see Section 14.6.3).
    - This display will be repeated for visits up to and including Week 52, using the data used for the primary Hgb analysis (i.e., including imputed values).
- The number and percentage of subjects with imputed data in the primary Hgb analysis will be provided by treatment group. The number and percentage of subjects by reason for data imputation will be provided. Reasons include: intermittent missing Hgb values, death before Week 28, death during Week 28 – 52, investigator site closed before Week 28, investigator site closed during Weeks 28-52, lost to follow-up before Week 28, lost to follow-up during Week 28 – 52, consent withdrawn before Week 28, consent withdrawn during Week 28 – 52, and other monotone missing Hgb values. Subjects will be further classified as either having observed all 7 scheduled EP Hgb values, having observed a partial schedule of EP Hgb values, having observed no scheduled EP Hgb values with at least one unscheduled EP Hgb value, or having observed no EP Hgb values, scheduled or unscheduled. For subjects with partial scheduled EP Hgb values, both the pattern of imputed data (intermittent, monotone) and the amount of imputed data (1 – 6 scheduled Hgb values missing) will be summarized. For subjects with partial scheduled EP Hgb values and a monotone imputed data pattern, the reason for the monotone imputed scheduled EP Hgb

values will be provided. Reasons include: death during Week 28-52, investigator site closed during Weeks 28-52, lost to follow-up during Week 28 – 52, consent withdrawn during Week 28 – 52, and other monotone imputed Hgb values. And for summaries of the amount of missing scheduled EP Hgb values, the presence or absence of additional unscheduled EP Hgb values will be summarized.

- The least square (LS) mean estimates and standard errors by treatment group, LS mean difference, two-sided 95% CI and one-sided non-inferiority p-value for the difference in the primary Hgb endpoint between the daprodustat and rhEPO arms from the ANCOVA model will be presented. The number of subjects contributing to the analysis and the associated mean and standard deviation of the baseline and EP Hgb values will also be displayed with the results of the ANCOVA model.
- The LS mean difference and associated two-sided 95% CI will be displayed on a forest plot together with supportive analysis results (excluding the Tipping Point Analysis).
- All available mean Hgb values (on and off-treatment, observed and imputed) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values and 95% CI by time will include horizontal reference lines to depict the hemoglobin analysis range (10-11.5 g/dL), vertical reference lines to identify the EP (weeks 28-52), and the number of subjects by treatment group contributing to each mean value.
- All available Hgb change from baseline values (on and off-treatment, observed and imputed) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values and 95% CIs by time will include vertical reference lines to identify the EP (Weeks 28-52), and the number of subjects by treatment group contributing to each mean value.
- A listing of all hemoglobin values will be provided, including treatment, most recent dose, site ID, unique subject ID, subject ID, visit, assessment date, selected demographic information and central laboratory and HemoCue Hgb values.

Model Results Interpretation

Non-inferiority will be achieved if the lower limit of the two-sided 95% CI of the treatment difference is greater than the pre-specified non-inferiority margin of -0.75 g/dL.

Sensitivity Statistical Analyses

Tipping Point (Multiple Imputation) Analysis

- Tipping point analysis will be performed using all available Hgb values (on and off-treatment) as a sensitivity analysis for the primary estimand.
- Tipping point 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 rhEPO arms will vary independently, and will include scenarios where subjects with missing data on daprodustat have worse outcomes than subjects with missing data on rhEPO.
    - Intermittent missing scheduled Hgb data in both arms through Week 52 will be imputed using PROC MI procedure with NIMPUTE = 200 and MCMC IMPUTE = monotone to generate 200 datasets with only monotone missing patterns. Burn in iterations (NBITER) and maximum iteration (MAXITER) will both be set to 500. The seed for reproducibility is set to 204837. The imputations will be done by study treatment, and region.

- For each of the monotone missing dataset (out of the 200 imputed as indicated above), the missing scheduled Hgb values in both arms through Week 52 will be imputed based on the MAR assumption and will be performed using PROC MI by treatment, and region. The monotone regression will include baseline Hgb, prior scheduled (possibly imputed) Hgb values, and may have region as a covariate (see Model Checking & Diagnostics, below). The seed for reproducibility is set to 204837.
- For each treatment arm separately, the imputed monotone missing Hgb values will vary from the MAR scenario by a multiple of delta, where delta represents a change in Hgb over a 4-week interval. No delta adjustments will be done for intermittent missing values. Beginning with the first missed visit (which could occur before Week 28), for every 4-weeks, the imputed Hgb value would shift an additional delta (for every 2-week interval, the imputed Hgb value would shift an additional 0.5 delta instead). For example, if the first missed visit is after Week 8, the first missed visit will use delta, the second missed visit will use 2*delta, etc. If the first missed visit is on or before Week 8, the first missed visit will use 0.5 delta, the second missed visit will use either (0.5+0.5)*delta, or (0.5+1)*delta depending on the 2- or 4-week interval in between the two visits, etc. The deltas explored for each treatment arm will range from -4 g/dL to 4 g/dL per 4-week interval with a 0.5 g/dL increment respectively. Delta scenarios which are known ahead of time not to possibly represent the tipping point may not be explored.
- The low and high cutoffs at Hgb values of 6 g/dL and 15 g/dL will be applied to all imputed Hgb values.
- EP Hgb values will be computed for each pair of deltas and compared across treatment groups using the primary ANCOVA model described above (including unscheduled visit). Rubin's rules [Rubin, 1987] will be used to combine results of the 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 95% CI can be calculated.

Model Checking & Diagnostics (for Multiple Imputation and Tipping Point Analyses)

- Intermittent missing data imputation:
  - If there are error and or warning messages related to the by statement (e.g. not enough observations to fit regression models), try by study treatment only.
  - If convergence issue occurs, the convergence precision may be set to 1E-3.
- Monotone missing data imputation:
  - When imputing for each of the monotone missing dataset (out of 200), if there are error and or warning messages related to the by statement and/or regression model (e.g. not enough observations with the Monotone statement), try 1) by study treatment with baseline Hgb and region as covariates, 2) impute by study treatment with baseline Hgb as covariates, until no error/warning messages.

Model Results Presentation (for Tipping Point Analysis)

- The delta pairs, their corresponding model-adjusted mean Hgb change from baseline to EP in the two treatment arms, the model-adjusted treatment difference, and two-sided 95% CI will be presented. The non-inferiority conclusion will be drawn if the lower confidence limit of the two-sided 95% CI is greater than -0.75, which will also be presented in the tables.

- Graphics depicting treatment difference and non-inferiority surfaces will be produced using an enhanced tipping point approach [Liublinska, 2014]; A colored heat map that illustrates the gradual change of treatment difference will be produced. Green borders will be used to highlight the delta combinations that result in rejecting the null hypothesis (i.e., non-inferiority established).

Supportive Statistical Analyses

While On-Treatment Evaluable Hgb Analysis

- Alternative "while on-treatment" estimand using only evaluable Hgb data (see Section 14.6.3):
  - This estimand utilizes the same endpoint, summary measure and target population as the primary Hgb estimand. For the intercurrent events of deaths, study treatment discontinuation, use of non-randomized ESA medication for any reason including rescue, and blood transfusions, a "while-on-treatment" strategy will be used.
  - This estimand reflects the effect of daprodustat treatment relative to rhEPO, while on treatment and without the use of non-randomized ESA medication or blood transfusions
  - For this analysis, the primary Hgb analyses and summaries described above will be performed using evaluable Hgb values (see Section 14.6.3). .
  - No data will be imputed in this analysis, so a summary of missing data will be provided instead of a summary of imputed data.
  - The LS mean treatment difference and associated two-sided 95% CI from this analysis will be included on a forest plot with the primary Hgb analysis results.
  - The number and percentage of subjects meeting each evaluable Hgb (see Section 14.6.3) exclusion criteria will be summarized by scheduled visit.
  - A tipping point analysis similar to the one described above will be performed as a sensitivity analysis for this estimand using evaluable Hgb values only.

PP Population Analysis

- The while on treatment evaluable Hgb analysis and summaries described above (with the exception of the missing data summary) will also be performed using the PP population and evaluable Hgb values (see Section 14.6.3).
- The LS mean treatment difference and associated two-sided 95% CI from this analysis will be included on a forest plot with the primary Hgb analysis results

Alternative EP (Week 28-36) Analysis

- The following analyses will be repeated using an alternative EP from Week 28-36:
  - The primary analysis and summaries (using on- and off-treatment, observed and imputed, Hgb values (see Section 14.6.3)
  - Supportive analyses and summaries of the alternative estimand that uses evaluable Hgb values and a while-on-treatment strategy for handling intercurrent events will be repeated using an alternative EP from Week 28-36.
- Summaries of imputed/missing Hgb values will not be repeated.
- The LS mean treatment difference and associated two-sided 95% CI from these analyses will be included on a forest plot with the primary Hgb analysis results.

Subgroup Analysis
• Subgroup analysis will be performed using all available observed and imputed Hgb values (on and off-treatment), and Rubin's rules [Rubin, 1987] will be used to combine results of the imputed datasets using SAS PROC MIANALYZE procedure. • Subgroup analysis will also be performed separately using evaluable Hgb values only (see Section 14.6.3). • Subgroup analysis details are discussed in Section 5.4.2.

7.2. Principal Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

Average monthly IV iron dose (mg)/participant to Week 52

7.2.2. Summary Measure

Model-adjusted mean treatment difference (LS mean difference) in average monthly IV iron dose (mg)/participant to Week 52.

7.2.3. Population of Interest

The principal secondary efficacy analyses will be based on the All Randomized (ITT) population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated will be effect while the participants were on their initial study treatment. All IV iron use from Day 1 to Week 52 up to the time of study treatment discontinuation will be included in the principal secondary efficacy analyses.

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
• Average monthly IV iron dose (mg)/participant to Week 52
Model Specification
• Average monthly IV iron dose (mg)/participant to Week 52 will be determined by calculating the total IV iron dose per subject from Day 1 to Week 52 while the participant was on study treatment and dividing by (the number of days the participant was on study treatment/30.4375 days). See Section 14.4.1 for the definition of on-treatment IV iron. • An ANCOVA model will be used to compare the difference in average monthly IV iron dose per participant between arms, adjusting for: o Treatment o Baseline monthly IV iron dose (see Section 5.2.1) o Region (as randomized, see Section 5.3 & Section 5.4.1)
Model Results Presentation
• The number and percentage of subjects with baseline IV iron use, on-treatment EP IV iron use, and on-treatment IV iron use to Week 52 will be summarized by treatment. Boxplots by study treatment will be created separately for on-treatment average monthly IV iron dose to week 52 and for post-randomization average monthly IV iron dose to week 52. • Average monthly IV iron dose at baseline, while on treatment during the EP, and while on treatment to Week 52 will be summarized by treatment group using mean, standard deviation, minimum, P25, median, P75, and maximum. • The least square (LS) mean estimates and standard errors by treatment group, LS mean difference, two-sided 95% CI and one-sided superiority p-value for the difference in average monthly IV iron dose/subject to Week 52 between the daprodustat and rhEPO arms from the ANCOVA model will be presented. The number of subjects contributing to the analysis and the associated mean and standard deviation of the baseline and Week 52 values will also be displayed with the results of the ANCOVA model. • A listing of average monthly IV iron dose will be provided including treatment, site ID, unique subject ID, subject ID, time period, and average monthly IV iron dose at Week 52.
Model Results Interpretation
• Conditional on the primary endpoint achieving non-inferiority at the one-sided 2.5% level, statistical testing will progress to the principal secondary endpoint with a focus on superiority using a one-sided 2.5% significance level.

Supportive Statistical Analyses
Average monthly IV iron dose (mg)/subject to Week 52 using on and off treatment IV iron records
• The summaries and analysis described above for the principal secondary average monthly IV iron dose/subject to Week 52 will be repeated using all available IV iron records during the Day 1 – Week 52 visits, regardless of whether or not a subject was on treatment (i.e. treatment policy estimand). • The average monthly IV iron dose (mg)/subject to Week 52 for this analysis will be determined by calculating the total IV iron dose per subject from Day 1 to Week 52 and

Supportive Statistical Analyses
dividing by (earliest of the (Week 52 visit date, study completion/withdrawal date) – Randomization date + 1 day/30.4375 days).
Subgroup Analysis
• Subgroup analyses will be performed for the principal secondary endpoint using ANCOVA model with terms for treatment group, baseline IV iron dose, region, subgroup and treatment by subgroup interaction. Subgroup analysis details are discussed in Section 5.4.2. • Subgroup analysis results will be presented graphically using a forest plot.

7.3. Additional Secondary Efficacy Analyses

7.3.1. Planned Secondary Efficacy Statistical Analyses

Hgb Variability

Secondary Efficacy Statistical Analyses: Hgb Variability
Endpoint / Variables
• Hgb change from baseline to Week 52 (Hgb change from baseline to Week 52 will be tested for non-inferiority using the -0.75 g/dL margin used in the primary analysis) • % time Hgb in analysis range (10-11.5 g/dL) during the evaluation period (EP, Week 28 to 52) (% time Hgb in analysis range will be tested first for non-inferiority, then for superiority. The non-inferiority analysis will use a margin of 15% less time in range) • N (%) responders, defined as mean Hgb within the Hgb analysis range 10-11.5 g/dL during the EP
Model Specification
• For the secondary analysis of Hgb change from baseline to Week 52, a mixed model repeated measures (MMRM) approach will be used with an unstructured covariance matrix to compare the difference in means between arms. The model will be fitted to Hgb data collected after baseline up to Week 52, excluding values collected during the stabilization period (Day 1 to Week 28). The model will include factors for treatment, time, prognostic randomization stratification factor (region, see Section 5.3), baseline Hgb and the baseline Hgb by time and treatment by time interaction terms. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors. This analysis will be performed using all available Hgb values (on and off-treatment) and separately using evaluable Hgb values only (see Section 14.6.3). In the analysis using all available Hgb values, subjects who withdraw from the study before Week 52 are considered to be missing at random and in the analysis using evaluable Hgb values, subjects who permanently discontinue study treatment before Week 52 are assumed to be missing at random. • For the analysis of % time in range, the method by Rosendaal [Rosendaal, 1993] will be used to calculate the percentage of time (days) a subject's Hgb is below, within and above the Hgb analysis range of 10 to 11.5 g/dL during the EP (Weeks 28-52). A van Elteren test (stratified Wilcoxon rank sum test) will be used to compare the percentage of time in range between treatment arms, adjusting for treatment and the prognostic randomization stratification factor (see Section 5.3). This analysis will be performed using evaluable Hgb

values only. Hodges-Lehmann estimate of the treatment difference will be used to assess non-inferiority in % time in range. • For the Hgb responder analysis, mean Hgb during the EP will be defined as in the while on-treatment evaluable Hgb supportive analysis (Section 14.6.3). Responders will be subjects with a mean Hgb during the EP that falls within the Hgb analysis range of 10-11.5 g/dL. A Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment and the prognostic randomization stratification factor (region as randomized, see Section 5.3), will be used to compare the number and % of responders between the treatment groups.
Model Results Presentation
• For the MMRM analysis of change from baseline in Hgb, an LSMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - rhEPO) at Week 52. The one-sided non-inferiority p-value for this test will be calculated. • For the responder analysis, the number and percentage of subjects with mean EP Hgb above, within and below the Hgb analysis range will be summarized by treatment group. • For the responder analysis, the number and % of responders by treatment group, difference in response rate (Dapro – rhEPO) and two-sided 95% CI will be provided along with the one-sided CMH p-value for the treatment group comparison. • The % time Hgb is above, in and below the Hgb analysis range (10-11.5 g/dL) during the EP will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. • For the percent time Hgb in analysis range for each treatment group, the stratified Mann-Whitey estimate of the treatment difference (daprodustat - rhEPO) and associated two-sided 95% CI [Kawaguchi, 2011] will be presented in addition to the one-sided superiority p-value from the van Elteren test. Hodges-Lehmann estimate of the treatment difference (daprodustat-rhEPO) and associated two-sided 95% CI will be presented.
Model Results Interpretation
• For the MMRM analysis of change from baseline in Hgb, the NI margin used in the primary analysis of Hgb (-0.75 g/dL) will be used for reference in this comparison. Thus generating support for non-inferiority if the lower bound of the two-sided 95% CI is above -0.75 g/dL. • For the responder analysis, the one-sided CMH p-value will be compared to 0.025 to assess nominal significance. • For the percent time in range analysis, a NI margin of -15% will be used as a reference in this comparison, thus generating support for non-inferiority if the lower limit of the two-sided 95% CI of Hodges-Lehmann estimate is above -0.15. If non-inferiority is established, nominal superiority will be achieved if the one-sided p-value is < 0.025
Subgroup Analyses
• Subgroup analyses will be performed for all Hgb variability endpoints, using the region and hyporesponder subgroups only (described in Section 5.3 & Section 5.4), in a method similar to that described for the subgroup analyses of the primary and principal secondary analyses

Time to Rescue

Secondary Efficacy Statistical Analyses: Time to Rescue
Endpoint / Variables
• Time to stopping study treatment due to meeting rescue criteria
Model Specification

• The Cox Proportional Hazards model will adjust for the following baseline categorical values:
  ○ Treatment
  ○ Region (as randomized, see Section 5.3 & Section 5.4.1)
• Confidence intervals for the rate per 100 person-years will also be reported. For within-group rates, the two-sided 95% CI will be obtained using an exact Poisson method. For difference in rates between treatments, the two-sided 95% CI will be constructed with a Normal approximation using Wald's method [Liu, 2006].
• Analysis will include only those efficacy endpoints occurring within the time period for treatment discontinuation. Calculation of time-to-event or censoring is described in further detail in Section 14.6.3.
• Time to stopping study medication due to meeting rescue criteria is defined as the time from Randomization until the date on which a subject permanently stops study medication due to meeting criteria for rescue.

Model Results Presentation

• Summaries will include (see Section 14.6.3):
  ○ the number and percentage of subjects meeting evaluation criteria for rescue and the number of occurrences (events),
  ○ the number and percentage of subjects unable to be evaluated for rescue, and
  ○ the number and percentage of subjects meeting rescue.
• The analysis model results presentation:
  ○ Number (%) of subject permanently stopping study treatment due to meeting rescue criteria within each treatment arm
  ○ Number (%) of subject censored
  ○ Incidence rate per 100 person-year and the associated two-sided 95% confidence intervals for each treatment arm
  ○ Hazard ratio and the associated two-sided 95% confidence interval
  ○ One-sided p-value for the test of superiority of daprodustat vs rhEPO
  ○ Absolute rate difference per 100 person-year and the associated two-sided 95% confidence interval
• A Kaplan-Meier plot of time to stopping study treatment due to meeting rescue criteria will be produced.

Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance
Subgroup Analyses
• Subgroup analyses will be performed for the time to rescue endpoint using the hyporesponder subgroup only (described in Section 5.4). Cox Proportional Hazards model will be adjusted for the covariates used in the original analysis (region, treatment), hyporesponder subgroup, and treatment by subgroup interaction.

7.4. Exploratory Efficacy Analyses

No statistical testing is planned for exploratory endpoints, unless otherwise noted.

7.4.1. Planned Exploratory Efficacy Display Details

Relationships between Daprodustat Exposure Parameters and Selected Efficacy Endpoints

Endpoint / Variables	
Daprodustat Efficacy Dose Parameters	
Avg Dose EP TIR	The average TIW daprodustat dose when the subject is on-treatment and in target Hgb range during the evaluation period (EP) Weeks 28-52. Evaluable Hgb values are used to determine time in range. Subjects who permanently stop study treatment before the beginning of the EP, and subjects who have 0% time in range (e.g., subjects who have an evaluable Hgb below or above range for the entire EP) will have a missing value for this parameter
Avg Dose EP	The average TIW daprodustat dose when the subject is on-treatment during the EP.
Avg Dose 52	The average TIW daprodustat dose when the subject is on-treatment over 52 weeks
Daprodustat Efficacy Special Parameters	
Cmax/1mg Dose	Cmax extrapolated to 1mg dose: Observed Cmax divided by dose administered on the PK day
Cmax/Avg Dose EP TIR	Cmax extrapolated to average dose during EP TIR: Cmax/1mg multiplied by the average TIW daprodustat dose when the subject is on-treatment and in target Hgb range during Weeks 28-52. Evaluable Hgb values are used to determine time in range.
Cmax/Avg Dose EP	Cmax extrapolated to average TIW dose during EP: Cmax/1mg multiplied by the average TIW daprodustat dose during the EP.
Planned Exploratory Displays	
• Scatter plot of % Time Evaluable Hgb in Range during EP vs. Cmax/Avg Dose EP TIR • Scatter plot of Mean Evaluable Hgb Change from Baseline during EP vs. Cmax/Avg Dose EP • Scatter plot of % Time Evaluable Hgb in Range during EP vs. Avg Dose EP TIR • Scatter plot of Mean Evaluable Hgb Change from Baseline during EP vs. Avg Dose 52 Daprodustat Efficacy Dose parameters (Avg Dose EP TIR, Avg Dose EP, Avg Dose 52) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. Efficacy Special parameters (Cmax/1mg Dose, Cmax/avg Dose EP TIR, Cmax/avg Dose EP,) will be summarized using mean, standard deviation, minimum, median, maximum, geometric mean, standard deviation of log-transformed data, and %CVb. A listing of the Efficacy Dose parameters and a listing of the Efficacy Special parameters will be provided.	

Hgb Variability

Endpoint/Variables
• Hgb observed and change from baseline across all visits • % of time Hgb is above, within and below the analysis range of 10 to 11.5 g/dL during the EP • Number (%) of participants with mean Hgb above, within and below the Hgb analysis range during the EP • Number (%) of participants with a Hgb <7.5 g/dL during the EP • Number of times Hgb <7.5 g/dL during the EP • Number (%) of participants with a >1 g/dL increase in Hgb within any 2-week period (assessed at Week 2 through Week 8), or with a >2 g/dL increase in Hgb within any 4-week period up to Week 52 • Number (%) of participants with a >1 g/dL decrease in Hgb within any 2-week period (assessed at Week 2 through Week 8), or with a >2 g/dL decrease in Hgb within any 4-week period up to Week 52 • N (%) of participants with a Hgb value ≥12 g/dL during the EP • Number of times Hgb ≥12 g/dL during the EP • % of time Hgb ≥12 g/dL during the EP
Planned Exploratory Displays
• All available Hgb values (on and off-treatment) will be summarized using mean, standard deviation, minimum, P25, median, P75 and maximum at each visit by treatment group (see Section 7.1.5). In addition to scheduled visits, the baseline value and mean EP and end of treatment values will be included (see Section 14.6.3). • All available Hgb change from baseline values (on and off-treatment) will also be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each post-baseline visit (see Section 7.1.5), including the mean EP and end of treatment values (see Section 14.6.3). • The % time Hgb is above, within and below the Hgb analysis range (10-11.5 g/dL) during the EP will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group (see Section 7.3.1). This summary will be presented using evaluable Hgb values only (see Section 14.6.3). • Number (%) of participants with mean Hgb above, within and below the Hgb analysis range during the EP will be summarized by treatment group (see Section 7.3.1). This summary will be presented using evaluable Hgb values only (see Section 14.6.3) • The number and percentage of subjects with a Hgb value < 7.5g/dL and the number of times a Hgb value < 7.5 g/dL occurs during the EP will be summarized by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 14.6.3). The central laboratory summary will be considered the primary summary of this data.

- The number and percentage of subjects with a >1 g/dL increase in Hgb over 2 weeks (assessed at Week 2 through Week 8) or a >2 g/dL increase in Hgb within any 4-week period up to Week 52 will be summarized by visit and overall at Week 52 by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 14.6.3). The central laboratory summary will be considered the primary summary of this data.
- The number and percentage of subjects with a >1 g/dL decrease in Hgb over 2 weeks (assessed at Week 2 through Week 8) or a >2 g/dL decrease in Hgb within any 4-week period up to Week 52 will be summarized by visit and treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 14.6.3). The central laboratory summary will be considered the primary summary of this data.
- The number and percentage of subjects with a Hgb value ≥ 12 g/dL and the number of times a Hgb value ≥ 12 g/dL occurs during the EP will be summarized by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 14.6.3). The central laboratory summary will be considered the primary summary of this data.
- The percentage of time Hgb is ≥ 12 g/dL during the EP will be calculated using the Rosendaal method as described in Section 7.3.1. The percentage of time Hgb is ≥ 12 g/dL during the EP will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. This summary will be presented using evaluable Hgb values only (see Section 14.6.3).In addition, the percentage of time Hgb is ≥ 12 g/dL for subjects with at least one Hgb ≥ 12 g/dL during the EP will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group calculated using evaluable Hgb values.

Iron Parameters

Endpoint / Variables

- Observed and change from baseline in hepcidin, ferritin, transferrin saturation (TSAT), total iron, total iron binding capacity (TIBC) across all visits
- Average quarterly ferritin
- Average quarterly TSAT
- Average quarterly IV iron dose/participant
- N (%) of participants who met iron management criteria
- N (%) of participants who reduced IV iron supplementation relative to baseline [defined as total iron (mg) over 4 weeks prior to randomization] during EP [defined as average monthly IV iron dose (mg) over Weeks 28 to 52]

Planned Exploratory Displays

- Hepcidin, ferritin and total iron on-treatment values will be log-transformed (see Section 5.2.2) and summarized using geometric mean, coefficient of variation, minimum, P25,

median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided.

- TSAT, TIBC, and UIBC on-treatment values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided except for UIBC.
- Percent change from baseline in log-transformed (see Section 5.2.2) hepcidin, ferritin and total iron on-treatment values will be summarized using geometric mean, 95% CI, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided.
- Change from baseline in TSAT, TIBC, and UIBC on-treatment values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided except for UIBC..
- Average quarterly IV iron dose/subject while on treatment will be summarized by presenting average monthly IV iron dose by quarter (see Section 14.6.3). Summaries will include mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. Graphical summaries will be provided.
- The number and percentage of subjects who used IV iron, oral iron and/or other iron while on-treatment will be summarized by quarter.
- Average quarterly TSAT while on treatment will be summarized by presenting average TSAT values for the quarters used to generate IV iron dose by quarter (see Section 14.6.3). Summaries will include mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. Graphical summaries will be provided.
- Average quarterly ferritin while on treatment will be summarized by presenting average ferritin values by quarter (see Section 14.6.3). Summaries will include geometric mean, coefficient of variation, minimum, P25, median, P75, and maximum by treatment group. Graphical summaries will be provided.
- The number and percentage of subjects that met the iron management criteria during the study while on treatment will be summarized by treatment group for each 3-month period of the study and across the entire study. There are two types of iron management thresholds: the first type requires that iron therapy be administered if subjects have ferritin and/or TSAT values that are too low; the second type requires that all iron (excluding multivitamins) must be stopped if ferritin and/or TSAT values are too high. It is also possible for a subject to meet starting and stopping criteria on the same day with a low ferritin and a high TSAT. These subjects will also be summarized (see Section 14.6.3). Assessment of meeting iron management thresholds will be made based on central laboratory data values. at the scheduled visits for ferritin and TSAT assessments, according to the schedule outlined in the Schedule of Activities table (see Section 14.2.1). Further, the subjects who met the threshold requiring iron administration to start or stop while on IV iron will be grouped by the action taken with IV iron therapy in the 8 weeks following the date the threshold was met (i.e., starting or increasing iron therapy, maintaining existing iron therapy, receiving no iron therapy, stopping or decreasing iron therapy with no increase, Section 14.6.3) according to concomitant medication records for IV iron.
- The number and percentage of subjects that reduced IV iron supplementation relative to baseline during the EP while on treatment will be summarized by treatment group (see Section 14.6.3).

• A stacked bar chart of on-treatment iron use will be created by treatment group to show the percentages of subjects with different types of iron use at baseline and at each quarter post-baseline.

RBC and Whole Blood Transfusions

Endpoint / Variables
• Number (%) of participants who receive at least one RBC or whole blood transfusion by Week 52 • Number of RBC and whole blood transfusion events per 100 patient years • Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years • Time to first RBC and whole blood transfusion
Planned Exploratory Displays
• Summary and analysis tables will use the All Randomized (ITT) population. • The total number of on-treatment RBC and whole blood transfusion events, transfusions and units for each subject will be derived as described in Section 14.6.3 • The number of on-treatment RBC and whole blood transfusion events per subject, the number of subjects with at least one RBC and whole blood transfusion event, and total number of RBC and whole blood transfusion events will be summarized. • The number of on-treatment RBC and whole blood transfusion events per 100 patient years will be summarized by treatment group. • The number of on-treatment RBC and whole blood transfusions per 100 patient years will be summarized by treatment group. • The number of on-treatment RBC and whole blood units per 100 patient years will be summarized by treatment group. • The reason for transfusion events will be summarized. • The above summaries will be produced for the Evaluation Period and Week 52. • An analysis of time to first RBC or whole blood transfusion will be performed as described in section 14.6.3, including a Kaplan-Meier plot. • All transfusion summaries will be repeated for the primary definition of ESA hyporesponder subgroups (see Section 14.6.2).

Dose Adjustment Scheme

Endpoint / Variables

• Assigned dose by visit and at Day 1, Week 28, and Week 52
• Most recent dose prior to Week 28, Week 52 and end of study treatment
• Number (%) of participants with 0, 1, 2, or >2 dose adjustments during the following periods:
  o Day 1 to < Week 28
  o Week 28 to ≤ Week 52
  o Day 1 to ≤ Week 52
• Number of dose adjustments during the following periods:
  o Day 1 to < Week 28
  o Week 28 to ≤ Week 52
  o Day 1 to ≤ Week 52
• Number of dose adjustments per year during Day 1 to ≤ Week 52
• Time dose held for Hgb ≥12 g/dL

Planned Exploratory Displays
• The assigned dose by visit will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. • The assigned dose by visit will also be summarized by treatment group using the number and percentage of subjects assigned to each dose level. Stacked bar graphs displaying assigned dose at all scheduled visits starting with Day 1 until Week 48 will be provided by treatment group. • The median assigned dose by treatment and visit will be displayed graphically for each scheduled study visit using a line plot. The line plot of median assigned dose along with the first and the third quartiles by time will include vertical reference lines to identify the EP as well as the number of subjects by treatment group contributing to each median value. • The number and percentage of patients with 0, 1, 2,….., 10 or > 10 dose adjustments will be summarized by treatment group. Summaries will be presented for the following categories of time: Day 1 – < Week 28, Week 28 – <= Week 52, and Day 1 – <= Week 52. This summary will be produced twice – the first time counting all dose adjustments, including adjustments related to periods of dose holds (i.e., no study treatment is given), the second time excluding dose adjustments related to periods of dose hold. The number and percentage of patients with dose adjustments by treatment group will also be summarized by Day 1 HemoCue Hemoglobin categories. • The number of dose adjustments per subject will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. Summaries will be presented for the following categories of time: Day 1 – < Week 28, Week 28 – <=Week 52, and Day 1 – <= Week 52. For the period of time from Day 1 - <= Week 52, the number of dose adjustments per year will be summarized as well. This summary will be produced twice – the first time counting all dose adjustments, including adjustments related to periods of dose holds (i.e., no study treatment is given), the second time excluding dose adjustments related to periods of dose hold. • The time (in days) that study treatment was withheld for HemoCue Hgb values ≥ 12 g/dL per subject will be summarized for all subjects and for subjects who had a dose hold using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group.

Summaries will be presented for the following categories of time: Day 1 – < Week 28, Week 28 – <=Week 52, and Day 1 – <= Week 52.

- Summary tables for the dose adjustment scheme endpoints will also be repeated for the following subgroups (see Section 5.4.2 for subgroup definitions):
    - rhEPO hyporesponders (primary definition)
    - Region
    - Race group
    - Baseline weight quartiles
- The median most recent dose by treatment and visit will be displayed graphically for each scheduled study visit using a line plot. The line plot of median most recent dose along with the first and the third quartiles by time will include vertical reference lines to identify the EP as well as the number of subjects by treatment group contributing to each median value. This plot will be created by treatment group and this plot will also be overlaid on a graph of corresponding Hgb values by visit.

8. SAFETY ANALYSES

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

8.1. Secondary Safety Analyses

Blood Pressure

Secondary Safety Statistical Analyses: Blood Pressure
Endpoint(s)
• Change from baseline in SBP, DBP and MAP at Week 52 and at the end of study treatment • Number of BP exacerbation events per 100 patient years • N (%) of subjects with at least one BP exacerbation event during study NOTE: Unless otherwise specified, for summaries and analyses of BP values, the post-dialysis BP values for subjects will be used.
Model Specification
• The difference in change from baseline in BP (SBP, DBP, and MAP) at Week 52 will be analyzed with a mixed model repeated measures (MMRM) approach with an unstructured covariance matrix to compare the difference in means between arms. The models will be fitted to scheduled BP data collected after baseline up to Week 52 (including Week 52 visit). Models will be run four times: o On-treatment BP values only, excluding values collected during the stabilization period (post-baseline up to but excluding Week 28 visit). o On-treatment BP values only, including values collected during the stabilization period. o On- and off-treatment BP values, excluding values collected during the stabilization period. o On- and off-treatment BP values, including values collected during the stabilization period. • The models will include factors for treatment, time, prognostic randomization stratification factor (Region, see Section 5.3), baseline BP parameter and the baseline BP parameter by time and treatment by time interaction terms. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors. For analyses using on- and off-treatment values, subjects who withdraw from the study before Week 52 are considered to be missing at random and in the analysis using on-treatment values only, subjects who permanently discontinue study treatment before Week 52 are assumed to be missing at random. • The difference in change from baseline in BP (SBP, DBP, and MAP) at the derived end of treatment (see Section 14.6.4) will be analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factor (Region, see Section 5.3) and the corresponding baseline BP parameter. This analysis will be performed using on-treatment BP values only. • The number of on-treatment BP exacerbation events per 100 patient years will be calculated (see Section 14.6.4). Confidence intervals for the rate per 100 patient years will also be reported. For within group rates and the ratio of model estimated exacerbation rates, the point estimates. two-sided 95% confidence intervals, and one-sided p-value for the treatment group

Secondary Safety Statistical Analyses: Blood Pressure
comparison will be obtained using a negative binomial model with treatment and the prognostic randomization strata as covariates and the logarithm of time on-treatment as an offset variable.
Model Results Presentation
• BP parameter values (SBP, DBP, and MAP) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each visit by treatment group. In addition to scheduled visits, the derived baseline value, and end of treatment values will be summarized (see Section 14.6.4). Summaries of on-treatment BP values only and on- and off-treatment BP values together will be produced for both pre- and post-dialysis BP. On-treatment BP parameter values will be plotted by visit using a line plot. • BP parameter change from baseline values (SBP, DBP, and MAP) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each post-baseline visit by treatment group. In addition to scheduled visits, the derived end of treatment values will be summarized (see Section 14.6.4). Summaries of on-treatment BP values only and on- and off-treatment BP values together will be produced for both pre- and post-dialysis BP. On-treatment BP parameter change from baseline values will be plotted by visit using a line plot. • For the MMRM analyses of change from baseline in BP parameters to Week 52, an LSMEANS statement will provide adjusted treatment group means, standard errors, a point estimate, a two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - rhEPO), and a one-sided superiority p-value for this test. • For the ANCOVA analyses of change from baseline in BP parameters to the derived end of treatment, the adjusted mean estimates and standard errors by treatment group, adjusted mean difference, two-sided 95% CI and one-sided superiority p-value for the difference in BP parameter between the daprodustat and rhEPO arms from the ANCOVA model will be presented. The number of subjects contributing to the analysis and the associated mean and standard deviation of the baseline and end of treatment values will also be displayed with the results of the ANCOVA model. • The model estimated on-treatment BP exacerbation rates per 100 patient years and associated 95% confidence intervals will be provided by treatment group.The ratio of model estimated on-treatment BP exacerbation rates and associated two-sided 95% confidence interval and one-sided p-value will also be provided for the comparison of daprodustat vs. rhEPO. • On-treatment BP exacerbations will be summarized as follows: The number and percent of subjects with 0, 1, 2, 3, 4, 5 and >5 on-treatment BP exacerbations will be provided by treatment group. Additionally, the number and percent of subjects with on-treatment BP exacerbations and number of on-treatment BP exacerbation events will be provided by treatment group, in total and by BP exacerbation type (see Section 14.6.4). The total treatment exposure in years and overall on-treatment BP exacerbation rate per 100 PY will be provided by treatment group. o The BP exacerbation summary above will be repeated for the following groups and BP values: ▪ (1) All subjects, all on-treatment BP values (including both pre-dialysis and post-dialysis BP values) ▪ (2) All subjects, on-treatment post-dialysis BP values only ▪ (3) All subjects, on-treatment pre-dialysis BP values only.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance.

8.2. Exploratory Safety Analyses

Exploratory Cardiovascular Safety Analysis

Exploratory CV Safety Analyses
Endpoint(s)[1]:
• MACE (composite of all-cause mortality, non-fatal MI, or non-fatal stroke) • MACE or a thromboembolic event (vascular access thrombosis, a symptomatic deep vein thrombosis or a symptomatic pulmonary embolism) • MACE or hospitalization for HF • All-cause mortality • CV mortality • MI (fatal and non-fatal) • Stroke (fatal and non-fatal) • CV mortality or non-fatal MI • All-cause hospitalization
Model Specification
• For all exploratory CV endpoints, confidence intervals for the rate per 100 person-years will be reported. For within-group rates, the 95% CI will be obtained using an exact Poisson method. For difference in rates between treatments, the two-sided 95% CI will be constructed with a normal approximation using Walds' method [Liu 2006]. • For the MACE endpoint, the calculation of time-to-event or censoring is described in further detail in Section 14.6.4. • First occurrence of adjudicated MACE for a subject is defined as the first adjudicated event, determined by the event date, which is indicated as all-cause mortality, non-fatal MI or non-fatal stroke with further details in Section 14.6.4. • For those endpoints or components of endpoints intended to go through the adjudication process, only the adjudicated results will be used.
Model Results Presentation
• A summary of the number and percentage of subjects having first-occurrence MACE will be provided by treatment group. The number and percentage of the types of events that make up the first occurrence of MACE will also be provided by treatment group. This summary table will be repeated for MACE plus thromboembolic events, for MACE plus hospitalization for heart failure and for MACE plus thromboembolic events or hospitalization for CHF. • A summary of all MACE including the number and percentage of subjects and number of events (including first and subsequent MACE) by type of event will be provided by treatment group. • A summary of the number and percentage of subjects having first-occurrence adjudicated COVID-19 MACE will be provided by treatment group. The number and percentage of the types of events that make up the first occurrence of adjudicated COVID-19 MACE will also be provided by treatment group. • Summaries of adjudication details of all-cause mortality will include the number and percentage of subjects by cause of death. • Summaries of adjudication details of MI will include the number and percentage of events by outcome of MI (fatal or non-fatal), type of MI, increased cardiac markers (y/n), ST segment classification [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial

Exploratory CV Safety Analyses
infarction (NSTEMI), ECG not interpretable, ECG not available], and Q wave classification (Q wave MI, Non Q wave MI, ECG not interpretable, ECG not available). • Summaries of adjudication details of stroke will include the number and percentage of events by outcome of stroke (fatal or non-fatal), type of stroke (ischemic, hemorrhagic, or undetermined) and ischemic details (with/without hemorrhagic transformation) and location if hemorrhagic (intraparenchymal, intraventricular, subarachnoid, retinal, unknown location). • Summaries of adjudication details of heart failure will include the number of events by type: hospitalization for heart failure, heart failure requiring urgent ER/ED visit, heart failure requiring urgent office/practice visit, and fatal heart failure events identified by cause of death only. • Summaries of adjudication details of thromboembolic events will include the number and percentage of events by type of thromboembolic event (DVT, PE, VAT). o Summaries of PEs will include outcome of PE (fatal or non-fatal). o Summaries of VATs will include type of VAT (AV fistula, AV graft, central venous catheter, other), method of diagnosis (ultrasound/Doppler, AV imaging, CVC imaging, other), and treatment (thrombolytic therapy, thrombectomy, angioplasty, stent, surgical intervention, not specified). • A summary of adjudicated supportive CV endpoints above (except all-cause hospitalization) will be provided to include the number and percentage of subjects and the number of events for each endpoint. • The model results presentation for the endpoints above plus MACE or Thromboembolic Events or Hospitalization for CHF will be provided to include within-group incidence rates per 100 person-years (along with two-sided 95% CI) and difference in rates between treatments (along with two-sided 95% CI). For composite endpoints, the number and percentage of the type of first occurrence will be provided by treatment group. • A summary of all-cause hospitalization will be provided by treatment group including summaries of the number of hospitalizations per subject, average length of stay per hospitalization, and primary diagnosis at discharge by system organ class and lower level term. • Time from Randomization to first occurrence of adjudicated MACE event or end of trial will be evaluated using Kaplan-Meier (KM) methodology and displayed graphically for the comparison of daprodustat vs. rhEPO. • Summary of concordance between events referred for adjudication and adjudicated endpoint events (Positively Adjudicated or Negatively Adjudicated) will be presented. • A listing of all MACE events occurring during the study will be provided and will include treatment, site ID, unique subject ID, Subject ID, select demographic information, event type, event date, and study day. • A listing of all all-cause mortality events that occur during the study will be provided. This listing will include treatment, site ID, unique subject ID, select demographic information, event date, study day, and cause of death.

[1] Adjudicated events used where available.

Rlationships between daprodustat C_{max}/dosing and MACE/Combined MACE-related endpoint

Endpoint / Variables	
Daprodustat Safety Dose Parameters	
Dose at first MACE	The TIW daprodustat dose at the time of the subject's first on-treatment adjudicated MACE. If the subject does not have an on-treatment adjudicated MACE, this value is missing.
Final Dose for Subjects without MACE	For subjects without an on-treatment adjudicated MACE, this is the subject's final TIW daprodustat dose during the study.
Dose at first MACE++	The TIW daprodustat dose at the time of the subject's first on-treatment adjudicated MACE + thromboembolic event + hospitalization for CHF If the subject does not have an on-treatment adjudicated MACE + thromboembolic event + hospitalization for CHF this value is missing.
Final Dose for Subjects without MACE++	For subjects without an on-treatment adjudicated MACE + thromboembolic event + hospitalization for CHF, this is the subject's final TIW dose during the study.
Daprodustat Safety Special Parameters	
Cmax/Dose at first MACE	Cmax extrapolated to dose at MACE: Cmax/1mg multiplied by the TIW daprodustat dose at the time of the subject's first on-treatment adjudicated MACE.
Cmax/Final Dose for subjects without MACE	For subjects without an on-treatment adjudicated MACE, this is the subject's Cmax/1mg multiplied by the subject's final TIW daprodustat dose during the study.
Cmax/Dose at first MACE++	Cmax extrapolated to dose at MACE + thromboembolic event + hospitalization for CHF: Cmax/1mg multiplied by the TIW daprodustat dose at the time of the subject's first on-treatment adjudicated MACE + thromboembolic event + hospitalization for CHF.
Cmax/Final Dose for subjects without MACE++	For subjects without an on-treatment adjudicated MACE + thromboembolic event + hospitalization for CHF, this is the subject's Cmax/1mg multiplied by the subject's final TIW daprodustat dose during the study.
Planned Exploratory Displays	
• Boxplot of Cmax/Dose at on-treatment MACE by subjects with or without on-treatment MACE	

- Boxplot of Cmax/Dose at on-treatment MACE + thromboembolic event + hospitalization for CHF by subjects with or without on-treatment MACE + thromboembolic event + hospitalization for CHF
- Boxplot of Average TIW Dose at on-treatment MACE by subjects with or without on-treatment MACE
- Boxplot of Average TIW Dose at on-treatment MACE + thromboembolic event + hospitalization for CHF by subjects with or without on-treatment MACE + thromboembolic event + hospitalization for CHF
- Average TIW daprodustat dose will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by participants with and without MACE.
- Average TIW daprodustat dose will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by participants with and without MACE + thromboembolic event + hospitalization for CHF.

Average TIW daprodustat dose = average TIW daprodustat dose while on study treatment for participants without MACE/Combined MACE-related endpoint and before the event for participants with MACE/Combined MACE-related endpoint.

For the figures and summaries described above, the "On-Treatment" time window ("last non-zero dose date +28 days", see Section 14.4.1) will be used to decide whether a subject should be considered with MACE/Combined MACE.

Daprodustat Safety Dose parameters (Dose at first MACE, Final Dose for Subjects without MACE, Dose at first MACE++, Final Dose for Subjects without MACE++) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by participants with and without MACE and MACE ++. Daprodustat Safety Special parameters (Cmax/ Dose at first MACE, Cmax/ Final Dose for subjects without MACE, Cmax/ Dose at first MACE++, Cmax/ Final Dose for subjects without MACE++) will be summarized using mean, standard deviation, minimum, median, maximum geometric mean, standard deviation of log-transformed data, and %CVb. A listing of the Safety Dose Parameters and a listing of the Safety Special Parameters will be provided.

Blood Pressure and Blood Pressure Medication Change

Endpoint / Variables
• Observed and change from baseline in SBP, DBP, and MAP by visit
• Number of BP medications per participant by visit
• Change from baseline in the number or dose of BP medications per participant by visit
• N (%) of participants who had no change in the number or dose of BP medications from baseline by visit
• N (%) of participants who had an increase in the number or dose of BP medications from baseline by visit

- N (%) of participants who had a decrease in the number or dose of BP medications from baseline by visit

Planned Exploratory Displays

- Observed and change from baseline in SBP, DBP, and MAP by visit are included in the summary of secondary safety analyses described in Section 8.1.
- The last on-treatment BP parameter change from baseline value (SBP, DBP, and MAP) recorded prior to the first change in BP medications will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. The first change in blood pressure medication occurs at the earliest time a new anti-hypertensive medication is administered or if the dose or frequency of an existing blood pressure medication is changed for any reason (increased, decreased, discontinued, or switched to another agent) in any anti-hypertensive medication, except medication records with frequencies of "Once only" and "PRN."
- Number of BP medications per subject while the subject was on treatment will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Number of BP medications for each subject at baseline is defined as the number of medications taken on the day before study treatment start date. For end of treatment, it is defined as the number of medications taken on last non-zero dose date + 1 day. The number of BP medications at all other nominal visits is defined as the number of medications taken on the day of the visit. Medication records with frequencies of "Once only" and "PRN" will be excluded from this summary.
- Change from baseline in the number of BP medications per subject while the subject was on treatment will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. The number of BP medications at baseline, end of treatment and all other nominal visits will be defined as described in the previous paragraph. Medication records with frequencies of "Once only" and "PRN" will be excluded from this summary.
- Additionally, the number and percentage of subjects who had no change, at least one change, an increase, a decrease, or a switch in the dosage or number of BP medications from baseline while the subject was on treatment will be summarized for each scheduled post-baseline visit by treatment group (see Section 14.6.4 for details of classifying BP medication changes). Medication records with frequencies of "Once only" and "PRN" will be excluded from this summary.
- Cumulative number of changes in on-treatment BP medications from baseline to Week 52 will be summarized by treatment group. For all records except with frequencies "Once only" and "PRN," the cumulative number of changes will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. The number of percentage of subjects with no change and at least one medication change will be displayed excluding "Once only" and "PRN" records. For subjects with at least one change, the number and percentage of subjects for each reason (increase, decrease, and switch) will be displayed (see Section 14.6.4 for details of counting BP medication cumulative changes) by treatment group. Number and percentage of subjects for each reason of BP medication change will be displayed by treatment group. Cumulative number of changes in on-treatment BP medication from baseline to Week 52 for "Once only" records only will be summarized using

mean, standard deviation, minimum, P25, median, P75, and maximum (see Section 14.6.4 for details of counting BP medication cumulative changes) by treatment group. • Number and percentage of subjects with at least one PRN record at baseline and on-treatment BP medication during the period from study treatment start date to Week 52 will be displayed by treatment group. • Number and percentage of subjects with any BP medication taken at baseline (the day before study treatment state date) and any on-treatment BP medication during the period from study treatment start date to Week 52 will be displayed by treatment group.

Lipid Parameters

Endpoint / Variables
• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)]
Planned Exploratory Displays
• Lipid parameter values for this study include total cholesterol, LDL-C (direct) and HDL-C. These values are collected according to the schedule outlined in the Schedule of Activities table (see Section 14.2.1). Lipid parameter values follow the derivation guidelines for laboratory values outlined in Section 14.6.4. The summaries described below will include summaries in both SI units and conventional units for each of the lipid parameters and will summarize log-transformed values. • Total cholesterol, LDL-C (direct), and HDL-C values will be log-transformed and summarized using geometric mean, CV, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. • Percent change from baseline in log-transformed total cholesterol, LDL-C (direct), and HDL-C on-treatment values will be summarized using geometric mean, 95% confidence interval, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group.

8.3. Adverse Events Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Adverse events analyses including the analysis of adverse events (AEs), Serious (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.

For the purpose of AE summaries and analysis, the investigator-reported AE details will be used, regardless of the adjudication outcome of the event.

See Section 14.4.1 for AE treatment-state definitions.

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

8.3.1. Analysis of Adverse Event of Special Interest (AESI)

A prespecified list of MedDRA terms will be used to identify AESIs. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from ongoing studies may highlight additional AESIs, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. The details of the planned displays are provided in Appendix 10: List of Data Displays.

AESIs are described in Section 14.6.4.

Summaries of AESIs will include the number, percentage, and rate per 100 person-years of subjects having at least one occurrence, the number of events, the number of subjects by number of occurrence, the characteristics of the AE (serious, drug-related, etc.), outcome, maximum intensity, time to first onset/worsening, and action taken summarized by treatment group. For each count, a subject will be summarized as follows:

- Serious/drug-related/severe/fatal: If any specific AE falls in the respective category, the subject will be counted in that category.
- Outcome: The subject will be counted within a category if there is at least one specific AE in that category.
- Maximum intensity: The specific AE with the maximum intensity will be counted for this purpose. For example, a subject will be counted in the 'severe' category if there is at least one specific AE with severe intensity. A subject will be counted in the 'moderate' category if there is at least one specific AE with moderate intensity and there is no specific AE with severe intensity.
- Time to first onset/worsening (days): The earliest of onset dates for the specific AE – treatment start + 1

If the AE onset date/AE worsening and/or resolution date is missing or incomplete in the database for any occurrence of the specific AE, time to first onset/worsening will be left missing for the subject. These summaries of special interest AEs will be provided for those AEs classified as treatment emergent, follow-up, and post-randomization.

The number and percentage of subjects reporting treatment emergent AESI will also be summarized by treatment group and by preferred term.

Cumulative incidence function (CIF) plots may be produced for each special interest AE summarizing the time to first occurrence of the special interest AE by treatment group, with the exception of the composite endpoint AESI (death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access). This endpoint will use a Kaplan-Meier plot. If there are less than 20 subjects total for both the daprodustat and rhEPO arm, then these plots will not be created. Competing risks for the AESI cumulative incidence plots include:

AE of Special Interest (Event of interest)	Competing Risk Events
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	Death due to any cause prior to the AESI
Cardiomyopathy	Death due to any cause prior to the AESI
Pulmonary artery hypertension	Death due to any cause prior to the AESI
Cancer-related mortality and tumor progression and recurrence	All other non-cancer-related death prior to the AESI (use death date as the competing risk date)
Esophageal and gastric erosions	Death due to any cause prior to the AESI
Proliferative retinopathy, macular edema, choroidal neovascularization	Death due to any cause prior to the AESI
Exacerbation of rheumatoid arthritis	Death due to any cause prior to the AESI
Worsening of hypertension	Death due to any cause prior to the AESI

Dot plots displaying the incidence of the treatment emergent event will be provided for AESIs by AESI term and treatment group. The incidence rate in each treatment group and corresponding two-sided 95% confidence interval for the relative risk of the daprodustat group compared to the rhEPO group will be provided.

8.3.2. Adverse Events

The number and percentage of subjects reporting at least one AE will be provided for each treatment group. These events will be summarized by treatment group, primary system organ class, and preferred term. Post-randomization, treatment emergent and follow-up AEs will be summarized separately.

Summaries of all treatment emergent AEs will be produced for the age group, gender, race group and weight quartile subgroups. Summaries of treatment emergent AEs by subgroup will be produced twice: by system organ class and preferred term and separately by overall frequency.

A listing of AE records for all subjects who reported AEs will be produced.

Summaries of all treatment emergent AEs will be provided by maximum intensity. For AEs reported more than once by a subject, the most severe intensity will be included in summaries where applicable. Analysis will be repeated for all drug-related treatment emergent AEs.

The number and percentage of subjects reporting the most common treatment emergent AEs (those occurring in ≥ 5% of subjects in any treatment group) will be summarized by preferred term and treatment group.

Additionally, the most common treatment emergent AEs will be summarized graphically by preferred term and treatment group. The incidence rate in each treatment group and corresponding two-sided 95% confidence interval for the appropriate comparator estimate (relative risk) of the daprodustat group compared to the rhEPO group will be provided. Displays will be sorted by magnitude of risk, from largest to smallest.

The number and percentage of subjects reporting treatment emergent AEs assessed by the investigator to be related to the study drug will be summarized by treatment group, primary system organ class, and preferred term and separately by overall frequency.

The number and percentage of subjects and the number of occurrences of common non-serious treatment emergent adverse events (those occurring in ≥ 5% of subjects in any treatment group) will be summarized by primary system organ class, preferred term, and treatment group and separately by overall frequency.

A listing of which subjects reported specific adverse events will be produced.

The hierarchical relationship between MedDRA SOCs, PTs, and verbatim text will be listed for all adverse events.

A listing of pre-treatment adverse events will be produced.

8.3.3. Serious and Other Significant Adverse Events

The number and percentage of subjects and the number of occurrences of SAEs will be provided for each treatment group. These events will be summarized by treatment group, primary system organ class, and preferred term. Pre-treatment, post-randomization, treatment emergent and follow-up SAEs will be summarized separately. Treatment emergent SAE preferred terms will also be summarized by treatment group and overall frequency.

A listing of reasons for considering as a SAE will be produced for all SAEs.

The number and percentage of subjects and the number of occurrences of treatment emergent drug-related SAEs, drug-related non-SAEs, fatal SAEs, non-fatal SAEs, and drug-related fatal SAEs will be summarized by treatment group: by primary system organ class and preferred term and separately by overall frequency.

A listing of fatal SAE records and a listing of non-fatal SAE records will be provided.

The number and percentage of subjects reporting treatment emergent SAEs will be summarized by treatment group, maximum intensity, primary system organ class, and preferred term.

The number and percentage of subjects reporting treatment emergent AEs leading to discontinuation of study treatment or withdrawal from the study will be summarized by treatment group, primary system organ class, and preferred term. Treatment emergent AEs leading to discontinuation of study treatment or withdrawal from the study will also be summarized by treatment group and overall frequency.

A listing of AEs leading to discontinuation of study treatment and a listing of AEs leading to withdrawal from study will be provided.

BP events and BP-related SAEs are defined in Section 14.6.4.

The number and percentage of subjects with at least one on-treatment BP event will be provided for each treatment group. In addition, this summary will include the number and percentage of subjects with at least one on-treatment BP event that is considered clinically significant and the number and percentage of subjects with at least one on-treatment BP event that is considered to be symptomatic.

The number and percentage of subjects reporting at least one treatment emergent BP-related SAE will be provided for each treatment group. In addition, the number of treatment emergent BP-related SAEs will be summarized by treatment group, primary system organ class, and preferred term.

A listing of other significant adverse events will be produced. Other significant adverse events are events that are not reported as fatal or serious but represent ICH-defined 'Other significant adverse events' (i.e., marked haematological and other laboratory abnormalities or led to an intervention, dose reduction, or significant additional concomitant therapy). For this study, other significant AEs will be defined as non-fatal non-serious AEs resulting in an action taken with study treatment of either 'dose interrupted/delayed' or 'dose reduced'.

8.3.4. Other CV Events

GSK has identified other CV events of interest for all clinical studies. In this study, investigators will be required to fill out the specific CV event page of the eCRF for the following CV AEs and SAEs or any event that may potentially be one of the categories listed:

- Arrhythmias
- Pulmonary hypertension (also an adverse event of special interest [AESI])
- Valvulopathy
- Revascularization

Electronically generated patient profiles for participants reporting these events will not be prospectively created.

8.4. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology 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.

Clinical chemistry, hematology and other laboratory tests are assessed in this study according to the schedule outlined in the Schedule of Activities table (see Section 14.2.1) and include the following tests:

Laboratory Assessments	Parameters		
Hematology	Platelet count	*RBC indices:*	Leukocyte (white blood cell) count with Differential
	Erythrocyte (red blood cell) count	Mean corpuscular volume (MCV)	Neutrophils (absolute and segmented)
	Hemoglobin	Mean corpuscular hemoglobin (MCH)	Lymphocytes
	Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
	Reticulocyte count	Erythrocytes (red cell) distribution width (RDW)	Eosinophils
			Basophils
Clinical Chemistry	Potassium (serum)	Aspartate aminotransferase (AST)	Albumin
	Calcium (albumin-corrected)	Alanine amintotransferase (ALT)	Blood Urea Nitrogen (BUN)
	Phosphate	Bilirubin (total, direct and indirect)	
Iron parameters	Iron (serum)	Ferritin	UIBC
	Hepcidin	TIBC	TSAT
Lipid parameters	Total cholesterol	LDL-C (direct)	HDL-C
Other laboratory tests	Serum pregnancy test	High-sensitivity C-reactive protein (hsCRP)	HemoCue Hgb
	Estradiol	Intact parathyroid hormone (iPTH)	Stored sample (blood)
	FSH	Erythropoietin (EPO)	
	Hemoglobin A1c (HbA1c)	Vascular Endothelial Growth Factor (VEGF)	

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; AST, aspartate transaminase; ALT, alanine transaminase; UIBC, unbound iron binding capacity; TIBC, total iron binding capacity; TSAT, transferring saturation; LDL-C, low density lipoprotein-C; HDL-C, high density lipoprotein-C;

Summaries of central laboratory Hgb values, HemoCue Hgb values, iron parameter values (serum iron, ferritin, hepcidin, TIBC, TSAT, UIBC), PD parameters (EPO, VEGF), and lipid parameter values (total cholesterol, direct LDL-C, HDL-C) are included in the separate efficacy, safety, and pharmacodynamic sections and will not be included with clinical laboratory displays. However, these parameters may be included in PCI summaries.

The clinical chemistry tests performed in this study include ALT, AST and bilirubin. In addition to being summarized with the clinical chemistry values, these laboratory values will be included in some of the Hepatobiliary (liver) displays.

In addition to the visits listed for the laboratory assessments in the Schedule of Activities table (see Section 14.2.1), any of these assessments may be performed at an unscheduled/retest visit at the discretion of the investigator. See Section 14.5.2 for handling of unscheduled values. The laboratory's normal range values will be provided by the central laboratory, and potential clinical importance thresholds are defined in Section 14.8.1.

All of the tabular summaries described below will include summaries in SI units; conventional units will also be provided for the following laboratory tests: MCHC, total calcium, albumin-corrected calcium, phosphate, albumin, BUN, total cholesterol, LDL-C, and HDL-C. Conversions from SI units to conventional units are included in Section 14.6.4. Hemoglobin summaries will only use conventional mg/dL units. Summaries of reticulocytes will be provided for the total count and percent of total erythrocytes and summaries of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be provided for total counts and differentials (percent of total leukocytes). TSAT will be reported in the conventional unit (%).

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

8.4.1. Planned Clinical Laboratory Safety Displays

Clinical Chemistry

Continuous on-treatment values (see Section 14.4.1) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit and for baseline and end of treatment (see Section 14.6.4) by treatment group.

Continuous on-treatment change from baseline values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit and for end of treatment (see Section 14.6.4) by treatment group.

The number and percentage of subjects with on-treatment worst case laboratory results relative to the normal range which are post-baseline relative to baseline will be summarized by laboratory test, category, and treatment group. See Section 14.6.4 for additional information on worst case values and normal range categories.

The number and percentage of subjects with on-treatment worst case laboratory results relative to PCI criteria (see Section 14.8.1) which are post-baseline relative to baseline will be summarized by laboratory test, category, and treatment group. See Section 14.6.4 for additional information on worst case values and PCI categories.

Hematology

The displays presented for clinical chemistry laboratory values will also be presented for the hematology central laboratory tests listed in Section 8.4.

Other Laboratory Tests

The displays presented for clinical chemistry laboratory values will also be presented for the other laboratory tests listed in Section 8.4.

The number and percentage of subjects with on-treatment worst case iron parameter results relative to PCI criteria (see Section 14.8.1) which are post-baseline relative to baseline will be summarized separately by laboratory test, category, and treatment group. See Section 14.6.4 for additional information on worst case values, normal range categories and PCI categories.

On-treatment hsCRP values will be log-transformed (see Section 5.2.2) and summarized using geometric mean, coefficient of variation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group.

Percent change from baseline in log-transformed (see Section 5.2.2) on-treatment hsCRP values will be summarized using geometric mean, 95% confidence interval, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group.

Hepatobiliary (Liver)

Please refer to the protocol for details of liver chemistry increased monitoring and stopping criteria.

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

Hepatobiliary laboratory abnormalities will be summarized by treatment group.

Medical conditions for subjects with liver stopping events and substance use for subjects with liver stopping events will be listed.

A scatter plot of maximum on-treatment ALT values versus baseline ALT values will be produced.

A scatter plot of maximum on-treatment total bilirubin (xULN) versus maximum on-treatment ALT (xULN) values will be produced.

All Laboratory

A listing of all chemistry data, a listing of all hematology data, and a listing of all other laboratory data will be provided.

In addition, for subjects with abnormalities of potential concern, a listing of all chemistry data, a listing of all hematology data, and a listing of all other laboratory data will be generated separately.

A listing of laboratory data with character results will be provided.

8.5. 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.

8.5.1. Electrocardiograms

A summary of the number and percentage of subjects who had normal, abnormal and/or clinically significant ECG findings will be displayed by treatment group. For all ECG parameters, change from baseline in ECG values at week 52 will be summarized by treatment group.

The number of subjects with maximum QTc values (i.e., worst case) post-baseline relative to baseline will be summarized by test (e.g., QTcB Interval, Aggregate) and category for each treatment group.

Subjects will also be summarized by a categorization of their maximum increase in QTc value (e.g., QTcB Interval, Aggregate) (i.e., worst case) post-baseline relative to baseline.

8.5.2. Vital Signs

Vital signs are assessed in this study according to the schedule outlined in the Schedule of Activities table (see Section 14.2.1) and include the following assessments:

- HR (pre- and post-dialysis)
- Weight (pre- and post-dialysis)
- Estimated Dry Weight (EDW, recorded in the eCRF only at Day 1, full study visits, and Week 52)

Summaries and analyses of BP values are described in earlier safety sections and will not be included with vital signs summaries. However, BP values will be included in PCI summaries.

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

Vital sign values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit and for baseline and end of treatment by treatment group. Separate summaries for HR and weight measured pre- and post-dialysis will be provided.

Vital sign change from baseline values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit and for end of treatment by treatment group. Separate summaries for HR and weight measured pre- and post-dialysis will be provided.

The number and percentage of subjects with on-treatment or post-treatment worst case vital sign results relative to PCI criteria (see Section 14.8.3) which are post-baseline relative to baseline will be summarized by test, category, and treatment group. See Section 14.6.4 for additional information on worst case values and PCI categories. Post-dialysis BP values and heart rate outside of the PCI range will be summarized separately.

The difference between on-treatment post-dialysis weight and estimated dry weight will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit and for baseline and end of treatment by treatment group. A corresponding line plot will be provided to display this data graphically.

A listing of all vital signs data for subjects with post-dialysis vital signs values outside of PCI criteria will be provided.

8.5.3. Pregnancy

A listing of all subjects who became pregnant during the study will be included.

8.5.4. COVID-19 Analyses

The following COVID-19 related displays will be provided.

A summary of the number and percentage of subjects for the following assessments will be produced: Case Diagnosis, COVID-19 Test performed, and Results of the COVID-19 test.

A summary of exposure adjusted incidence rates over time (see Section 14.6.4) will be produced by treatment group for any AE, any SAE, and any Severe AE, for two periods – pre COVID-19 pandemic and during COVID-19 pandemic. The summary will be produced overall, by Country, Region, Sex, and by Age at randomization (Grouping 2) (see Section 5.4.2). A summary of exposure adjusted incidence rates by treatment group will also be produced for Common (>5%) AEs for two periods – pre COVID-19 pandemic and during COVID-19 pandemic.

9. PATIENT REPORTED OUTCOMES ANALYSIS

This study includes the following patient reported outcomes (PROs) that are assessed according to the schedule in the Schedule of Activities table in Section 14.2.1:

- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change (PGI-C)

Additional details on these questionnaires can be found in Section 14.6.7.

Except for baseline, only on-treatment post-baseline PGI-S and PGI-C will be summarized/analyzed, unless otherwise specified.

Patient Reported Outcomes Statistical Analyses: Symptom Severity & Change
Secondary Endpoint(s)
• Change from Baseline at Wk 8,12, 28, 52 in PGI-S
Exploratory Endpoint(s)
• Shift tables (Baseline to Weeks 8, 12, 28, and 52) in PGI-S • N (%) of patients within each PGI-C symptom change level at Weeks 8, 12, 28, 52
Model Specification
• Scoring for the PGI-S and PGI-C parameters is outlined in Section 14.6.7. • The mean change from baseline in PGI-S score will be analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in means between arms. The models will be fitted to data collected after baseline up to Week 52. The model will include factors for treatment, time, region, baseline PGI-S score value and the baseline PGI-S score by time and treatment by time interaction terms. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.
Model Results Presentation
• PGI-S scores will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Change from baseline in PGI-S values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • For the MMRM analyses of change from baseline in PGI-S, an LSMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - rhEPO) and a one-sided superiority p-value for this test at Weeks 8, 12, 28, and 52. • Additionally, shift tables by treatment group will be generated that display the number and percentage of subjects in each PGI-S category at baseline and the resulting PGI-S category at each scheduled visit. • Stacked bar charts will be produced by treatment group that display the percentage of subjects with each PGI-S response at baseline and Weeks 8, 12, 28 and 52. • The number and percentage of subjects in each PGI-C category at each scheduled visit will be summarized.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance.

Patient Reported Outcomes Statistical Analyses: Symptom Severity & Change
• Clinically meaningful effects for PRO assessments will be specified in a separate reimbursement RAP.

10. PHARMACOKINETIC ANALYSES

10.1. Secondary Pharmacokinetic Analyses

10.1.1. Endpoint / Variables

- Plasma daprodustat, GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6) and GSK2531401 (M13) PK parameters pre-dose trough (Ctrough) and Cmax

10.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 14.5.3 Reporting Standards for Pharmacokinetic)

10.1.1.2. Derived Pharmacokinetic Parameters

- Pharmacokinetic parameters described in Table 2 will be determined from the plasma concentration-time data, as data permits.

Table 2 Derived Pharmacokinetic Parameters for daprodustat, and/or GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6) and GSK2531401 (M13)

daprodustat, GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6) and GSK2531401 (M13)	
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
Ctrough	Post-baseline sample pre-dose concentration
Cmax	Maximum observed concentration of all five post-baseline PK samples, determined directly from the concentration-time data.
Planned Exploratory Displays	
• Plasma concentration-time data for daprodustat and its six metabolites will be summarized by dose level at the PK sampling using mean, standard deviation, minimum, median and maximum. A listing of Daprodustat and its six metabolities PK plasma concentration-time data will be produced. • Plasma PK parameters (C_{max}, t_{max}, and C_{trough})) for daprodustat and its six metabolites will be summarized by dose level at the PK sampling using mean, standard deviation, minimum, median, maximum geometric mean, standard deviation of log-transformed data, and %CVb. A listing of PK parameters for daprodustat and its six metabolites will be provided.	

10.1.2. Population of Interest

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

11. PHARMACODYNAMIC ANALYSES

11.1. Exploratory Pharmacodynamic Analyses

Endpoint / Variables
• Maximum observed change from baseline in EPO • Maximum observed % change from baseline in VEGF • Change from baseline in hematocrit, RBC count, and reticulocyte count
Planned Exploratory Displays
• Observed EPO and change from baseline in EPO will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by visit, sample time, PD visit dose, and treatment group. Maximum observed post-baseline EPO and maximum observed change from baseline in EPO will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by PD visit dose and treatment group. • Observed VEGF will be summarized using geometric mean, CV(%), 95% CI, minimum, P25, median, P75, and maximum by visit, sample time, PD visit dose, and treatment group. Percent change from baseline in VEGF will be summarized using geometric mean, 95% CI, minimum, P25, median, P75, and maximum by visit, sample time, PD visit dose, and treatment group. Maximum observed post-baseline VEGF and maximum observed change from baseline in VEGF will be summarized using geometric mean, CV(%) (for maximum observed VEGF only), 95% CI, minimum, P25, median, P75, and maximum by PD visit dose and treatment group. (Summary statistics for VEGF will be calculated based on log-transformed values. See Section 5.2.2 for details of log-transformation.) • Change from baseline in hematocrit, RBC count, and reticulocyte count are included in the summary of clinical laboratory analyses described in Section 8.4.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

- The primary goal of this analysis is to characterize the pharmacokinetic/ pharmacodynamic relationship of parent daprodustat and efficacy and safety endpoints in the “All Randomized (ITT)” or the “Pharmacokinetic” population from this study. Please refer to Section 7.4, Section 8.2, Section 10.1 and Section 11.1 for further details of related PK/PD analyses. Any changes to the proposed analyses would be described in the CSR.

13. REFERENCES

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14. APPENDICES

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

All deviations are to be tracked in GSK Protocol Deviation Management System (PDMS). Protocol deviations will be reviewed by the study team and important protocol deviations will be identified according to the Protocol Deviation Management Plan.

14.1.1. Exclusions from Per Protocol Population

Exclusions from the PP population include events that, if they should occur, might:

- Directly impact the hemoglobin efficacy endpoint; or
- Lead to permanent discontinuation of study treatment or study withdrawal and hence indirectly impact the efficacy endpoint by causing data to be missing.

The following criteria define the events which, if they occur prior to the end of the EP, may lead to exclusion of a subject from the PP population. Exclusions from the PP Population will be subject to blinded review by the study team. Protocol deviations meeting the exclusion criteria and programmatically-identified exclusions, including those, which are not considered to be protocol deviations, will be reviewed by the study team. The study team will also review the listing of unique concomitant medication terms to identify the prohibited medications. These reviews will occur before database has been unblinded for analysis.

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

Number	Exclusion Description
01	Baseline HemoCue Hgb value outside of Randomization (Day 1) Hgb entry criteria range
02	Less than 5 out of 7 scheduled evaluable[2] Hgb values[1] from the EP
03	Non-compliance with study treatment (compliance category of under compliant or over compliant) during the EP, based on eCRF study treatment and compliance record forms
04	Inadequate iron status during EP, defined as ferritin $\leq$ 100 ng/mL on two consecutive scheduled visits or TSAT $\leq$ 20% on two consecutive scheduled visits
05	Subject received prohibited medication[3] for more than two weeks during EP

NOTES:

1. Based on central laboratory Hgb values. If central laboratory Hgb value is missing, a non-missing HemoCue Hgb value will be used.
2. See Section 14.6.3.
3. Prohibited medications include strong inhibitors of CYP2C8 (e.g., gemfibrozil) and strong inducers of CYP2C8 (e.g., rifampin/rifampicin).

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

14.2.1.1. Schedule of Activities for Participants on Randomized Study Treatment

Procedure Visit window of ±3 days for Weeks 2 to 8, and ±1 week for all other visits. All visit timings are relative to Day 1. All assessments will be performed pre-dialysis unless otherwise specified.	**Screening (Week -4)**	**Treatment Period: Day 1 through Week 52**					**Follow-up Visit (4 to 6 weeks after last dose)**
		Day 1 [1]	**Full Study Visit Week 4, 16, 28, 40**	**Abbreviated Study Visit Week 2, 6, 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled** [2]	
Informed consent	X						
IRT system transaction [3]	X	X	X	X	X	X	X
Inclusion and exclusion criteria	X	X					
Randomization [4]		X					
Study Treatment Dispensing [5, 6]		X	X	X [7]		X [7]	
Study Treatment Compliance [6]			X	X [7]	X	X [7]	
Participant reminder to report changes in health [8]		X					
Medical history (including past and current medical conditions, hospitalization and transfusion) [9]	X						
Demography, height	X						
Weight (pre- and post-dialysis) and EDW [10]	X	X	X	X	X	X	X
SBP/DBP, HR (pre- and post-dialysis)	X	X (triplicate)	X	X	X (triplicate)	X	X
Kt/Vurea [11]		X	X		X		
12-lead ECG [12]	X				X		
Ultrasound of kidneys and adrenal glands [13]	X						
Estradiol and FSH (females only, if required) [14]	X						
Serum pregnancy test (WOCBP only) [15, 16]	X	X	X		X		X
HemoCue Hgb	X	X	X	X	X	X	
Hematology [17]	X	X	X	X (Hgb only)	X	X	X

Procedure Visit window of ±3 days for Weeks 2 to 8, and ±1 week for all other visits. All visit timings are relative to Day 1. All assessments will be performed pre-dialysis unless otherwise specified.	Screening (Week -4)	Treatment Period: Day 1 through Week 52					Follow-up Visit (4 to 6 weeks after last dose)
		Day 1 [1]	Full Study Visit Week 4, 16, 28, 40	Abbreviated Study Visit Week 2, 6, 8, 12, 20, 24, 32, 36, 44, 48	Week 52	Unscheduled [2]	
Clinical chemistry [17]	X	X	X		X	X	X
Ferritin, total iron and UIBC [17]	X	X	X		X		X
Lipids (non-fasting) [17]		X	X		X		
iPTH, hsCRP, HbA1c [17, 18]		X	Wk 28		X		
Hepcidin [17, 19]		X	Wk 4, 16, 28		X		
PD: EPO, VEGF [17]		X	X (once from Wk 28 to Wk 52) [20]				
PK		X	X (once from Wk 8 to Wk 52) [21]				
Stored samples for biomarkers [22]		X	Wk 28		X		
Genetic sample [23]		X					
Patient Global Impression of Severity (PGI-S) [24]		X	Wk 28	Wk 8, 12	X		
Patient Global Impression of Change (PGI-C) [24]			Wk 28	Wk 8, 12	X		
Non-serious AEs, SAEs, AEs of Special Interest, clinical events	X [25]	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X
Iron therapy, transfusions, rescue medications [26, 27]	X	X	X	X	X	X	X
Hospitalization or kidney transplant [26]			X	X	X	X	X

DBP, diastolic blood pressure; ECG, electrocardiogram; EDW, estimated dry weight; FSH, follicle stimulating hormone; HbA1c, glycated hemoglobin; HR, heart rate; hsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; UIBC, unsaturated iron binding capacity; VEGF, vascular endothelial growth factor; WOCBP, woman of childbearing potential.

Note: Pre-dialysis assessments should be performed in the following order, where applicable: patient reported outcomes, ECG, BP/HR, blood sample collection.

1. All assessments to be performed pre-dose.
2. If additional study treatment is required prior to the next scheduled study visit, it is not necessary to perform the unscheduled visit assessments other than dispensing study treatment.
3. Study treatment will be dispensed every 4±1 weeks, with the exception that it may be every 2 weeks ± 3 days up to the Week 6 visit. An IRT transaction will be required to dispense study treatment. Additional IRT transactions may occur if needed to dispense additional study treatment.
4. In circumstances where randomization of an eligible participant cannot be completed at the Day 1 visit, the visit may be rescheduled up to 1 week later. Clinical laboratory assessments performed at the original visit, no more than 1 week prior, do not need to be repeated, except for the HemoCue hemoglobin and the Q2 hemoglobin.

5. Study treatment will be dispensed, i.e., allocated to a specific participant, and stored at the dialysis center or research site. Participant may take study treatment tablets at home in preparation for PD visit. See protocol Section 7 for further study treatment details.
6. In circumstances where a new supply of study treatment (including a new dose) cannot be dispensed on the day of the study visit, the new supply of study treatment can be dispensed at the next dialysis session. Prior study treatment should be continued unless on dose interruption, e.g., Hgb ≥12 g/dL. Compliance is deferred until study treatment is returned.
7. At the Week 2, Week 6 or unscheduled visits, if dose is not changed, new study treatment does not need to be dispensed and use of existing study treatment is continued. Compliance checking is required if new study treatment is dispensed.
8. Participant will be instructed to promptly notify site staff in the event of any changes to his or her health. Health changes include new symptoms, medical problems (e.g., pregnancy, hospitalization), and medication changes.
9. Medical history (including CV medical history/risk factors) will be assessed at screening (Week -4). Medical history will be re-assessed at Day 1 to confirm eligibility prior to randomization.
10. Estimated Dry Weight (EDW) to be recorded in the eCRF only at Day 1, full study visits, and Week 52.
11. A historical Kt/Vurea measurement within the last 12 weeks can be used. If a Kt/Vurea measurement is not available, then a urea reduction ratio (URR) measurement is acceptable.
12. The Week -4 (screening) ECG must be performed pre-dialysis, and may be performed on any dialysis day from the Week -4 visit to the Day 1 visit, except during the first dialysis session of the week. The result of the screening ECG, including physician interpretation, must be available to confirm eligibility prior to randomization. All other ECG assessments may be performed either pre- or post-dialysis. See protocol Section 9.4.3..
13. Ultrasound of the kidneys and adrenal glands will be performed between the Week -4 and Day 1 visits. If the results of the kidney and adrenal ultrasound require follow-up testing, then the screening period may be extended by 1 additional week. A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria, provided the size and cyst category has been reported. If a more sensitive imaging study [e.g., magnetic resonance imaging (MRI), computed tomography (CT)] has been performed within this timeframe and a report is available, this may be used in place of the ultrasound. See protocol Section 9.4.4..
14. Only required to confirm menopausal status if in question.
15. Repeat pregnancy test prior to study treatment re-administration if study treatment was interrupted for >7 days and there was also a lapse in contraceptive use, regardless of the reason for the interruption.
16. In Argentina only, pregnancy testing will be performed every 4 weeks for WOCBP as required by local law.
17. See details for laboratory assessments in protocol Section 9.4.5.
18. HbA1c assessment is applicable only for participants with diabetes on Day 1 or diagnosed during the study.
19. At each visit specified in the table, a hepcidin sample will be collected prior to dosing with either study treatment and prior to administration of any iron supplementation.
20. Post-baseline PD samples (i.e., EPO and VEGF) may be taken during any week from Week 28 to Week 52, inclusive, preferably at the earliest opportunity. See protocol Section 9.6 for additional details and requirements for the collection of PD samples.
21. Post-baseline PK samples will be taken at any one of the post-baseline visits indicated in the table, preferably at the earliest opportunity. See protocol Section 9.5 for additional details and requirements for the collection of PK samples.
22. Biomarker samples will be collected and stored for potential future analysis for all participants, except if not permitted by local regulations or IRB/EC, or refused by participant.
23. Participation in genetics research is optional. A separate informed consent signature is required for participation. See protocol Section 9.7 for additional details.
24. Participants who are unable to or require assistance to read must not complete the questionnaires. See protocol Section 9.9 for additional details.
25. Only SAEs, which are assessed as related to study participation or a GlaxoSmithKline (GSK) product, are collected at this visit. See protocol Section 9.2.1 for additional details.
26. Record in the eCRF, if applicable.

27. See details on Rescue in protocol Section 7.9.

14.2.1.2. Schedules of Activities for Participants Who Permanently Discontinue Study Treatment

Procedure	Early Treatment Discontinuation Visit (within 2 weeks of discontinuing study treatment)	Day 1 through Week 52 [0]	
		Week 4, 16, 28, 40, 52 ± 2 weeks	Un-scheduled
IRT system transaction	X	X	X
SBP/DBP, HR (pre- and post-dialysis)	X (triplicate)	X	X
12-lead ECG [0]	X		
Iron therapy, transfusions [0]	X	X	X
Serum pregnancy test (WOCBP only)	X [0]		
HemoCue Hgb	X	X	X
Hematology [0]	X	X	
Clinical chemistry [0]	X	X	
Ferritin, total iron, UIBC, lipids, iPTH [0]	X		
Hospitalization, kidney transplant [0]	X	X	X
Non-serious AEs, SAEs, AEs of Special Interest, clinical events	X	X	X
Review concomitant medications	X	X	X
PGI-S and PGI-C [0]	X		

1. Participants will attend those study visits up to Week 52 which have not been completed at the time of early treatment discontinuation. Phone visits are acceptable in exceptional circumstances.
2. ECG assessment may be recorded pre- or post-dialysis.
3. Record in the eCRF, if applicable.
4. Additional pregnancy test required at subsequent visit. Must be at least 4 weeks after the end of study treatment.
5. See details for laboratory assessments in protocol Section 9.4.5.
6. Participants who are unable to or require assistance to read must not complete the questionnaires. See protocol Section 9.9for additional details.

14.3. Appendix 3: Assessment Windows

- Data for continuous variables that are not related to time-to-event will be summarized according to the scheduled visit time period for which they were recorded in the eCRF. Unscheduled assessments will not be slotted to a particular time point, but will remain as unscheduled if they are either summarized or listed unless otherwise specified (i.e. Hgb endpoints described in Section 14.6.3 and BP endpoints described in Section 14.6.4).

14.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

14.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the treatment start and stop dates and last non-zero dose date (see Section 14.6.1).

14.4.1.1. Study Phases for Hgb, Iron Parameters, IV Iron Dose Endpoints, Iron Use Summaries, Transfusion and PRO Data

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 1 day
Post-Treatment	Date > Study Treatment Stop Date + 1 day
Post-Randomization	Randomization Date < Date

NOTES:

- If the treatment stop date is missing and the treatment start date is non-missing, and Date > Treatment Start Date, then the assessment will be considered to be On-Treatment

14.4.1.2. Study Phases for CV Endpoint Data

Study Phase	Definition
Pre-Treatment	Date < Treatment Start Date
On-Treatment	Treatment Start Date ≤ Date ≤ Last Non-Zero Dose Date + 28 days
Post-Treatment	Date > Last Non-Zero Dose Date + 28 days
Post-Randomization	Randomization Date ≤ Date

NOTES:

- If the last non-zero dose date is missing and the treatment start date is non-missing, and Date ≥ Treatment Start Date, then the assessment will be considered to be On-Treatment
- Study phase definitions use the imputed CV endpoint date

14.4.1.3. Study Phases for BP, Lipid Parameters, Clinical Chemistry, Hematology, Other Laboratory Tests, Hepatobiliary (Liver), ECG and Vital Signs Data

Study Phase	Definition
Pre-Treatment	Date ≤ Treatment Start Date
On-Treatment	Treatment Start Date < Date ≤ Last Non-Zero Dose Date + 1 day
Post-Treatment	Date > Last Non-Zero Dose Date + 1 day
Post-Randomization	Randomization Date < Date

NOTES:

- If the last non-zero dose date is missing and the treatment start date is non-missing, and Date > Treatment Start Date, then the assessment will be considered to be On-Treatment
- Post-dialysis BP measured on treatment start date is considered on-treatment

14.4.1.4. Study Phase for AE Data

All AEs (non-serious AEs and serious AEs) will be collected and recorded on the eCRF from the start of treatment until the follow-up visit at the time points specified in the SoA from Section 14.2. Serious AEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded on the eCRF from the time a participant consents to participate in the study up to and including any follow-up contact. AE of worsening of an on-going event will be counted once in a particular study phase.

Study Phase	Definition
Pre-treatment	• For subjects with a non-missing screen failure date, if AE onset is on or before the screen failure date: AE Start Date ≤ Screen Failure Date • For randomized subjects with a missing treatment start date, all AEs are considered pre-treatment • For randomized subjects with a non-missing treatment start date, if AE onset date is before treatment start date: AE Start Date < Treatment Start Date
Post-randomization	If AE onset date or AE worsening date is on or after the randomization date Randomization date ≤ AE Start Date Randomization date ≤ AE Worsening Date AE worsening during post-randomization will be defined relative to the maximum intensity of AE prior to randomization date. AE worsening date is the first date in the post-randomization period, when AE intensity increased relative to the maximum intensity of the AE prior to randomization date.
Treatment emergent	If AE onset date or AE worsening date is on or after treatment start date & on or before the last non-zero dose date plus 1 day. Treatment Start Date ≤ AE Start Date ≤ Last Non-Zero Dose Date + 1 day Treatment Start Date ≤ AE Worsening Date ≤ Last Non-Zero Dose Date + 1 day AE worsening during treatment emergent period will be defined relative to the maximum intensity of AE prior to study treatment start date. AE worsening date is the first date in the treatment emergent period, when AE intensity increased relative to the maximum intensity of the AE prior to study treatment start date.
Follow-up	If AE onset date or AE worsening date is after the last non-zero dose date plus 1 day. AE Start Date > Last Non-Zero Dose Date + 1 day AE Worsening Date > Last Non-Zero Dose Date + 1 day AE worsening during follow-up will be defined relative to the maximum intensity of AE prior to study treatment start date. AE worsening date is the first date in the follow-up period, when AE intensity increased relative to the maximum intensity of the AE prior to study treatment start date.
Onset /Worsening Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date: AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date: AE Onset Date - Treatment Start Date +1 If Treatment Start Date > AE Worsening Date: AE Worsening Date - Treatment Start Date

Study Phase	Definition
	If Treatment Start Date ≤ AE Worsening Date: AE Worsening Date - Treatment Start Date +1 Missing otherwise.
Onset/Worsening Time Since Last Dose (Days)	If Last Non-Zero Dose Date ≤ AE onset date: AE onset date – last non-zero dose date + 1 If Last Non-Zero Dose Date > AE onset date: AE onset date – last non-zero dose date If Last Non-Zero Dose Date ≤ AE worsening date: AE worsening date – last non-zero dose date + 1 If Last Non-Zero Dose Date > AE worsening date: AE worsening date – last non-zero dose date Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date/AE Worsening Date + 1
Drug-related	If relationship is marked 'YES' on eCRF or if the value is missing.

NOTES:

- AEs that occur or worsen during interruptions of randomized study treatment will be classified as treatment emergent and post-randomization.
- If the last non-zero dose date is missing and the treatment start date is non-missing and the AE onset date or AE worsening date is on or after the treatment start date, then the AE will be considered to be treatment emergent.
- If AE onset date or AE worsening date is missing and AE resolution date is before the treatment start date, then the AE will be classified as Pre-treatment.
- If AE onset date or AE worsening date is missing and AE resolution date is either missing or on or after treatment start date, then the AE will be classified as treatment emergent and post-randomization.

14.4.1.5. Study Phases for Concomitant Medication (Other Than IV Iron Dose Endpoints and Iron Use Summaries)

Pre-treatment medications are those taken (i.e., started) before the start date of study treatment. On-treatment medications are those taken (i.e., started or continued) at any time between the study treatment start date and the last non-zero dose date + 1 day, inclusive. Pre-treatment medications that were continued during this on-treatment period are also considered to be on-treatment medications. Post-treatment medications are those taken (i.e., started or continued) at any time after the last non-zero dose date + 1 day. On-treatment medications that were continued during this post-treatment period are also considered to be post-treatment medications. Post-randomization medications are those taken (i.e., started or continued) at any time on or after the randomization date.

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

Illustrations of the pre-treatment, on-treatment, and post-treatment treatment states are included below:

	Pre-treatment	On-treatment			Post-treatment		Pre-treatment medication	On-treatment medication	Post-treatment medication
		Randomized Treatment Start Date		Last Non-zero Dose Date + 1 Day	Last Non-zero Dose Date + 2 Days				
(a)	x———x						Y	N	N
(b)	x———		———x				Y	Y	N
(c)	x———		———			———x	Y	Y	Y
(d)			x———x				N	Y	N
(e)			x———			———x	N	Y	Y
(f)						x———x	N	N	Y
(g)	?——— x						Y	N	N
(h)	?———		———x				Y*	Y	N
(i)	?———		———			———x	Y*	Y*	Y
(j)	x———		———			———?	Y	Y**	Y**
(k)			x———			———?	N	Y	Y**
(l)						x———?	N	N	Y
(m)	?—— ———		———			———?	Y***	Y***	Y***
(n)	x———	x					Y	Y	N
(o)	?—— ———	x					Y*	Y	N
(p)		x	———x				N	Y	N
(q)		x	———	x			N	Y	N
(r)				x	——	———x	N	Y	Y
(s)				x	——	———?	N	Y	Y**
(t)					x	———x	N	N	Y
(u)					x	———?	N	N	Y
(v)			x———	——	x		N	Y	Y

x = start/stop date of medication

? = missing start/stop date of medication

* If a medication is stopped On-treatment or Post-treatment and no start date is recorded it will be assumed that the medication was ongoing from the Pre-treatment phase

** If a medication is started Pre-treatment or On-treatment and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study

*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the Pre-treatment phase to the Post-treatment phase

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: gsk1278863/mid204837
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1). • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from system independent (SI) to SDTM	
Generation of RTF Files	
• RTF files will be generated for Tables	

14.5.2. 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
• In all displays (TFLs) the term “Subjects”, which reflects CDISC and GSK Data Display Standards terminology, will be used to refer to the “Participants”. In this Reporting and Analysis Plan, “subject” and “participant” are used interchangeably.

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 randomization will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • All scheduled visits, regardless of deviation from the planned assessment times and/or scheduled visit days, will be used in tables, figures and formal statistical analyses unless otherwise stated.

• The derived end of treatment value (see Section 14.6.1) will also be included in displays of data by visit. • Tables presenting data values by visit will also include values from scheduled visits occurring on or before the Day 1 visit, despite the description contained in the title (e.g., post-randomization, evaluable, or on-treatment). The description in the title refers to the post-randomization values that are included in the table. • For the purpose of statistical summary and analysis, unless otherwise specified, the data for visits after discontinuation of study treatment recorded under Early Trt Disc Wk xx visit will be summarized and analyzed along with the corresponding Wk xx visits for subjects who complete the study treatment. • 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. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables, with the following exceptions: • If the table includes a row for all post-baseline assessments, unscheduled visits will be included in this row. • Some Hgb endpoints will include unscheduled Hgb values (See Section 14.6.3) • Some BP endpoints will include unscheduled BP values (see Section 14.6.4) • Unscheduled visits will not be included in figures, with similar exceptions: • If the figure includes a data value for all post-baseline assessments, unscheduled visits will be included in this value. • Some Hgb endpoints will include unscheduled Hgb values (See Section 14.6.3) • Some BP endpoints will include unscheduled BP values (see Section 14.6.4) • All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

14.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
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 v5.0 for descriptive summary statistics/analysis and summarized graphical displays only. Note: PC WNL file or NONMEM/Pop PK is Not applicable for Non-compartmental analysis.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Clinical Programmer: Ctrough, Cmax, tmax Formulas for these derivations are given in Section 14.6.5.

Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.   ○ Triplicate BP and HR measurements are expected at certain time points (See Section 14.2.1) • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Randomization Date
• Date subject was randomized
Treatment Start Date
• First randomized treatment dose start date
Last Non-Zero Dose Date
• Date of last actual dose of active study treatment from the eCRF Study Treatment/Compliance Record Form.   ○ The dose steps used by the dosing algorithm described in the protocol include a dose hold or a zero dose. If subjects are assigned by the algorithm to a zero dose, they only receive placebo and saline, and do not receive active study treatment for that period. When a dose interruption is required, both active treatment and placebo/saline will be interrupted. Hence, it would be possible for a subject to complete the study, while still following the dosing algorithm, but not actually taking any active study treatment. The last non-zero dose date, then captures the latest date in the study that a subject physically took a dose of active study treatment.
Treatment Stop Date
• Calculated as the latest study treatment dose stop date, after excluding the records for missed dose.
End of Treatment Value
• Only defined for subjects with a non-missing treatment start date • Hgb, iron, transfusion and PRO parameter: the latest value on or before the treatment stop date + 1 day. • Blood pressure, central laboratory, and vital signs parameters: the latest value on or before the last non-zero dose date + 1 day.

Study Completion/Withdrawal Date
• Date of withdrawal for subjects withdrawing (i.e., subjects who actively withdraw or are deemed lost to follow-up) from study or date of completion of study for subjects who complete the study. • Note: Subjects who die while on study are considered as having completed the study
Planned/Actual Visit Dates
• Planned/actual visit dates will be defined as follows: o Week 28 date: Non-missing Week 28 visit start date (from SV domain), otherwise randomization date + 28*7 o Week 36 date: Non-missing Week 36 visit end date (from SV domain), otherwise randomization date + 36*7 o Week 52 date: Non-missing Week 52 visit end date (from SV domain), otherwise randomization date + 52*7
Stabilization Period
Defined as the period between and including the randomization date + 1 day - <Week 28 visit, using planned/actual dates.
Alternative Evaluation Period (Alt. EP)
Defined as the period between and including Week 28 visit – Week 36 visit, using planned/actual dates.
Evaluation Period (EP)
Defined as the period between and including Week 28 visit – Week 52 visit, using planned/actual dates.
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
Treatment Day
• Calculated as the number of days from treatment start date: • Treatment Start Date = Missing → Treatment Day = Missing • Ref Date < Treatment Start Date → Treatment Day = Ref Date – Treatment Start Date • Ref Data ≥ Treatment Start Date → Treatment Day = Ref Date – (Treatment Start Date) + 1
Last Study Contact Date
• Latest visit date from an unscheduled visit or a clinic, telephone, designated third party, healthcare provider or medical records, or other contact with subject (mail, email, text, social media, etc.) visit.
Time Definitions (per GSK standard principles)
• 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days
Production of Two-Sided p-values
• The majority of the efficacy and safety analyses in this study will use one-sided 2.5% p-values assess statistical significance. Should two-sided p-values be required for publication purposes after the study is complete, the corresponding two-sided p-values will be produced at that time.

14.6.2. Study Population

14.6.2.1. Demographics & Baseline Characteristics

Demographics & Baseline Characteristics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: o Any subject with a missing day will have this imputed as day '15'. o Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
High Level Race
• Geographic ancestry data will be combined into five high level race categories: o American Indian or Alaskan Native o Asian (Asian-East Asian Heritage, Asian-Japanese Heritage, Asian-Central/South Asian Heritage, Asian-South East Asian Heritage, Mixed Asian Race) o Black or African American o Native Hawaiian or Other Pacific Islander o White (White-Arabic/North African Heritage, White-White/Caucasian/European Heritage, Mixed White Race) o Mixed Race (Multiple high level races are selected) Note: A subject will only be counted in one category. Mixed Asian Race includes subjects who have more than one Asian category selected, but no other categories. Mixed White Race includes subjects who have more than one White category selected, but no other categories.
Race Detail
• Geographic ancestry data will be combined into race detail categories: o American Indian or Alaskan Native o Asian-Central/South Asian Heritage o Asian-East Asian Heritage o Asian-Japanese Heritage o Asian-South East Asian Heritage o Mixed Asian Race o Black or African American (African American/African Heritage) o Native Hawaiian or Other Pacific Islander o White-Arabic/North African Heritage o White-White/Caucasian/European Heritage o Mixed White Race o Mixed Race (Multiple high level races are selected) Note: A subject will only be counted in one category. Mixed Asian Race includes subjects who have more than one Asian category selected, but no other categories. Mixed White Race includes subjects who have more than one White category selected, but no other categories.
Prior ESA Type and Standardized Prior ESA Dose (U/week) at Randomization
• During the screening period, subjects may be receiving ESAs in multiple ways, including: epoetin IV or SC, darbepoeitin IV or SC, or methoxy PEG-epoetin beta IV or SC. • A subject's prior ESA type will be determined from the records that contribute to the subject's standardized prior ESA dose. The following categories of prior ESA type will be summarized:

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- Darbepoetin alfa only
- Epoetin only
  - This group contains subjects using any of the following types of epoetin: epoetin alfa, epoetin beta, epoetin lambda, epoetin theta, and epoetin zeta.
- Methoxy PEG-epoetin beta only
  - This group contains subjects using methoxy PEG-epoetin beta and pegzerepoetin alfa.
- Multiple
  - This group contains subjects using any combination of the ESA types.
- Missing

- The dose of ESA will be standardized to obtain a continuous single unit prior ESA dose in terms of epoetin IV U/week for the period from the Week -4 visit to the day before the Randomization date.

- All prior ESA therapy concomitant medication records from screening will be selected and ordered by start date and end date.

- The standardization will be carried with the following formula:
- For subjects taking epoetin IV:
  - Standardized ESA dose (U/week) = epoetin IV dose (U)*frequency
- For subjects taking epoetin SC:
  - Standardized ESA dose (U/week) = (161/113)*epoetin SC dose(units)*frequency
- For subjects taking darbepoetin IV or SC:
  - Standardized ESA dose (U/week) = 250* darbepoetin dose (μg)*frequency
- For subjects taking methoxy PEG-epoetin beta:
  - Standardized ESA dose (U/week) = 208*methoxy PEG-epoetin beta dose (μg)*frequency

Note: Frequency and Gap Factors defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)	Gap Factor
One time dose	see below	n/a
Four times per week	4	0.75 day
Three times per week	3	1.33 days
Two times per week	2	2.5 days
Every week	1	6 days
Every 10 days	0.70	9 days
Every 2 weeks	0.50	13 days
Every 3 weeks	0.33	20 days
Every 4 weeks	0.25	27 days
Every 5 weeks	0.20	34 days
Every 6 weeks	0.167	41 days
Every 8 weeks	0.125	55 days

- If the frequency of the record is not 'one time dose', then duration is calculated as follows:

Demographics & Baseline Characteristics

- If the concomitant medication record start date ≥ Randomization date, the duration of the record is 0.
- If the concomitant medication record end date + gap factor < Week -4 visit date, the duration of the record is 0.
- If the concomitant medication record end date + gap factor ≥ Week -4 visit date, the duration of a record will be calculated as Stop Date – Start Date +1 day, where:
  - Start date will be the latest of (concomitant medication record start date and the Week -4 visit date).
  - Stop date will be the concomitant medication record end date + gap factor.

- If the frequency of the record is 'one time dose', then:
  - If the concomitant medication record start date ≥ Randomization date, the duration of the record is 0.
  - If Week -4 visit date ≤ concomitant medication record start date, then:
    - Frequency (for standardization formula) = 1
    - Duration = 7 days
  - If concomitant medication record start date < Week -4 visit date, then:
    - Frequency (for standardization formula): 7/ [earliest of (the day before the next sequential prior ESA concomitant medication record start date and the day before randomization) – start date of record + 1 day]
    - If the earliest non-missing date of (the day before the next sequential prior ESA concomitant medication record start date and the day before randomization) < Week -4 visit date, the duration of the record is 0.
    - If the earliest non-missing date of (the day before the next sequential prior ESA concomitant medication record start date and the day before randomization) ≥ Week -4 visit date, the duration of the record is calculated as Stop Date – Start Date + 1, where:
      - Start date will be the Week -4 visit date.
      - Stop date will be the earliest of (the day before the next sequential prior ESA concomitant medication record start date and the day before randomization)

- The total dose for each prior ESA record will be: Standardized dose*duration/7days

- A weighted mean will then be used to obtain the prior ESA dose:
  Mean prior ESA dose = [(ESA total dose$_{\text{Record 1}}$) + ... + (ESA total dose$_{\text{Record n}}$)]/[(Randomization Date – Week -4 Visit Date)/7days]

Baseline Erythropoietin Resistance Index (ERI, U/kg/wk/g/L)

- Calculated by dividing the standardized prior ESA dose (U/week) at randomization by the baseline estimated dry weight (in kg) and then dividing by the achieved Day 1 Hgb (in g/L).
- Note: the central laboratory Hgb value from Day 1 should be used to calculate ERI, however if this value is missing and there is a corresponding non-missing HemoCue Hgb value available, the Day 1 HemoCue Hgb value will be used.

rhEPO Hyporesponders

- A subject will be considered to be a hyporesponder if:
  - ERI ≥ 2.0 U/kg/wk/g/L

  Or
  - Prior ESA dose (U/week) at baseline divided by the baseline estimated dry weight (in kg) ≥ 450 U/kg/week

Demographics & Baseline Characteristics

- Note: an ERI ≥ 2.0 U/kg/wk/g/L for epoetin-treated subjects corresponds to an ERI ≥0.008µg/kg/wk/g/L for darbepoetin-treated subjects and ≥0.01 µg/kg/wk/g/L for methoxy-PEG-epoetin-treated subjects.
- Supportive analyses will be used in the summary of demographics and baseline characteristics and will use the following alternative hyporesponder definitions:
  1) an ERI cut-point of ≥ 1.5 U/kg/wk/g/L only
  2) subjects with prior ESA dose (U/week) at baseline in the top 20th percentile of the randomized study population.

Baseline Post-Dialysis Body Mass Index (BMI)

Calculated as baseline post-dialysis weight (kg) / [height (m)]^2

Cardiovascular Risk Score

A risk score for two-year cardiovascular mortality and morbidity in a hemodialysis population has been developed [Anker, 2016] and will be calculated at baseline for each HD participant.

The following table describes how the published risk score is calculated:

ARO Cardiovascular Morbidity and Mortality Risk Score For Patients on Chronic Hemodialysis			
Parameter (unit) and values	**Risk Score Points**	**Parameter (unit) and values**	**Risk Score Points**
Age [years]		Intradialytic Weight Change [kg]	
≤39	CCI	< -2.2	CCI
40 to 49		-2.2 to < -1.7	
50 to 59		-1.7 to < -1.2	
60 to 69		> -1.2	
70 to 79		Haemoglobin [g/L]	
≥80		<100	
Smoking Status:		100 to <120	
Current		≥120	
Former		Reactive Protein [mg/L]	
Non smoker		< 2.4	
CVD history		2.4 to < 6.8	
Yes		6.8 to < 18.0	
No		≥ 18.0	
Pre-dialysis SBP [mmHg]		Serum Albumin [g/L]	
<120		<35	
120 to <130		≥35	
130 to <140		Creatinine [µmol/L]	
140 to <160		< 436	
≥160		436 to < 542	
CKD Aetiology:		542 to < 678	
Hypertension/vascular		≥ 678	
Glomerulonephritis		Calcium [mmol/L]	
Diabetes		<2.1	
Tubulo-interstitial		2.1 to <2.6	
Polycystic Kidney Disease		≥2.6	
Unknown renal diagnosis		Total Cumulated Risk Points	

It should be noted that creatinine is not routinely collected in this study and will be assumed to be the same in all HD participants (i.e. <436, resulting in 3 risk score points).

Demographics & Baseline Characteristics

CVD history is defined as having a yes response to any of the following medical history conditions: angina pectoris, myocardial infarction , stroke, coronary artery disease, transient ischaemic attack, heart failure, atrial fibrillation, cardiac arrest, and/or valvular heart disease.

Intradialytic weight change will be calculated using the Week -4 post-dialysis weight in kg – the Week -4 pre-dialysis weight in kg.

Baseline Hgb categories will be defined based on g/dL units (i.e. <10, 10-<12 and >12) and will use central laboratory Hgb values if available. If a baseline central laboratory Hgb value is not available, a baseline HemoCue Hgb value will be used.

Risk score points for CKD aetiology will be determined based on the following approach:

i. Participants with diabetic renal disease are assigned 4 points
ii. All other participants who have hypertensive renal disease are assigned 1 point
iii. All other participants who have interstitial nephritis are assigned -1 point
iv. All other participants who have a medical history of polycystic kidney, autosomal dominant or do not have any of these medical history terms selected are assigned 0 points

The overall CV risk score is determined by summing up the individual risk scores for the 11 risk factors.

History of Diabetes

- Subjects are considered to have a history of diabetes if they have a yes response to any of the following medical history conditions: diabetes, diabetic autonomic neuropathy, diabetic neuropathy peripheral, diabetic dermopathy, diabetic renal disease, diabetic retinopathy.
- If subjects have indicated that they do not have any of the listed diabetic medical history conditions above, they are considered not to have a history of diabetes.
- If subjects have not been classified as having or not having a history of diabetes and are missing a response to any of the listed medical history conditions, their diabetes history status will be missing.

History of Stroke

- Subjects are considered to have a history of stroke if they have a yes response to the stroke medical history condition.
- Subjects who have indicated that they do not have a history of stroke will be summarized accordingly.
- If a subject is missing a response to the stroke medical history condition, their stroke history status will be missing.

History of MI

- Subjects are considered to have a history of MI if they have a yes response to either of the following medical history conditions: myocardial infarction, cardiac arrest.
- Subjects who have indicated that they do not have a medical history of myocardial infarction or cardiac arrest will be considered not to have a history of MI.
- If subjects have not been classified as having or not having a history of MI, and are missing a response to either the myocardial infarction or cardiac arrest medical condition, their MI history status will be missing.

History of Cancer

- Subjects are considered to have a history of cancer if they have a yes response to either of the following medical history conditions: neoplasm malignant or unknown/unspecified, allogeneic bone marrow transplant.
- Subjects who have indicated that they do not have a medical history of neoplasm malignant or unknown/unspecified or allogeneic bone marrow transplant will be considered not to have a history of cancer.

Demographics & Baseline Characteristics
• If subjects have not been classified as having or not having a history of cancer and are missing a response to either the neoplasm malignant or unknown/unspecified or allogeneic bone marrow transplant medical condition, their cancer history status will be missing.
History of Heart Failure
• Subjects are considered to have a history of heart failure if they have a yes response to any of the following medical history conditions: heart failure, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, pulmonary hypertension. • Subjects who have indicated that they do not have a medical history of all of the terms listed above will be considered not to have a history of heart failure. • If subjects have not been classified as having or not having a history of heart failure and are missing a response to any of the medical condition terms listed above, their heart failure history status will be missing.

Demographics & Baseline Characteristics
History of Thromboembolic Events
• Subjects are considered to have a history of thromboembolic events if they have a yes response to any of the following medical history conditions: pulmonary embolism, deep vein thrombosis, retinal vein occlusion, arteriovenous graft thrombosis, arteriovenous fistula thrombosis, central venous catheter thrombosis. • Subjects who have indicated that they do not have a medical history of all of the terms listed above will be considered not to have a history of thromboembolic events. • If subjects have not been classified as having or not having a history of thromboembolic events and are missing a response to any of the medical condition terms listed above, their thromboembolic event history status will be missing.
History of Cardiovascular Disease
• Subjects are considered to have a history of cardiovascular disease if they have a yes response to any of the following medical history conditions: angina pectoris, myocardial infarction, stroke, coronary artery disease, transient ischaemic attack, heart failure, atrial fibrillation, cardiac arrest, valvular heart disease. • Subjects who have indicated that they do not have a medical history of all of the terms listed above will be considered not to have a history of cardiovascular disease. • If subjects have not been classified as having or not having a history of cardiovascular disease and are missing a response to any of the medical condition terms listed above, their cardiovascular disease history status will be missing.
Baseline Iron Use & Standardized Baseline IV Iron Dose
See Section 14.6.3
Phosphate Binder Use at Randomization
• Phosphate binder use at randomization will be summarized as follows: ○ Iron-based phosphate binders ○ Calcium-based phosphate binders ○ Non-calcium and non-iron based phosphate binders ○ No phosphate binder use ○ Subjects will be counted in each applicable group, based on the concomitant medications they are receiving on the day of randomization.
Concomitant Medication Use at Randomization
• Concomitant medication records on the day of randomization will be used to determine the following classifications of concomitant medication use at randomization: ○ ACEI/ARB ○ Vitamin D ○ Beta blockers ○ SGLT2i ○ Statin ○ Aspirin ○ Vitamin K ○ Insulin ○ Calcimimetics ○ Diabetic medication

14.6.2.2. Study Treatment Discontinuation and Study Withdrawal

Study Treatment Discontinuation and Study Withdrawal
Study Treatment Discontinuation
• Study Treatment Discontinuation Censored Time (days) = Treatment stop date – Treatment start date +1 If the death date ≤ the treatment stop date + 3 days for a subject, the subject will be censored and will not be counted as an event for treatment discontinuation summaries that exclude subjects who die while on treatment.
• Time to Study Treatment Discontinuation (days) = Treatment stop date – Treatment start date +1
• Study Treatment Person Years = (Cumulative total of time to study treatment discontinuation for subjects who discontinued study treatment + Cumulative total of study treatment discontinuation censoring time for subjects who did not discontinue study treatment) / 365.25
• Study Treatment Discontinuation Incidence Rate (per 100 person years) = 100* Number of subjects who discontinued study treatment / study treatment person years
Study Withdrawal
• Study Censored Time (days) = Study completion date – Randomization date +1
• Time to Study Withdrawal (days) = Study withdrawal date – Randomization date +1
• Study Person Years = (Cumulative total time to study withdrawal for subjects withdrawing from the study + Cumulative total of study censoring time for subjects who did not withdraw from study) / 365.25
• Study Withdrawal Incidence Rate (per 100 person years) = (100 * Number of subjects who have withdrawn from study) / Stud Person Years

14.6.2.3. Prior and Concomitant Medications

Prior and Concomitant Medications
Non-randomized ESA use during treatment period
• Subjects will be considered to have non-randomized ESA use during the treatment period if they have any ESA concomitant medication records with one of the following two reasons for medication: o Non-randomized rhEPO treatment in addition to study treatment o Non-randomized rhEPO treatment instead of study treatment during treatment period
Duration of non-randomized ESA use during treatment period
• If there is only one concomitant medication record of non-randomized ESA use during the treatment period, then: o Duration (days) = earliest of (concomitant medication record end date, last non-zero dose date + 1 day) – latest of (concomitant medication start date, treatment start date) + 1 day • If there are multiple concomitant medication records of non-randomized ESA use during the treatment period, then the duration of non-randomized ESA use will add the durations for all records, subtracting any overlapping days that may exist between the multiple records.

14.6.2.4. Exposure and Compliance

Exposure and Compliance

Exposure

- Exposure (days) = Treatment stop date – treatment start date + 1 day

Compliance

- Compliance will be calculated based on data recorded in the Study Treatment/Compliance Record eCRF pages (blinded and unblinded) and will only be calculated for subjects with a non-missing treatment start date, and will not be calculated after a subject's treatment stop date, or study conclusion date for subjects who have a non-missing treatment start date and a missing treatment stop date.
- A compliance category will be assigned to each study treatment exposure visit according to the following tables. Exposure records corresponding to periods of dose hold/zero-dose as assigned by the IRT will be categorized in the compliant category (given no active treatment doses are taken) and any gaps between exposure records will be categorized in the under compliant category.

  - Daprodustat and rhEPO

Under Compliant	Compliant	Over Compliant
Compliance for the exposure record < 80%	Compliance for the exposure record ≥ 80% and ≤ 120%	Compliance for the exposure record > 120%
Where compliance for each visit is calculated as (Total Cumulative Dose/Planned Dose)x100		

- Planned Dose [1]

Visit	Daprodustat TIW dose	rhEPO Weekly dose
Completed Day 1	Assigned dose x 6	Assigned dose x 2
Completed Week 2 – Week 6	Assigned dose x 6	Assigned dose x 2
Completed Week 8 – Week 48	Assigned dose x 12	Assigned dose x 4
Uncompleted Visit.	Expected Number of doses taken (dose stop date – dose start date+1)*0.428571428	Expected Number of doses taken (dose stop date – dose start date+1)* 0.1428571428
	Assigned dose * Expected Number of doses	Assigned dose * Expected Number of doses
	0.428571428 is 3 divided by 7	0.1428571428 is 1 divided by 7

[1] Assigned Dose: Dose assigned by the IRT as the start of the Visit.

- Actual Dose

Exposure and Compliance

Duration of Exposure Record	Daprodustat (mg)	rhEPO (U)
Day 1 to Week 48 individual dose record	Container Dose x Number of tablets taken	Dose recorded on eCRF [2]

[2] DOSE entered on open eCRF or if "Did subject receive correct treatment? is No then DOSE from unblinded eCRF.

Each visit will fall into one of the 3 categories and the percentage of time that a subject spent in each of the 3 categories above or with missing compliance data will be determined using the duration of treatment in each visit with the total duration of treatment.

- Compliance will be summarized for the following time periods: Day 1 - < Week 28, Week 28 - ≤ Week 52, and Day 1 - ≤ Week 52 (Overall compliance).
- Within each period, the percentage of time that a subject spent in each of the 3 categories above or with missing compliance data will be determined.

14.6.3. Efficacy

14.6.3.1. Hemoglobin Endpoints

Hemoglobin Values

Central Laboratory and HemoCue Hgb Values

- When source of Hgb measurement is not specified:
  - 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 will be used. This approach will be used for the primary Hgb analysis.
- Some displays may be created for either central laboratory Hgb values only or HemoCue Hgb values only. The central laboratory summary will be considered the primary summary in this case.

Evaluable Hemoglobin Values

- Evaluable Hgb values are on-treatment Hgb values (see Section 14.4.1) that are not taken within the 8 weeks following a red blood cell transfusion, a whole blood transfusion, or a non-randomized ESA treatment which occurs on or after the randomization date.
- Red blood cell transfusions, whole blood transfusions and non-randomized ESA treatments occurring on or after the randomization date are identified by comparing the start and stop date of the respective transfusion or ESA concomitant medication record to the randomization date.

Imputed Hemoglobin Values

- For each missing value between baseline to Week 52 (inclusive), 200 imputed values will be generated using the multiple imputation method (see Section 7.1.5). The average of these 200 imputed values will be used as the value for this missing value in the summary tables and figures.

Hemoglobin Values

- For primary efficacy Hgb analysis and the corresponding subgroup analyses using all available observed and imputed Hgb values (on and off-treatment), Rubin's rules [Rubin, 1987] will be used to combine results of the imputed datasets using SAS PROC MIANALYZE procedure.

EP Hemoglobin Value for Primary Hgb Analysis

- For each subject, the mean of all available (on and off treatment) Hgb values during the EP (See Section 14.6.1) including any imputed and unscheduled Hgb values that were taken during this time period.
- Should the assessment dates for Hgb values from the Early Treatment Discontinuation visit fall within the EP, then these values will be included as unscheduled Hgb values. Hgb values from the Follow-up visit will not be included in the EP mean.

EP Hemoglobin Value for While On-Treatment Evaluable Hgb Supportive Analysis

- For each subject, the mean of all evaluable Hgb values during the EP (See Section 14.6.1), including any evaluable unscheduled Hgb values that were taken during this time period.
- Should the assessment dates for Hgb values from the Early Treatment Discontinuation visit fall within the EP, then these values will be included as unscheduled Hgb values. Hgb values from the Follow-up visit will not be included in the EP mean.

EP Hemoglobin Value for Alternative EP Supportive Analyses

- For each subject, the mean of all Hgb values during the Alt. EP (See Section 14.6.1), including any imputed and unscheduled Hgb values that were taken during this time period. This analysis will be conducted using all available (on and off treatment) Hgb values and separately using evaluable Hgb values only.
- Should the assessment dates for Hgb values from the Early Treatment Discontinuation visit fall within the Alt. EP, then these values will be included as unscheduled Hgb values. Hgb values from the Follow-up visit will not be included in the Alt. EP mean.

Use of Unscheduled Hemoglobin Values and Multiple Hgb Values on the Same Date

- The scenarios outlined below provide guidance on the use of unscheduled Hgb values and multiple Hgb values occurring on the same date. Each row represents a single calendar date.
- Rows outlining scenarios where there is at least one central lab Hgb and at least one HemoCue Hgb on the same date apply only for the derivation of Hgb values to be used in the primary Hgb analysis, where central lab values are used if they are available and if the central lab value is missing, then a corresponding non-missing HemoCue Hgb value is used.
- Rows outlining scenarios involving combinations of scheduled and unscheduled Hgb values of the same type apply to all Hgb summaries and analysis.

Scheduled Central Lab Hgb Value	Unscheduled Central Lab Hgb Value	Scheduled HemoCue Hgb Value	Unscheduled HemoCue Hgb Value	Value to Use	Type/Label
x				Scheduled central lab Hgb value	Scheduled visit
	x			Unscheduled central lab Hgb value	Unscheduled
		x		Scheduled HemoCue Hgb value	Scheduled visit
		multiple[1]		Average of scheduled HemoCue Hgb values	Scheduled visit
			x	Unscheduled HemoCue Hgb value	Unscheduled
	multiple			Average of unscheduled central lab Hgb values	Unscheduled

Hemoglobin Values

			multiple	Average of unscheduled HemoCue Hgb values	Unscheduled
x	x			Average of central lab Hgb values	Scheduled visit
x		x		Scheduled central lab Hgb value	Scheduled visit
x			x	Scheduled central lab Hgb value	Scheduled visit
	x	x		Unscheduled central lab Hgb value	Unscheduled
	x		x	Unscheduled central lab Hgb value	Unscheduled
		x	x	Average of HemoCue Hgb values	Scheduled visit

1: The dose adjustment algorithm will require sites to obtain two HemoCue Hgb values at some visits.

Time In Range

Time in Range During the EP

- Number of days that a subject's evaluable Hgb is within the analysis range of 10-11.5 g/dL inclusive during the EP (See Section 14.6.1), including any unscheduled evaluable Hgb values that were taken during this time period.
- Use of unscheduled Hgb values follows the scenarios for unscheduled and multiple Hgb values.
- Linear interpolation is used to estimate Hgb between visits, accounting for any intermittent missing values (Rosendaal, 1993).

Percent Time in Range During the EP

- Time in Range During the EP / [Earlier of (Treatment Stop Date+1, Week 52 visit date) – Week 28 visit date]
- Note: Percent time in/below/above range during the EP is only defined for subjects with a Treatment Stop Date that is after their Week 28 visit date, and have at least two evaluable Hgb values on different days, where at least one evaluable Hgb value is contained within the EP and another evaluable Hgb value occurs within the range of the Week 16 visit through 4 weeks following the Week 52 visit, inclusive.

14.6.3.2. Iron Endpoints

Iron Endpoints

Iron Medications

- During the study, subjects may be receiving iron in multiple routes, including:
  - IV iron
  - Oral iron
  - Other iron (including intramuscular, subcutaneous, and hemodialysis/dialysate)
- Note: The iron route categories above will be determined using the route on the Prior/Concomitant Medication – Iron Therapy record. In addition, ferric citrate records recorded on the Prior/Concomitant Medication – Metabolic Bone Disease Therapy eCRF form will also be summarized as oral iron use.

Iron Endpoints

Baseline Iron Use

- The number and percentage of subjects in the following iron use categories at baseline will be summarized:
    - IV iron use only
    - Oral iron use only
    - Other iron use only
    - IV and oral iron use only
    - IV and other iron use only
    - Oral and other iron use only
    - IV, oral, and other iron use
    - No iron use
- When determining baseline iron use, the gap factors mentioned below in the IV iron standardization algorithm will be applied to the end date for each iron record, and the baseline period of 12 weeks before the Randomization date until the day before the Randomization date will also be used.

Standardized IV Iron Dose (mg/week) to Determine Iron Management Action

- In order to compare between IV iron records, to determine the action taken with IV iron therapy in the 8 weeks following the date the IV management threshold was met, the dose of IV iron in each associated record will be standardized in terms of mg/month.
- IV iron therapy concomitant medication records that occur or are ongoing during the 8 weeks following the date the IV management threshold was met (inclusive), will be selected and ordered by start and end date.
    - If there is a record has a start date on the date the IV management threshold was met, and a prior record has an end date on the day before the IV management threshold was met, this prior record will be selected and considered as well.
- The standardization will be carried out with the following formula:
    - Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency

Note: Frequency defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)
2 times per week	2
3 times per week	3
4 times per week	4
5 times per week	5
BID	14
Once daily	7
One time dose	1
Every 12 Hours	14
Every 2 weeks	0.5
Every 4 weeks	0.25
Once a month	0.23
Once a week	1

Iron Endpoints			
	TID	21	

Standardized Baseline IV Iron Dose (mg/month)

- In order to calculate the baseline average monthly IV iron dose, the dose of IV iron will be standardized to obtain a continuous single unit IV iron dose in terms of mg/month for the period from 12 weeks before the Randomization date to the day before the Randomization date.
- IV iron therapy concomitant medication records that occur or are ongoing during the period from (the Randomization date – 12 weeks) to the day before the Randomization date will be selected and ordered by start and end date.
- The standardization will be carried out with the following formula:
    - Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency

Note: Frequency and Gap Factors defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)	Gap Factor
2 times per week	2	2.5 days
3 times per week	3	1.33 days
4 times per week	4	0.75 day
5 times per week	5	0.4 day
BID	14	0 days
Once daily	7	0 days
One time dose	1	n/a
Every 12 Hours	14	0 days
Every 2 weeks	0.5	13 days
Every 4 weeks	0.25	27 days
Once a month	0.23	29 days
Once a week	1	6 days
TID	21	0 days

- If the frequency of the record is not 'one time dose', then duration is calculated as follows:
    - If the concomitant medication record start date ≥ Randomization date, the duration of the record is 0.
    - If the concomitant medication record end date + gap factor < (Randomization date – 12 weeks), the duration of the record is 0.
    - If the concomitant medication record end date + gap factor ≥ (Randomization date – 12 weeks) or the record is ongoing, the duration of the record will be calculated as Stop Date – Start Date +1 day where:
        - Start date will be the latest of (concomitant medication record start date and the (the Randomization date – 12 weeks).
        - Stop date will be the earliest of (concomitant medication record stop date + gap factor and the day before randomization).
- If the frequency of the record is 'one time dose', then:

Iron Endpoints

- If concomitant medication record start date < Randomization date - 12 weeks, or if Randomization date ≤ concomitant medication record start date, then duration of the record is 0.
- If Randomization date -12 weeks ≤ concomitant medication record start date < Randomization date, then:
  - Frequency (for standardization formula) = 1
  - Duration = 7 days

- The total dose for each IV iron record will be: Standardized dose*duration/7 days
- A weighted mean will then be used to obtain the baseline monthly IV iron dose:
  Mean baseline monthly IV iron dose = [(IV iron total dose$_{\text{Record 1}}$) + ... + (IV iron total dose$_{\text{Record n}}$)]/ [(12* 7)/30.4375 days].

Standardized IV Iron Dose (mg/month) from Randomization to Week 52

- In order to calculate the average monthly IV iron dose from Randomization to Week 52, the dose of IV iron will be standardized to obtain a continuous single unit IV iron dose in terms of mg/month for the period from the Randomization date to the Week 52 visit date while the subject is on treatment.
  - Note: Subjects who are randomized but never treated will not have a value for average monthly IV iron from Randomization to Week 52.
- IV iron therapy concomitant medication records that occur or are ongoing during the period from the subject's (Randomization date – 12 weeks) to the Week 52 visit date will be selected and ordered by start date and end date.
- The standardization will be carried out with the following formula:
  - Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency

Note: Frequency and Gap Factors defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)	Gap Factor
2 times per week	2	2.5 days
3 times per week	3	1.33 days
4 times per week	4	0.75 day
5 times per week	5	0.4 day
BID	14	0 days
Once daily	7	0 days
One time dose	1	n/a
Every 12 Hours	14	0 days
Every 2 weeks	0.5	13 days
Every 4 weeks	0.25	27 days
Once a month	0.23	29 days
Once a week	1	6 days
TID	21	0 days

- If the frequency of the record is not 'one time dose', then duration is calculated as follows:

Iron Endpoints

- If the concomitant medication record start date > earliest of (treatment stop date + 1 and Week 52 visit date), the duration of the record is 0.
- If the concomitant medication record end date + gap factor < Randomization date, the duration of the record is 0.
- If the concomitant medication record end date + gap factor ≥ Randomization date or the record is ongoing, the duration of the record will be calculated as Stop Date – Start Date +1 day where:
  - Start date will be the latest of (concomitant medication record start date, randomization date, treatment start date).
  - Stop date will be the earliest of (concomitant medication record stop date + gap factor, treatment stop date + 1, and the Week 52 visit date).

- If the frequency of the record is 'one time dose', then:
  - If concomitant medication record start date < treatment start date, or if earliest of (treatment stop date + 1 and Week 52 visit date) < concomitant medication record start date, then duration of the record is 0.
  - If latest of (Randomization date, treatment start date) ≤ concomitant medication record start date ≤ earliest of (treatment stop date + 1 and Week 52 visit date), then:
    - Frequency (for standardization formula) = 1
    - Duration = 7 days
- The total dose for each IV iron record will be: Standardized dose*duration/7 days
- A weighted mean will then be used to obtain the monthly IV iron dose from Randomization to Week 52:

  Mean monthly IV iron dose from Randomization to Week 52 while on treatment = [(IV iron total dose$_{\text{Record 1}}$) + ... + (IV iron total dose$_{\text{Record n}}$)] / {[earliest of (treatment stop date + 1, Week 52 Visit Date) – treatment start date + 1] / 30.4375 days}.

Standardized Monthly IV Iron Dose (mg/month) from Week 28 to Week 52 (EP Average Monthly IV Iron Dose)

- In order to calculate the average monthly IV iron dose from Week 28 to Week 52, the dose of IV iron will be standardized to obtain a continuous single unit IV iron dose in terms of mg/month for the period from the Week 28 visit date to the Week 52 visit date while the subject is on treatment.
  - Note: Subjects who are randomized but never treated or who permanently discontinue study treatment on or before the Week 28 visit date will not have a value for average monthly IV iron from Week 28 to Week 52.
- IV iron therapy concomitant medication records that occur or are ongoing during the period from the subject's Week 24 visit date to the Week 52 visit date will be selected and ordered by start date and end date.
- The standardization will be carried out with the following formula:
  - Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency

Note: Frequency and Gap Factors defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)	Gap Factor

Iron Endpoints

2 times per week	2	2.5 days
3 times per week	3	1.33 days
4 times per week	4	0.75 day
5 times per week	5	0.4 day
BID	14	0 days
Once daily	7	0 days
One time dose	1	n/a
Every 12 Hours	14	0 days
Every 2 weeks	0.5	13 days
Every 4 weeks	0.25	27 days
Once a month	0.23	29 days
Once a week	1	6 days
TID	21	0 days

- If the frequency of the record is not 'one time dose', then duration is calculated as follows:
  - If the concomitant medication record start date > earliest of (treatment stop date + 1 and Week 52 visit date), the duration of the record is 0.
  - If the concomitant medication record end date + gap factor < Week 28 visit date, the duration of the record is 0.
  - If the concomitant medication record end date + gap factor ≥ Week 28 visit date or the record is ongoing, the duration of the record will be calculated as Stop Date – Start Date +1 day where:
    - Start date will be the latest of (concomitant medication record start date, and the Week 28 visit date).
    - Stop date will be the earliest of (concomitant medication record stop date + gap factor, treatment stop date + 1, and the Week 52 visit date).
- If the frequency of the record is 'one time dose', then:
  - If concomitant medication record start date < Week 28 visit date, or if earliest of (treatment stop date + 1 and Week 52 visit date) < concomitant medication record start date, then duration of the record is 0.
  - If Week 28 visit date ≤ concomitant medication record start date ≤ earliest of (treatment stop date + 1 and Week 52 visit date), then:
    - Frequency (for standardization formula) = 1
    - Duration = 7 days
- The total dose for each IV iron record will be: Standardized dose*duration/7 days
- A weighted mean will then be used to obtain the monthly IV iron dose from Week 28 to Week 52:

  Mean monthly IV iron dose from Week 28 to Week 52 while on treatment =
  [(IV iron total dose$_{\text{Record 1}}$) + ... + (IV iron total dose$_{\text{Record n}}$)] / {[earliest of (treatment stop date + 1, Week 52 Visit Date) – Week 28 Visit Date + 1]/30.4375 days}.

Iron Endpoints

Iron Use by Quarter

- The number and percentage of subjects in the following iron use categories defined by route will be summarized by quarters listed below for Average Quarterly IV Iron Dose:
    - IV iron use only
    - Oral iron use only
    - Other iron use only
    - IV and oral iron use only
    - IV and other iron use only
    - Oral and other iron use only
    - IV, oral, and other iron use
    - No iron use
- When determining iron use by quarter, the gap factors mentioned in the IV iron standardization algorithm will also be applied to the end date for each iron record.
- Baseline iron use will also be included in summaries of iron use by quarter.

Average Quarterly IV Iron Dose

- The standardized IV iron (mg/month) dose will be summarized by quarters, where quarters will be defined using study visits as follows:
    - Baseline
    - For summaries of on & off treatment IV iron dose:
        - Quarter 1 = [Randomization date – Week 12)
    - For summaries of on-treatment IV iron dose:
        - Quarter 1 = [Treatment start date + 1 – Week 12)
        - Quarter 2 = [Week 12 – Week 24)
        - Quarter 3 = [Week 24 – Week 36)
        - Etc.
- To determine the planned start date and end date of quarters, the visit end date (from the SV domain) will be used. If there is not a corresponding visit, or if the subject is missing that visit, the planned visit date (Randomization date + 7*x) will be used, where x is the scheduled week (e.g., Week 24, x = 24).
- A subject's quarterly average IV iron dose will end at the earliest of the following:
    - For summaries of on & off treatment IV iron dose: death date, study completion/withdrawal date, and the planned quarter end date.
    - For summaries of on-treatment IV iron dose: death date, study completion/withdrawal date, treatment stop date + 1, and the planned quarter end date.
- The standardization algorithm for IV iron described earlier in the table will be used to determine the standardized IV iron dose (mg/month) during each quarter.
- Standardized baseline IV iron dose will also be included in summaries of average quarterly IV iron dose.

Iron Endpoints
Reduction in IV Iron Supplementation
• A reduction in IV iron supplementation relative to baseline occurs when Baseline average monthly IV iron > EP average monthly IV iron, when both baseline IV iron and EP average monthly IV iron are non-missing.
TIBC
• TIBC will be calculated automatically by the central laboratory using: o TIBC = UIBC + total iron
TSAT
• TSAT will be calculated automatically by the central laboratory using: o TSAT = 100 * (Serum Iron/TIBC)
Average Quarterly TSAT and Ferritin
• The average TSAT and Ferritin values will be summarized by quarters, where quarters will be defined as they are for Average Quarterly IV Iron Dose, with the following exception: o Baseline average quarterly ferritin and TSAT will take the average of all available records before or on randomization ferritin and TSAT values. Note: any unscheduled values falling within these quarters will be used in the calculation of the quarterly average value.
Meeting Iron Management Criteria
Iron therapy will be administered if at any visit: • Ferritin ≤ 100 ng/mL and/or TSAT ≤ 20% All iron must be stopped if at any visit: • Ferritin > 800 ng/mL and TSAT >20%, or • TSAT > 40% Subjects meeting iron management criteria requiring starting and stopping of iron administration on the same day: • Ferritin <= 100 ng/mL and TSAT > 40%

14.6.3.3. Time to Rescue

Time to Stopping Study Treatment Due to Meeting Rescue Criteria
Meeting Rescue Evaluation Criteria and Rescue Criteria
• Subjects meeting evaluation criteria for rescue are identified from the Anemia Intervention and Rescue eCRF. Subjects with a record on this form are considered to have met evaluation criteria for rescue. It is possible that a subject could be evaluated for rescue more than once, and in that case a subject would have multiple records on this form. • Subjects unable to be evaluated for rescue are subjects who met evaluation criteria for rescue, but were unable to be assessed at the 4 week check (e.g., subjects who died, permanently discontinued study treatment or withdrew from the study before the 4 week check). The outcome of initial intervention eCRF field on the Anemia Intervention and Rescue eCRF will be blank for these subjects.

Time to Stopping Study Treatment Due to Meeting Rescue Criteria
• Subjects meeting rescue are identified by the response "If met rescue criteria, check all that apply" to the outcome of initial intervention question on the Anemia Intervention and Rescue eCRF.
Event Date
• Treatment stop date when the primary reason and subreason for study treatment stop are: o Primary reason: Subject reached protocol-defined stopping criteria o Subreason: Rescue
General Definitions
• Time to event (days) = date of event – randomization date +1 • Censored time (days) = censoring date – randomization date + 1
• Rescue person years = (cumulative total time to stopping study treatment for subjects who stopped study treatment due to meeting rescue criteria + cumulative total of censoring time for subjects who did not stop study treatment due to meeting rescue criteria) / 365.25 • Rescue incidence rate (per 100 person years) = (100 * number of subjects who stopped study treatment due to meeting rescue criteria) / rescue person years • Rescue absolute rate difference (per 100 person years) = daprodustat rescue incidence rate (per 100 person years) – rhEPO rescue incidence rate (per 100 person years)
Time Period for Treatment Discontinuation
The period for treatment discontinuation begins at randomization. The end of this time period is defined as follows: • For subjects who did not take study treatment, use the date of randomization • For subjects whose treatment stop date is missing and who took study treatment, use study conclusion date • For subjects either continuing on study past treatment stop date or completing/withdrawing on the same day as treatment stop date, use treatment stop date Any events that occurred before the start of this time period are considered to be prior to the time period for treatment discontinuation, and any endpoints that occurred after the end of this time period are considered to be post the time period for treatment discontinuation.

14.6.3.4. RBC and Whole Blood Transfusion Endpoints

Number of RBC and Whole Blood Transfusions
• The number of transfusions associated with each RBC and Whole Blood Transfusion record is determined by the frequency, start date, end date and number of units, as described below • Only on-treatment transfusions are included. "End date" below refers to the end date defined for the transfusion, or the end of the on-treatment period, if sooner (see Section 14.4.1.1). • For records with a frequency of "Once only" or "Continuous infusion", each record is considered to be a single transfusion (regardless of start and end dates or number of units) • For records with a frequency of "Once daily", the number of transfusions will equal the duration (end date – start date +1)

- For records with a frequency of "PRN", the number of transfusions for each record will be equal to the number of units recorded
- For other transfusion records, the number of transfusions will equal the duration (end date – start date +1) times a multiplier, as defined below. The number of transfusions should be rounded to nearest integer.

Frequency	Multiplier
QM	0.033
Every 2 weeks	0.071
Once a week	0.14
Q4D	0.25
2 times per week	0.29
Q3D	0.33
3 times per week	0.43
Every other day	0.5
4 times per week	0.57
5 times per week	0.71
BID	2
Q12H	2
TID	3
Q8H	3
QID	4
Q6H	4
5 times per day	5
Q4H	6

Number of RBC and Whole Blood Transfusion Events

- RBC and Whole Blood Transfusion Events are defined by grouping together on-treatment transfusion records
- Transfusion records are grouped into the same Transfusion Event if the transfusion start/end dates match with or are contained within an Admission/Discharge period, (based on the Hospitalization page in the eCRF). For example the following transfusion records would be grouped into a single Transfusion Event, because each transfusion is contained within the same hospital admission/discharge period:

Dose	Frequency	Transfusion Dates		Hospitalisation		Comment
		Start Date	End Date	Admission	Discharge	
1 unit	Once only	16FEB2019	16FEB2019	15FEB2019	26FEB2019	1 Transfusion Event
1 unit	Once only	19FEB2019	19FEB2019	15FEB2019	26FEB2019	

- Transfusion records not matching with an Admission/Discharge period are considered to be the same Transfusion Event if the gap between transfusions is 5 days or less, with further details provided below. For any subject where the frequency is PRN and the transfusion start date ≠

end date, the dates of individual transfusions are unknown and the number of transfusion events will be set to missing/unknown.

- In the case of a sequence of more than two transfusions, transfusions are considered to be the same Transfusion Event if the gap between each transfusion and the first transfusion in the sequence (the "anchor" transfusion) is 5 days or less. The first transfusion that is greater than 5 days after the "anchor" transfusion is not included in the Transfusion Event, and it becomes the new "anchor" transfusion for a new Transfusion Event.
- In the example below, transfusion records 1 and 2 would be grouped into a single Transfusion Event, because the gap between the transfusions (17JAN2019 to 18JAN2019) was 5 days or less. Record 3 falls outside this Transfusion Event because the gap between the start date (22JAN2019) and the previous anchor date (16JAN2019) is more than 5 days. Therefore 22JAN2019 becomes the new "anchor" transfusion used to define the next Transfusion Event. This pattern is repeated, if necessary. N.B. "anchor" transfusions are shown in bold.

#	Dose	Frequency	Transfusion Dates		Comment
			Start Date	End Date	
1	1 unit	Once only	**16JAN2019**	**16JAN2019**	1 Transfusion Event
2	1 unit	Once only	19JAN2019	19JAN2019	
3	1 unit	Once only	**22JAN2019**	**22JAN2019**	1 Transfusion Event
4	1 unit	Once only	25JAN2019	25JAN2019	
5	1 unit	Once only	**28JAN2019**	**28JAN2019**	1 Transfusion Event

Number of Units

- The number of RBC and whole blood units are derived from blood transfusion records. The number of units associated with each record is determined by the frequency, start date, end date and dose (i.e. number of units recorded), as described below.
- Only units associated with on-treatment transfusions are included. "End date" below refers to the end date defined for the transfusion, or the end of the on-treatment period, if sooner (see Section 14.4.1.1).
- For records with the frequency recorded as "Once only" or "Continuous infusion", the total number of units associated with each record is the number of units recorded (regardless of start and end dates)
- For records with the frequency recorded as "Once daily", the total number of units associated with each record will equal the number of units recorded multiplied by the duration (end date – start date +1)
- For records with the frequency recorded as "PRN", the total number of units will be equal to the number of units recorded (regardless of start and end dates)
- For other records, the number of units will equal to the number of units recorded multiplied by the duration (end date – start date +1) times a multiplier, as defined for Number of RBC and Whole Blood Transfusions above
- The table below provides multipliers for converting various reported units to Units (which should be rounded to nearest integer). For example, a transfusion of 450ml represents a single unit:
  (450 x 0.0025) = 1.125 (rounded to 1 Unit)

Reported Units	Multiplier
Units	1
Milliliters (ml or CC)	0.0025
Milligram (mg)	0.0025
Milligrams/millilitres (mg/ml)	0.0025

- Where a non-integer number of units has been entered on the eCRF, this will be rounded up to the nearest integer prior to any subsequent derivation (if necessary).

Evaluation Period (Weeks 28 to 52)

- Only transfusion events with a start date from date of week 28 visit to the date of the week 52 visit will be included
- Patient Years (PY) = (cumulative total time from date of week 28 visit to the date of the week 52 visit, for subjects who did not withdraw from study treatment during the evaluation period + cumulative time from date of week 28 visit to the date of withdrawal from study treatment, for subjects who withdrew from study treatment during the evaluation period) / 365.25
- Transfusion Events per 100 PY = (100 * number of on-treatment RBC or whole blood transfusion events during the evaluation period) / Patient Years (PY)
- Transfusions per 100 PY = (100 * number of on-treatment RBC or whole blood transfusions during the evaluation period) / Patient Years (PY)
- Units per 100 PY = (100 * number of on-treatment RBC or whole blood transfusion units during the evaluation period) / Patient Years (PY)

Randomization to Week 52

- Only transfusion events with a start date from the date of randomization to the date of the week 52 visit will be included
- Patient Years (PY) = (cumulative total time from date of randomization to the date of the week 52 visit, for subjects who did not withdraw from study treatment prior to week 52 + cumulative time from date of randomization to the date of withdrawal from study treatment, for subjects who withdrew from study treatment prior to week 52) / 365.25
- Transfusion Events per 100 PY = (100 * number of on-treatment RBC or whole blood transfusion events from the date of randomization to the date of the week 52 visit) / Patient Years (PY)
- Transfusions per 100 PY = (100 * number of on-treatment RBC or whole blood transfusions from the date of randomization to the date of the week 52 visit) / Patient Years (PY)
- Units per 100 PY = (100 * number of on-treatment RBC or whole blood transfusion units from the date of randomization to the date of the week 52 visit) / Patient Years (PY)

Time to First On-Treatment RBC or Whole Blood Transfusion

- Event Date = Start date for the first on-treatment RBC or whole blood transfusion received after treatment start date
- Censoring Date = date of stopping study treatment for subjects who stopped study treatment, or date of study completion for subjects who did not stop study treatment
- Time to event (days) = date of event – treatment start date +1
- Censored time (days) = censoring date – treatment start date + 1

- Person years (PY) = (cumulative total time to event date, for subjects who received at least one on-treatment RBC or whole blood transfusion + cumulative total of censoring time for subjects who did not receive at least one on-treatment RBC or whole blood transfusion) / 365.25
- Incidence rate per 100 PY = (100 * number of subjects who received at least one on-treatment RBC or whole blood transfusion) / person years
- Absolute rate difference (per 100 person years) = daprodustat incidence rate (per 100 person years) – rhEPO incidence rate (per 100 person years)

Time Period for On-Treatment Transfusions

The period for capturing on-treatment transfusions begins on the treatment start date. The end of this time period is defined as follows:

- For subjects whose treatment stop date is missing and who took study treatment, use date of study withdrawal/completion
- For subjects continuing on study past the treatment stop date, use (treatment stop date)
  For subjects whose study withdrawal/completion date is on or before (treatment stop date), use date of study withdrawal/completion

Model Specification

- Analysis of time to first RBC or whole blood transfusion will be performed using a Cox proportional hazards model adjusted for treatment and region.
- Analysis will include only transfusion occurring during the on-treatment period

Model Results Presentation

- The hazard ratio, two-sided 95% CI, and one-sided p-value for the superiority test will be presented for the comparison of daprodustat vs. rhEPO using the Cox Proportional Hazards model.
- Number and percentage of subjects who received at least one on-treatment RBC or whole blood transfusion and the number and percentage of censored subjects will be provided by treatment group. The incidence rate per 100 PY (95% CI) within each treatment group and the absolute rate difference per 100 PY (95% CI) will be displayed with the results of the Cox proportional hazards regression model. For within-group rates, the two-sided 95% CI will be obtained using an exact Poisson method. For difference in rates between treatments, the two-sided 95% CI will be constructed with a Normal approximation using Wald's method [Liu, 2006].
- A Kaplan-Meier plot will be produced showing the survival function for time to first RBC or whole blood transfusion.

14.6.3.5. Dose Adjustment Scheme Endpoints

Dose Adjustment Scheme Endpoints
General
• The IRT system assigns all study treatment doses in accordance with the dose adjustment scheme specified in the protocol. • During the study, it is possible for subjects to change study treatment doses at both scheduled and unscheduled visits. • Sites are instructed to complete an exposure record for every dose taken/planned.

Dose Adjustment Scheme Endpoints

Tablet Combinations to Achieve Prescribed Daprodustat or Placebo Treatment

Sites will enter the dose of daprodustat into exposure records. The dose steps of daprodustat are shown below:

Dosage Level [1] (mg)	Total Number of Tablets	Active Treatment for Daprodustat Randomized Participants						Inactive (Placebo) Treatment for Epoetin Alfa Randomized Participants	
		7 mm Placebo	2 mg Dapro	4 mg Dapro	6 mg Dapro	8 mg Dapro	10 mg Dapro	7mm Placebo	9 mm Placebo
0	1	1						1	
2	1		1					1	
4	1			1				1	
8	1					1			1
12	2				2				2
16	2					2			2
20	2						2		2
24	3					3			3
32	4					4			4
48	6					6			6

1. Dose to be administered three-times weekly

Number of Vials and Vial Combinations to Achieve Prescribed Epoetin Alfa or Saline Treatment

Sites will enter each dose of epoetin alfa into exposure records. The dose steps of epoetin alfa (including the corresponding total weekly doses) are shown below:

Total Weekly Dose (Units)	Dose and Frequency	Epoetin Alfa Randomized Participants [1,2]					Inactive (Saline) Treatment for Daprodustat Randomized Participants
		Saline [3] (1 mL)	2000 U/1mL	3000 U/1mL	4000 U/1mL	10000 U/1mL	Saline [3] (1 mL)
0	0 U once a week	1					1
1500 [4]	1500 U once a week		0.75				0.75
2000	2000 U once a week		1				1
3000	3000 U once a week			1			1
4000	4000 U once a week		2				2
5000	5000 U once a week		1	1			2
6000	6000 U once a week		1		1		2
8000	8000 U once a week				2		2
10,000	10,000 U once a week		1		2		3
12,000	4000 U three times a week				1		1
15,000	5000 U three times a week		1	1			2
18,000	6000 U three times a week		1		1		2
21,000	7000 U three times a week			1	1		2
24,000	8000 U three times a week				2		2
27,000	9000 U three times a week		1	1	1		3
30,000	10,000 U three times a week					1	1
36,000	12,000 U three times a week		1			1	2
42,000	14,000 U three times a week				1	1	2
48,000	16,000 U three times a week		1		1	1	3
60,000	20,000 U three times a week					2	2

1. The vial combinations used to achieve a specific weekly dose of epoetin alfa (and number of saline syringes for the corresponding inactive dose) may be adjusted by the sponsor based on changes to the commercial availability of epoetin alfa or other supply considerations. Any change to the vial combinations will be made globally across the study in order to maintain the blind, and it will be managed centrally through the IRT system. Details of any changes will be detailed in the SRM.
2. Each epoetin alfa vial should be administered using a separate syringe.

Dose Adjustment Scheme Endpoints
3. For saline doses, the number of 'vials' indicated in the table refers to the number of syringes containing 1 mL of saline that will be administered in order to maintain the blind. 4. The 1500 U epoetin alfa dose will be achieved by administering 0.75 mL of a 2000 U/mL vial. The corresponding 1500 U saline dose, for daprodustat randomized participants, will be achieved by administering 0.75 mL of saline.
Assigned Dose At A Scheduled Visit
• The assigned dose at a particular visit refers to the dose the subject assigned based on new IRT instruction received at that visit, as recorded in the eCRF. The assigned dose at Visit X is the dose from the earliest exposure record with a start date on or after the Visit X date, but before the Visit X+1 date. o For example, the assigned dose at the Week 28 visit is the dose from the earliest exposure record with a start date on or after the Week 28 visit date, but before the Week 32 visit date.
Most Recent Dose Prior to A Scheduled Visit / End of Treatment
• The most recent dose prior to a particular visit refers to the dose recorded in eCRF for the subject in the period directly preceding the visit. The most recent dose prior to Visit X is the dose from the latest exposure record with a start date that is on or after the Visit X-1 date and before the Visit X date. o For example, the most recent dose prior to Week 28 is the dose from the latest exposure record with a start date that is on or after the Week 24 visit date and before the Week 28 visit date. • If a subject permanently stops study treatment after Visit X-1 and on or before Visit X, the most recent dose prior to Visit X will be the dose from the subject's final exposure record.
Two Approaches to Dose Adjustment Summaries
• The first approach counts all dose adjustments, including dose adjustments related to periods of dose holds (i.e., IRT assignment of a 0-dose). • The second approach does not count dose adjustments related to periods of dose holds. However, should the dose that a subject receives following a period of dose hold be different from the dose the subject received before the dose hold, this would still count as a dose adjustment in this approach.
Number of Dose Adjustments per Year During Day 1 - < End of Treatment
• The number of dose adjustments per year will be determined by dividing the total number of dose adjustments between Day 1 and End of Treatment by [(Treatment Stop Date – Day 1 date + 1 day) / 365.25].

14.6.4. Safety

14.6.4.1. CV Safety Endpoints

CV Safety Endpoints
Dates for Investigator Reported CV Safety Endpoints
• All-cause hospitalization: admission date • All-cause hospital re-admission: admission date within 30 days following a discharge date • Death: date of death from the Death eCRF page

CV Safety Endpoints

- Myocardial infarction: date of onset of Myocardial Infarction/Unstable Angina symptoms from the MI/UA eCRF page
- Stroke: start date of neurological symptoms from the Stroke/TIA eCRF page
- Hospitalization for HF: Earliest of (ER admission date, Hospital admission date) from Heart Failure eCRF page
- Thromboembolic event: date of onset of thromboembolic event from the Thromboembolic Event eCRF page

Dates for Adjudicated CV Safety Endpoints

- Death: event date reported by CEC
- Myocardial infarction: event date reported by CEC
    - Fatal MI events only identified through a primary cause of death, without a corresponding positively adjudicated MI event: death event date reported by CEC
- Stroke: event date reported by CEC
    - Fatal stroke events only identified through a primary cause of death, without a corresponding positively adjudicated stroke event: death event date reported by CEC
- Hospitalization for HF: event date reported by CEC
    - Fatal heart failure/cardiogenic shock events only identified through a primary cause of death, without a corresponding heart failure event: death event date reported by CEC
- Thromboembolic event (DVT, PE, VAT): event date reported by CEC
    - Fatal PE events only identified through a primary cause of death, without a corresponding positively adjudicated PE event: death event date reported by CEC

Due to the design of the CRF, a fatal MI is reported as both an MI and a death. Both of these events will go through the adjudication process. It is possible that the MI could be negatively adjudicated, while the death is positively adjudicated with a primary cause of acute MI. The rationale for this is that the definition of a positively adjudicated MI (contained in the CEC charter) is more explicit than the definition of acute MI as a primary cause of death. Therefore, in analyses that include MI events without including all-cause mortality, the primary approach will be to include only those fatal MI events that correspond to a positively adjudicated MI event. These analyses will then be repeated for supportive purposes using all fatal MI events – including those fatal MI events only identified through a primary cause of death (i.e., acute MI) without a corresponding positively adjudicated MI event.

Additionally, a fatal MI event could have an event date that differs from the death date because the subject may have died as a result of the MI but not on the same day. For analysis of first occurrence MACE, MI or any other composite endpoint that includes both MI and death, if both the MI and death events are positively adjudicated, the MI date will be used as the event date. For analysis of CV mortality only and all-cause mortality only, the death date will be used.

Similarly, fatal stroke events are reported as both a stroke and a death. In analyses that include stroke events without including all-cause mortality, the primary approach will be to include only those fatal stroke events that correspond to a positively adjudicated stroke event. These analyses will be repeated for supportive purposes using all fatal stroke events – including those fatal stroke events only identified through a primary cause of death (i.e., stroke) without a corresponding positively adjudicated stroke event. For analysis of first occurrence MACE, stroke, or any other composite endpoint that includes stroke and death, if both the stroke and death events are positively adjudicated, the stroke date will be used as the event date. For analysis of CV mortality only and all-cause mortality, the death date will be used.

CV Safety Endpoints

Fatal heart failure events are reported as both a heart failure and a death. In analyses that include hospitalization for heart failure events without including all-cause mortality, a single approach which includes only those fatal hospitalization for heart failure events that correspond to a positively adjudicated hospitalization for heart failure event will be used. The definition of the hospitalization for heart failure endpoint includes requirements around hospitalization which are not captured in the associated primary cause of death (heart failure/cardiogenic shock), so identification of hospitalization for heart failure events through only a primary cause of death is not possible. However, supportive analyses of the hospitalization for heart failure endpoint may include all heart failure events. These supportive analyses would then be able to include fatal heart failure events from the death page (i.e. primary cause of death = heart failure/cardiogenic shock) that do not correspond to a positively adjudicated heart failure event. For analysis of hospitalization for heart failure or any composite endpoint that includes hospitalization for heart failure and death, if both the hospitalization for heart failure and death events are positively adjudicated, the hospitalization for heart failure date will be used as the event date. For analysis of CV mortality only and all-cause mortality, the death date will be used.

Fatal pulmonary embolism events are reported as both a pulmonary embolism and a death. In analyses that include pulmonary embolism events (i.e., thromboembolic events) without including all-cause mortality, the primary approach will be to include only those fatal pulmonary embolism events that correspond to a positively adjudicated pulmonary embolism event. These analyses may be repeated for supportive purposes using all pulmonary embolism events – including those fatal pulmonary embolism events only identified through a primary cause of death (i.e., pulmonary embolism) without a corresponding positively adjudicated pulmonary embolism event. For analysis of pulmonary embolism or any composite endpoint that includes pulmonary embolism and death, if both the pulmonary embolism and death events are positively adjudicated, the pulmonary embolism date will be used as the event date. For analysis of CV mortality only and all-cause mortality, the death date will be used.

In the situation that there is a fatal MI (or fatal stroke, hospitalization for heart failure, or pulmonary embolism) that does not have both an MI (or stroke, hospitalization for heart failure, or pulmonary embolism) endpoint and a death endpoint reported, the date of the event that is reported will be used in the analysis of all relevant endpoints. This would additionally apply to situations where the MI (or stroke, hospitalization for heart failure, or pulmonary embolism) may occur within an analysis period and the death may occur outside of the analysis period; the endpoint with the date in the analysis period will be used for all relevant endpoints.

Missing or Partial Endpoint Dates

- If event dates are missing or partial and there is not sufficient information to classify the time period of the event, the event will be classified as occurring on-treatment and post-randomization. The event will also be considered to have occurred during the follow-up for cardiovascular events as defined in Section 14.6.4.
- The following rules for missing or partial event dates for events other than death will be implemented as long as the imputed date is after the randomization date. If the imputed date is prior to the randomization date, then the date of randomization will be imputed for the event date.
    - If only the day of the month is missing, impute the first day of the month (e.g., --FEB2016 would impute as 01FEB2016)
    - If the month and day of the month are missing, impute 01JAN (e.g., -----2016 would impute as 01JAN2016)
    - If the year, month, and day of month are missing, impute the randomization date
- The following rules for missing or partial death dates will be implemented as long as the imputed date is after the randomization date. If the imputed date is prior to the randomization date, then the date of randomization will be imputed for the death date.
    - The latest clinic visit, telephone visit, other contact with subject visit, CV endpoint (other than death), AE or SAE date, or date last known to be alive will be determined. If the year,

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month, and day of month of the death are missing then the death date will be imputed as the latest of the dates.

- If only the day of the month of death is missing, then impute the first day of the month (e.g., --FEB2016 would impute as 01FEB2016). However, if this imputed date results in a date that is prior to the latest clinic visit, telephone visit, other contact with subject visit, CV endpoint (other than death), AE or SAE date, or date last known to be alive then impute the missing day of death as equal to this date instead. For example:
  - If –FEB2016 is given as the death date and there is a non-fatal MI on 08FEB2016, then the imputed date of death would be 08FEB2016 rather than 01FEB2016 such that the death is not before the non-fatal MI.
  - If –MAR2016 is given as the death date and the latest date is a non-fatal MI on 08FEB2016 then the imputed date of death would be 01MAR2016.
- If the month and day of the month of death are missing, then impute as 01JAN (e.g., -----2016 would impute as 01JAN2016). However, if this imputed date results in a date that is prior to the latest clinic visit, telephone visit, other contact with subject visit, CV endpoint (other than death), AE or SAE date, or date last known to be alive then impute the missing month and day of death as equal to this date instead. For example:
  - If -----2016 is given as the death date and the latest date is a non-fatal MI on 08FEB2016 then the imputed date of death would be 08FEB2016 rather than 01JAN2016 such that the death is not before the non-fatal MI.
  - If -----2017 is given as the death date and the latest date is a non-fatal MI on 08FEB2016 then the imputed date of death would be 01JAN2017.
- For deaths that occur after subjects have prematurely withdrawn from the study, missing or partial dates will be imputed as specified above except if the imputation places the death prior to or on the premature withdrawal date. In this case the death date will be imputed as the premature withdrawal date + 1 day.

Order of CV Safety Endpoint Events

- If multiple events occur on the same day or have imputed dates that place them on the same day, but it is not clear which event occurred first, then the following order will be applied:
  1. MI
  2. Stroke
  3. Hospitalization for Heart Failure
  4. Thromboembolic Event: DVT
  5. Thromboembolic Event: VAT
  6. Thromboembolic Event: PE
  7. Death

CV Mortality

- CV mortality includes all deaths indicated as having a cardiovascular primary cause of death (including fatal MI and fatal stroke events) as well as deaths with an undetermined primary cause of death that are indicated to be either presumed sudden death or presumed cardiovascular death. Deaths with an undetermined primary cause of death that are indicated to be an unknown death will not be included as a CV mortality event.

Heart Failure Events

- The primary heart failure event of interest in this study is hospitalization for heart failure. However, investigators are requested to report all potential heart failure events for adjudication, even if there was no hospitalization associated with the event.
- The CEC will categorize heart failure events into one of the following adjudicated event types:
  - Hospitalization for Heart Failure

CV Safety Endpoints

- Urgent ER/ED Visit for Heart Failure
- Urgent Office/Practice Visit for Heart Failure
- Negative adjudication (i.e., not one of the heart failure events above)

- For purposes of endpoints that contain hospitalization for heart failure as a component, only the events adjudicated by the CEC as Hospitalization for Heart Failure will be included.

Investigator-reported Endpoint Events for Concordance

- For purposes of concordance tables, events with an investigator-reported event date ≥ randomization date during the time period for follow-up of cardiovascular events, that meet the following final diagnosis criteria will be considered to be investigator-reported endpoint events:

Endpoint	Investigator-reported final diagnosis (from eCRF)
Myocardial infarction	Myocardial infarction
Stroke	Primary ischemic stroke (with or without hemorrhagic transformation), Primary intracranial hemorrhage, Retinal/ocular hemorrhage or infarction, Unknown type of stroke
Hospitalization for Heart Failure	Systolic heart failure, Diastolic heart failure, Heart failure - unspecified type Additional criteria: *If admission/discharge times are non-missing, at least one of the following must be true (1-3):* 1. Time in hospital is >=24 hours 2. Time in ED/ER is >=24 hours 3. Consecutive time in hospital + time in ED/ER is >=24 hours *Or if admission/discharge times are missing, then at least one of the following must be true (4-6):* 4. Change in calendar date between hospital admission and discharge 5. Change in calendar date between ED/ER admission and discharge 6. Change in calendar date between consecutive hospital and ED/ER admission and discharge
Thromboembolic Event (DVT, PE, VAT)	Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Vascular Access Thrombosis
All-cause mortality	Any death record
CV mortality	Any Cardiovascular primary cause of death
Non-CV mortality	Any Non-Cardiovascular primary cause of death
Unknown (sub-category of All-cause mortality)	Any Unknown primary cause of death

Events with an adjudication record, but without an investigator reported record, will also be included in the concordance summaries

All-cause Hospitalization

- All-cause hospitalization events are defined to be hospital admissions recorded on the Hospitalization eCRF form with a hospitalization duration ≥ 24 hours.

- Hospitalization rate (per year) across the study = number of all-cause hospitalization events / [follow-up time (days) / 365.25].

General Definitions

- Time to event (days) = date of event – randomization date +1
- Censored time (days) = censoring date – randomization date + 1

CV Safety Endpoints
• First event person years = (cumulative total time to first event for subjects who have the event + cumulative total of censoring time for subjects without the event) / 365.25 • First event incidence rate (per 100 person years) = (100 * number of subjects with at least 1 event) / first event person years • First event absolute rate difference (per 100 person years) = daprodustat incidence rate (per 100 person years) – rhEPO incidence rate (per 100 person years)

Evaluation Time Periods for CV Endpoints
Time Period for Follow-up of Cardiovascular Endpoints
The period for capturing CV safety endpoints begins at randomization. The end of this time period is the date of study completion/withdrawal, with the exception that if a death has been reported in the clinical database after this time, then the death will be included in the analysis. Any endpoints that occurred before the start of this time period are considered to be prior to the time period for follow-up of cardiovascular safety events, and any endpoints that occurred after the end of this time period are considered to be post the time period for follow-up of cardiovascular safety endpoints.
Time Period for Vital Status
The period for capturing vital status begins at the date of randomization. The end of this time period is defined as follows: • For all subjects known to have died, use the date of death • For all subjects who complete the study, use the study completion date (see Section 14.6.1) • For all subjects who withdraw from the study, but vital status has been ascertained, *and are known to have not died* – use the latest date last known to be alive. If vital status has not been ascertained following study withdrawal, use the study withdrawal date Any endpoints that occurred before the start of this time period are considered to be prior to the time period for vital status, and any endpoints that occurred after the end of this time period are considered to be post the time period for vital status.
Time Period for On-treatment Cardiovascular Endpoints
The period for capturing on-treatment CV safety endpoint events begins at the treatment start date. The end of this time period is defined as follows: • For subjects whose last non-zero dose date is missing and who took study treatment, use date of study withdrawal/completion • For subjects continuing on study past the last non-zero dose date +28 days, use (last non-zero dose date + 28) • For subjects whose study withdrawal/completion date is on or before (last non-zero dose date +28), use date of study withdrawal/completion If the censoring date as defined above for on-treatment CV safety endpoints is after the censoring date as defined for the analysis during the time period for follow-up of CV safety endpoints, then use the censoring date for the analysis during the time period for follow-up of cardiovascular endpoints.

Evaluation Time Periods for CV Endpoints
Any endpoints that occurred before the start of this time period are considered to be prior to the time period for on-treatment cardiovascular safety endpoints, and any endpoints that occurred after the end of this time period are considered to be post the time period for on-treatment cardiovascular safety endpoints.

14.6.4.2. Blood Pressure Endpoints

Blood Pressure Endpoints

Pre- and Post- Dialysis BP

- Unless otherwise specified, for summaries and analyses of BP values, the post-dialysis BP values will be used.

End of Treatment BP Value

- See Section 14.6.1

Mean Arterial Pressure (MAP)

- MAP = [(2*DBP)+SBP]/3

Blood Pressure Exacerbations

- BP exacerbations will be defined as (SBP ≥ 25 mmHg increase from baseline or SBP ≥ 180 mmHg or DBP ≥ 15 mmHg increase from baseline or DBP ≥ 110 mmHg) and grouped by type as follows:
    - BP exacerbations
        - SBP exacerbations
            - SBP ≥ 25 mmHg increase from baseline or
            - SBP ≥ 180 mmHg
                - SBP ≥ 180 mmHg and baseline SBP < 180 mmHg (including subjects with a missing baseline SBP)
                - SBP ≥ 180 mmHg and baseline SBP ≥ 180 mmHg
        - DBP exacerbations
            - DBP ≥ 15 mmHg increase from baseline or
            - DBP ≥ 110 mmHg
                - DBP ≥ 110 mmHg and baseline DBP < 110 mmHg (including subjects with a missing baseline DBP)
                - DBP ≥ 110 mmHg and baseline DBP ≥ 110 mmHg

Notes:

- BP values used to assess BP exacerbations must be on-treatment (see Section 14.4.1), unless otherwise specified.
- BP values used to assess BP exacerbations can be scheduled or unscheduled.
- For visits where BP is measured in triplicate, the average of the 3 BP values will be used to assess BP exacerbations.
- BP exacerbations identified using post-dialysis BP values will be used in summaries and analyses of BP exacerbations, unless otherwise specified.
- Subjects with multiple exacerbation events on the same calendar date for each type defined above are considered to have one exacerbation event for event counts by type. For example, a subject with a SBP and a DBP exacerbation on the same date would count in each of the SBP and DBP types, but would only count as one BP exacerbation event in the total BP exacerbation type.

Blood Pressure Endpoints
Blood Pressure Exacerbation Event Date
• Date of BP exacerbation
On-Treatment BP Medication
• See Section 14.4.1 for treatment states for concomitant medications.
General
• Censored time (days) = last non-zero dose date– treatment start date + 1
• BP exacerbation person years = (cumulative total of censoring time for all subjects) / 365.25 • BP exacerbation event incidence rate (per 100 person years) = (100 * number of BP exacerbations) / BP exacerbation person years
Changes in Blood Pressure Medications
• No change: no new anti-hypertensive records since baseline (day before study treatment start date) and no change to anti-hypertensive records from baseline until date of visit while on study treatment. • Increase: addition of new anti-hypertensive records for any reason or a change with a primary reason for changing dose/frequency or stopping of 'increased to…' since baseline until date of visit while on study treatment • Decrease: discontinuation of an anti-hypertensive record with primary reason for change starting with "discontinued" or a change with a reason of 'Decreased due to…' since baseline until date of visit while on study treatment • Switch = change with a reason of 'switched to another agent.' since baseline until date of visit while on study treatment
Cumulative Changes in Blood Pressure Medications
• For the summary of cumulative changes excluding "Once only" and "PRN" records, cumulative change will be counted from the date of first study treatment to the Week 52 visit date while on study treatment. If a new anti-hypertensive medication is added during this time, it will be counted as one change. If the medication also stops during this period, then it will count as two changes (one change due to starting, and one change due to stopping). The cumulative number of changes will be calculated by adding up the changes for all records during this time period. The same steps will be repeated for the period starting from the date of first study treatment to End of Treatment • For the summary of cumulative changes for "Once only" records only, cumulative change will be counted from the date of first study treatment to the Week 52 visit date while on study treatment. Since "Once only" doses will have same start and stop dates, a new anti-hypertensive medication record during this period will be counted as one change. As "once only" doses are likely administered to control BP during dialysis, so they are considered part of a single titration regimen, hence multiple "once only" records on the same date will be counted as one change. The same steps will be repeated for the period starting from the date of first study treatment to End of Treatment

14.6.4.3. Adverse Events

Adverse Events
AEs of Special Interest
Adverse events of special interest are classified as follows:

Adverse Events
• Death, myocardial infarction (MI), stroke, heart failure, thromboembolic events, thrombosis of vascular access • Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis • Cardiomyopathy • Pulmonary artery hypertension • Cancer-related mortality and tumor progression and recurrence • Esophageal and gastric erosions • Proliferative retinopathy, macular edema, choroidal neovascularization • Exacerbation of rheumatoid arthritis • Worsening of hypertension Potential AESIs will be identified through a pre-defined terms of interest process in which pre-defined lists of AE preferred terms corresponding with each AESI will be used to identify events considered to be potential AESIs. Sites will be prompted via query to complete any necessary additional information for these AESIs in the eCRF. For the category of thrombosis and/or tissue ischemia secondary to excessive erythropoiesis, after the terms of interest list has been applied, the additional Hgb criteria described below will be applied to identify only those events that are considered to be secondary to excessive erythropoiesis as meeting the AESI definition for thrombosis and/or tissue ischemia secondary to excessive erythropoiesis.
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 (measured pre-dialysis) • Hgb increase > 2 g/dL over 2 weeks (+1 week) o Note: for programming purposes, a +1 week window is applied, corresponding to the allowable visit window, to look for increases > 2 g/dL over 3 weeks • Hgb increase > 4 g/dL over 4 weeks (+1 week) o Note: for programming purposes, a +1 week window is applied, corresponding to the allowable visit window, to look for increases > 4 g/dL over 5 weeks. To identify Hgb increases that meet the increase criterion above, all Hgb values taken within [AE start date – 58 days, AE start date + 15 days] will be identified. This corresponds to identifying Hgb values that occurred 4 weeks before the [AE start date – 30 days, AE start date +15 days] window of interest. HemoCue Hgb and

Adverse Events

central laboratory Hgb values will then be evaluated separately to identify increases, so that HemoCue and central laboratory Hgb values are not compared to each other to identify an increase.

For HemoCue Hgb and separately for central laboratory Hgb values, if there is a Hgb value (or daily Hgb average) within the [AE start date – 30 days, AE start date +15 days] window and an earlier Hgb value (or daily Hgb average) that is within the larger [AE start date – 58 days, AE start date + 15 days] window, and the amount of time between the two Hgb values is:

- Between 1 day and 3 weeks, inclusive, then the Hgb values will be compared to determine if there has been a Hgb increase > 2g/dL.
- Between 15 days and 5 weeks, inclusive, then the Hgb values will be compared to determine if there has been a Hgb increase > 4g/dL.

Unscheduled Hgb values will also be used in the assessment of secondary to excessive erythropoiesis following the guidance specified in Section 14.6.3 for unscheduled Hgb values and multiple Hgb values on the same date.

Pre-defined Lists of AE Preferred Terms Corresponding with Each AESI

Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis

- Narrow SMQ: Embolic and thrombotic events, arterial
- Narrow SMQ: Embolic and thrombotic events, venous
- Narrow SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous
- Broad SMQ: Thrombophlebitis
- Additional Preferred Terms:
  - Vascular access site occlusion
  - Vascular access site complication
  - Retinal vascular occlusion
  - Administration site ischaemia
  - Anterior segment ischaemia
  - Application site ischaemia
  - Biliary ischaemia
  - Bone marrow ischaemia
  - Brain stem ischaemia
  - Catheter site ischaemia
  - Cerebellar ischaemia
  - Cerebral ischaemia
  - ECG signs of myocardial ischaemia
  - Gastrointestinal ischaemia
  - Graft ischaemia
  - Hepatic ischaemia
  - Implant site ischaemia
  - Infusion site ischaemia
  - Injection site ischaemia
  - Intestinal ischaemia
  - Ischaemia
  - Macular ischaemia
  - Medical device site ischaemia
  - Myocardial ischaemia
  - Stoma site ischaemia
  - Subendocardial ischaemia
  - Uterine ischaemia
  - Vaccination site ischaemia
  - Vestibular ischaemia
  - Cerebral small vessel ischaemic disease
  - Colitis ischaemic
  - Delayed ischaemic neurological deficit
  - Hypoxic-ischeaemic encephalopathy
  - Ischaemic cardiomyopathy
  - Ischaemic cerebral infarction
  - Ischaemic contracture of the left ventricle
  - Ischaemic enteritis
  - Ischaemic gastritis
  - Ischaemic heart disease prophylaxis
  - Ischaemic hepatitis
  - Ischaemic limb pain
  - Ischaemic mitral regurgitation
  - Ischaemic nephropathy
  - Ischaemic neuropathy
  - Ischaemic pancreatitis
  - Ischaemic skin ulcer
  - Ischaemic stroke
  - Necrosis ischaemic

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- Peripheral ischaemia
- Renal ischaemia
- Retinal ischaemia
- Spinal cord ischaemia
- Ocular ischaemic syndrome
- Optic ischaemic neuropathy
- Reversible ischaemic neurological deficit
- Transient ischaemic attack

Cardiomyopathy

- Narrow SMQ: Cardiomyopathy

Pulmonary artery hypertension

- High Level Term: Pulmonary hypertensions
- Additional Preferred Terms:
  - Right ventricular dilatation
  - Right ventricular dysfunction
  - Right ventricular ejection fraction decreased
  - Right ventricular enlargement
  - Right ventricular failure
  - Right ventricular hypertrophy

Cancer-related mortality and tumor progression and recurrence

- Narrow SMQs:
  - Biliary malignant tumours
  - Biliary tumours of unspecified malignancy
  - Breast malignant tumours
  - Breast tumours of unspecified malignancy
  - Liver malignant tumours
  - Liver tumours of unspecified malignancy
  - Malignancy related conditions
  - Haematological malignant tumours
  - Non-haematolgoical malignant tumours
  - Haematological tumours of unspecified malignancy
  - Non-haematological tumours of unspecified malignancy
  - Malignant lymphomas
  - Myelodysplastic syndrome
  - Oropharyngeal neoplasms
  - Ovarian malignant tumours
  - Ovarian tumours of unspecified malignancy
  - Prostate malignant tumours
  - Prostate tumours of unspecified malignancy
  - Tumour lysis syndrome
  - Skin malignant tumours
  - Skin tumours of unspecified malignancy
  - Uterine and fallopian tube malignant tumours
  - Uterine and fallopian tube tumours of unspecified malignancy
- Additional Preferred Terms:
  - Aplastic anaemia
  - Cytopenia
  - Pancytopenia
  - Aplasia pure red cell

Esophageal and gastric erosions

- High Level Terms:
  - Duodenal ulcers and perforation
  - Gastric ulcers and perforation
  - Gastrointestinal ulcers and perforation, site unspecified
  - Oesophageal ulcers and perforation
  - Peptic ulcers and perforation
- Additional Preferred Terms:
  - Haematemesis
  - Gastrointestinal haemorrhage
  - Upper gastrointestinal haemorrhage
  - Helicobacter duodenitis
  - Helicobacter gastritis
  - Melaena

Adverse Events

Proliferative retinopathy, macular edema, choroidal neovascularization

- Broad SMQ: Retinal disorders

Exacerbation of rheumatoid arthritis

- High Level Term: Rheumatoid arthropathies
- Additional Preferred Terms:
  - Rheumatoid factor increased
  - Rheumatoid factor positive
  - Rheumatoid factor quantatative increased

Worsening of hypertension

- Narrow SMQ: Hypertension

Blood Pressure Events

BP events will be identified during the study via programmatic sweeps of AE and SAE terms entered into the eCRF (using the narrow SMQ for hypertension). AEs identified this way will require an additional BP Exacerbation eCRF page to be completed that characterizes the event as clinically significant and/or symptomatic.

In addition, subjects that experience BP values that meet the following criteria at any visit will also be considered to have a BP event and be required to complete the Blood Pressure Exacerbation eCRF page:

- SBP: an increase from baseline of $\geq$ 25 mmHg or SBP $\geq$ 180 mmHg
- DBP: an increase from baseline of $\geq$ 15 mmHg or DBP $\geq$ 110 mmHg

BP-related SAEs are those SAEs that have been identified via the BP Exacerbation eCRF page.

General Definitions

- Post-Randomization last contact date for censoring (subjects not having AE) will be defined as the study completion date.
- Treatment emergent last contact date for censoring (subjects not having AE) will be defined as follows:
  - 1 day after the last non-zero dose date (last non-zero dose date + 1) for subjects not having treatment emergent AE and continuing on study past (last non-zero dose date + 1)
  - Last non-zero dose date for all other subjects
- AE Patient Years: (Cumulative total of time to AE for subjects who have the AE + Cumulative total of censoring time for subjects without the AE) / 365.25
  - For treatment emergent AEs, the start date of the patient years value for each subject should be the treatment start date.

Adverse Events
○ For post-randomization AEs, the start date of the patient years value for each subject should be the randomization date. ○ For follow-up AEs, the start date of the patient years value for each subject should be two days after the last non-zero dose date (last non-zero dose date + 2).
• Incidence Rate (per 100 patient years): (100 * Number of subjects with at least 1 AE) / AE person years
• For the analysis of the time to AE onset/worsening, if the AE onset/worsening date is missing then the time to AE onset/worsening will be counted as 1 day.

14.6.4.4. Laboratory Parameters

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. ○ 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
• If there is more than one laboratory value on the same date for the same laboratory test, then the laboratory values associated with scheduled visits will be used. Hgb summaries and analyses are an exception and should use the data handling conventions outlined in Section 14.6.3.
• For purposes of flagging worst-case post baseline laboratory values: ○ If there are multiple scheduled values on the same day, or only multiple unscheduled values on the same day, then the average of the values on that day should be used for the purpose of determining the worst-case value.
• The following will be used to convert laboratory values from SI units to conventional units [Iverson, 2007]: • MCHC and Albumin: Divide the g/L value by 10 to get the g/dL value. • Albumin-corrected calcium: Divide the mmol/L value by 0.25 to get the mg/dL value. • Phosphate: Divide the mmol/L value by 0.323 to get the mg/dL value. • BUN: Divide the mmol/L value by 0.357 to get the mg/dL value. • Total cholesterol, LDL-C and HDL-C: Divide the mmol/L value by 0.0259 to get the mg/dL value.
Normal Range Categories, PCI Criteria Categories and Worst Case Values
• Normal range categories are: To Low, To Normal or No Change, To High • PCI criteria categories are: To Low, To w/in Range or No Change, To High • Subjects with a missing baseline value are to be assumed to have a normal/within range baseline value. • The determination of the worst case post baseline value takes into account both planned and unscheduled assessments. • Worst case can be either High or Low. ○ If a subject has both a decrease 'To Low' and an increase 'To High', then the subject is counted in both the 'To Low' and 'To High' categories.

Laboratory Parameters
○ If a subject was High at baseline and decreases to Low during the time interval, then the subject is counted in the 'To Low' category. Likewise, if a subject was low at baseline and increases to high during the time interval, then the subject is counted in the 'To High' category. ○ Subjects are only counted in the 'To Normal or No Change' or 'To w/in Range or No Change' category if their values are: ▪ When using normal ranges: Normal at baseline and have no high and no low values; When using PCI ranges: Within range at baseline and have no high and no low values ▪ High at baseline and do not change to low ▪ Low at baseline and do not change to high

14.6.4.5. Vital Signs

Vital Signs
Pre- and Post- Dialysis HR & Weight
• Both pre- and post- dialysis HR & weight values will be measured • Unless otherwise specified, for summaries of HR & weight values, the post-dialysis HR & weight values will be used.
• If there is more than one vital sign value on the same date for the same vital sign value, then the vital sign values associated with scheduled visits will be used. • If there are multiple values from a scheduled visit on the same date (e.g., BP is collected in triplicate at some visits), then the average of the scheduled values will be used.
• For purposes of flagging worst-case post baseline vital sign values: ○ If there are multiple scheduled values on the same day, or only multiple unscheduled values on the same day, then the average of the values on that day should be used for the purpose of determining the worst-case value.

14.6.4.6. COVID-19

COVID-19
Exposure Duration
• For subjects who DO NOT experience the event, the exposure duration is calculated as: (treatment stop date or end date of time block, whichever occurs sooner – treatment start date or start date of time block, whichever occurs later + 1)/365.25 • For subjects who DO experience the event, the exposure duration is calculated as: (start date of AE – treatment start date or start date of time block, whichever occurs later + 1)/365.25
Exposure Adjusted Incidence Rate
• Exposure adjusted incidence rate (rate/100 PY) = (number of subjects with the adverse event during the time block / total exposure duration across all subjects) * 100
Time Periods
• Pre COVID-19 pandemic period: the date of interests is prior to the country specific start date of COVID-19 pandemic measures. For example, for recruitment and demographic summaries, pre

COVID-19
COVID-19 period is defined as the randomization date of the subject is prior to the country specific start date of COVID-19 pandemic measures. • During COVID-19 pandemic period: the date of interests is after the country specific start date of COVID-19 pandemic measures. For example, for recruitment and demographic summaries, during COVID-19 period is defined as the randomization date of the subject is after the country specific start date of COVID-19 pandemic measures. • There is currently no post COVID-19 period.

14.6.5. Pharmacokinetic

Daprodustat, M2, M3, M4, M5, M6, M13	
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
Ctrough	Post-baseline sample pre-dose concentration
Cmax	Maximum observed concentration of all five post-baseline PK samples, determined directly from the concentration-time data.

14.6.6. Pharmacodynamic (and / or Biomarker)

Pharmacokinetic Parameters
• Maximum observed change from baseline in EPO • Maximum observed % change from baseline in VEGF

14.6.7. Patient Reported Outcomes

PGI-S
General
• The PGI-S is a 1-item questionnaire designed to assess a subject's impression of disease severity on a 5-point disease severity scale (absent, mild, moderate, severe, or very severe). • Scores range from [redacted] as follows: ○ [redacted]

PGI-C
General
• The PGI-C is a 1-item questionnaire designed to assess a subject's impression of change in their anemia of CKD on a 7-point Likert-type response scale (very much improved, moderately improved, minimally improved, no change, minimally worse, moderately worse, or very much worse).

PGI-C
General
• Scores range from [redacted] to [redacted] as follows: ○ CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. ○ ○ ○ ○ ○ ○

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

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completing all study periods of the study through the Week 52 visit, with the following exception: A participant who dies while on study is also considered to have completed the study. • Withdrawn subjects will not be replaced in the study. • All available data from participants 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. • Per protocol, subjects may prematurely discontinue study drug but are encouraged to remain in the study.

14.7.2. 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: ○ 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. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, 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. • The recorded partial date will be displayed in listings.
CV Safety Endpoint Events	Discussed in Section 14.6.4

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. Laboratory Values

Clinical Chemistry			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
Albumin	g/L	< 30 g/L	> 55 g/L
Aspartate Aminotransferase	IU/L		≥ 3x ULRR
Alanine Aminotransferase	IU/L		≥ 3x ULRR
Bilirubin (total)	μmol/L		≥ 2x ULRR
Calcium (albumin-corrected)	mmol/L	< 1.87 mmol/L	> 2.56 mmol/L
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

Hematology			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
Platelet Count	GI/L	< 80 GI/L	> 500 GI/L
Leukocytes (white blood cell count)	GI/L	< LLRR	> 5x ULRR
Neutrophils	GI/L	< 0.5x LLRR	
Lymphocytes	GI/L	< 0.5x LLRR	

Iron Parameters			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
Ferritin	ng/mL	< 100 ng/mL	> 800 ng/mL
TSAT	%	<15%	> 40%

Other PCI Values			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
iPTH	ng/L		> 9x ULRR

14.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	<300 ms	>500 ms
Absolute PR Interval	msec	<130 ms	>250 ms
Absolute QRS Interval	msec		>150 ms
Change from Baseline			
Increase from Baseline QTc	msec		>60 ms

14.8.3. 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	bpm	≤ 40 bpm	≥ 110 bpm

Notes:

- At visits where BP and HR are assessed in triplicate, the average of the 3 values will be used to assess PCI criteria.
- The post-dialysis BP and HR values will be used to assess PCI criteria, unless otherwise specified.

14.9. Appendix 9: Abbreviations & Trade Marks

14.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
Alt EP	Alternative Evaluation Period
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice a Day
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CEC	Clinical Endpoint Committee
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIF	Cumulative Incidence Function
CKD	Chronic Kidney Disease
COVID	Corona Virus Disease
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CV	Cardiovascular, Coefficient of Variation
DBF	Database Freeze
DBP	Diastolic Blood Pressure
DBR	Database Release
DP	Decimal Places
DVT	Deep Vein Thrombosis (DVT)
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EDW	Estimated Dry Weight
EP	Evaluation Period
EPO	Erythropoietin
ERI	Erythropoietin Resistance Index
ESA	Erythropoiesis Stimulating Agent
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HbA1c	Hemoglobin A1c
HD	Hemodialysis
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure

Abbreviation	Description
Hgb	Hemoglobin
HR	Heart Rate
hsCRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IG	Implementation Guide
IP	Investigational Product
iPTH	Intact Parathyroid Hormone
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IV	Intravenous
LDL-C	Low Density Lipoprotein Cholesterol
LLRR	Lower Limit of Reference Range
LS	Least Squares
MACE	Major Adverse Cardiovascular Event
MAP	Mean Arterial Pressure
MAR	Missing at Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PE	Pulmonary Embolism
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PP	Per Protocol
PPD	Pharmaceutical Product Development
PRN	As Needed
PRO	Patient Reported Outcome
PT	Preferred Term
PY	Patient Years
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
RTF	Rich Text Format
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure

Abbreviation	Description
SC	Subcutaneous
SDAC	Statistical Data Analysis Center
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	System Independent
SMQ	Standard MedDRA Query
SOC	System Organ Class
SP	Stabilization Period
SRT	Safety Review Team
TFL	Tables, Figures & Listings
TIBC	Total Iron Binding Capacity
TID	Three Times A Day
TSAT	Transferrin Saturation
UIBC	unsaturated iron binding capacity
ULN	Upper Limit of Normal
ULRR	Upper Limit of Reference Range
US	United States
VAT	Vascular Access Thrombosis
VEGF	Vascular Endothelial Growth Factor
WK	Week

14.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

14.10. Appendix 10: List of Data Displays

14.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.001 to 1.00n	1.001 to 1.00n
Efficacy	2.001 to 2.00n	2.001 to 2.00n
Safety	3.001 to 3.00n	3.001 to 3.00n
Patient Reported Outcome	4.001 to 4.00n	4.001 to 4.00n
Pharmacokinetic	5.001 to 5.00n	5.001 to 5.00n
Pharmacodynamic	6.001 to 6.00n	6.001 to 6.00n
Section	**ICH Listings**	**Non-ICH Listing**
Study Population	1.001 to 1.00n	1.00n+1 to 1.00x
Efficacy	2.001 to 2.00n	2.00n+1 to 2.00x
Safety	3.001 to 3.00n	3.001+1 to 3.00x
Patient Reported Outcome	4.001 to 4.00n	4.00n+1 to 4.00x
Pharmacokinetic	5.001 to 5.00n	5.00n+1 to 5.00x
Pharmacodynamic	6.001 to 6.00n	6.00n+1 to 6.00x

14.10.2. Mock Example Shell Referencing

Example mock shells for data displays are developed as a separate document.

Unless otherwise specified in the IDSL/Example Shell or Programming Notes' column, TFL shell name will follow the format shown below:

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
Pharmacodynamic	PD_Fn	PD_Tn	PD_Ln

14.10.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

14.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.001	All Randomized (ITT)	POP_T5	Summary of Subject Status and Reasons for Study Withdrawal	Reasons for withdrawal will be presented in the order they are displayed on the eCRF Outcome of Adverse Events Which Led to Study Withdrawal is determined by first identifying the subjects with reason for study withdrawal as adverse event in the disposition records. For those subjects, the adverse event records for each subject are checked to see if any of the adverse events that lead to withdrawal from study were fatal in the adverse event records. If any of the records are fatal then the subject will be counted in the fatal category in the display.	SAC
1.002	All Randomized (ITT)	POP_T5	Summary of Subject Status and Reasons for Study Withdrawal by Region		SAC
1.003	All Randomized (ITT)	POP_T5	Summary of Subject Status and Reasons for Study Withdrawal by Country		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.004	All Randomized (ITT)	POP_T6	Summary of Study Treatment Status and Reasons for Discontinuation of Study Treatment	Regarding "Treatment Discontinuation Related to Study Treatment/Primary Reason" see IDSL Subject Disposition core standard section 1.1.3 for how to summarize those primary reasons for IP discontinuation that were related to the treatment. Note: For the primary reason of Adverse Event, the relatedness to study treatment is not collected and is instead to be determined from the adverse event records. Deaths with death date > Treatment End Date + 3 Days are considered "Did Not Die While Taking Study Treatment". Deaths with death date ≤ Treatment End Date + 3 Days are considered "Died While Taking Study Treatment"	SAC
1.005	All Randomized (ITT)	POP_T6	Summary of Study Treatment Status and Reasons for Discontinuation of Study Treatment by Region		SAC
1.006	All Randomized (ITT)	POP_T6	Summary of Study Treatment Status and Reasons for Discontinuation of Study Treatment by Country		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.007	Screened	POP_T2	Summary of Screening Status and Reasons for Screen Failure	Reason(s) for Failure: see eCRF SCREEN FAILURE form. Note that the reasons for rescreened subjects who initially failed but subsequently enrolled are not included in the display. A subject may have more than one reason for screen failure. Since screen failures are not assigned to treatment groups, the display has only one subject-group column Used with Summary of Study Populations and Summary of Subject Disposition to create Consort diagram.	SAC
1.008	Screened	POP_T2.1	Summary of All Screening Attempts and Associated Reasons for Screen Failure		SAC
1.009	Enrolled	POP_T8	Summary of Number of Subject by Region, Country and Site ID	Sort regions in RAP order, sort countries alphabetically, sort centers by decreasing total frequency (if ties, sort alphabetically by investigator)	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.010	All Randomized (ITT)	POP_T9	Summary of Subject Contact at Week 52		SAC
1.011	All Randomized (ITT)	POP_T14	Summary of Subject Survival Status		SAC
Protocol Deviation					
1.012	All Randomized (ITT)	POP_T15	Summary of Important Protocol Deviations		SAC
1.013	All Randomized (ITT)	POP_T30	Summary of Inclusion/Exclusion Criteria Deviations		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Population Analysed					
1.014	Screened	POP_T1	Summary of Study Populations	Include all study population defined in the RAP The footnote should match the population definitions in the RAP The column 'No Treatment' is included if there are any subjects that did not get assigned a treatment, e.g., subjects who were screened but did not get enrolled into the study which includes both screening failures and subjects that were not used, enrolled subjects that did not get randomized or assigned treatment, a subject passed screening but withdrew consent prior to randomization.	SAC
1.015	All Randomized (ITT)	POP_T3	Summary of Exclusions from the Per Protocol Population	"Reason for Exclusion": see RAP Section 14.1.1	SAC
1.016	All Randomized (ITT)	POP_T4	Summary of Exclusions from the Safety Population		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
1.017	All Randomized (ITT)	POP_T16	Summary of Demographic and Baseline Characteristics for the All Randomized (ITT) Population	Mode of Dialysis at Screening: Although only Hemodialysis is expected at screening, other dialysis modes, such as peritoneal dialysis (PD), should be added and displayed here if captured in the eCRF at screening.	SAC
1.018	All Randomized (ITT)	POP_T16	Summary of Demographic Characteristics among Subjects Who are Hyporesponders	Remove the Alternate Definitions of rhEPO hypo-responsiveness section from this table	SAC
1.019	Safety	POP_T16	Summary of Demographic and Baseline Characteristics for the Safety Population		SAC
1.020	Enrolled	POP_T17	Summary of Age Ranges	The column 'No Treatment' is included if there are any subjects that did not get assigned a treatment, e.g. a subject passed screening but withdrew consent prior to randomization	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.021	All Randomized (ITT)	POP_T18	Summary of Race and Racial Combinations	All five of the high level race categories and the two Asian subcategories must be appear on the display even if there are no subjects in a particular category, but combinations that do not exist in the data do not need to be represented. A subject will only be represented in a single category. A subject who selects a combination of races will be counted in a row within "MIXED RACE" or within the "MIXED ASIAN RACE", not in each of the constituent terms. Therefore, the counts will add up to the total number of subjects with a response, and the percentages will add to 100%.	SAC
1.022	All Randomized (ITT)	POP_T19	Summary of Smoking History		SAC
1.023	All Randomized (ITT)	POP_T21	Summary of Dialysis Modality and Frequency at Baseline, Week 28 and Week 52		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.024	All Randomized (ITT)	POP_T22	Summary of Dialysis Modality Changes		SAC
Prior and Concomitant Medications					
1.025	All Randomized (ITT)	POP_T20	Summary of Medical Conditions	.	SAC
1.026	All Randomized (ITT)	POP_T24	Summary of Pre-treatment Medications by ATC Level and Ingredient	Medications will be sorted in descending order of total incidence across treatment groups for the ATC level 1 and in descending order of total incidence for the ingredient within each ATC level. If the total incidence for any two or more ingredients is equal, the events will be presented in alphabetical order.	SAC
1.027	All Randomized (ITT)	POP_T24	Summary of On-treatment Medications by ATC Level and Ingredient	See above	SAC
1.028	All Randomized (ITT)	POP_T24	Summary of Post-treatment Medications by ATC Level and Ingredient	See above	SAC
1.029	Safety	POP_T25	Summary of On-treatment Non-randomized ESA Use Instead of Study Treatment	Based on the corresponding "Reason for Medication" in CONCOMITANT MEDICATIONS – rhEPO form	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.030	Safety	POP_T25	Summary of On-treatment Non-randomized ESA Use in Addition to Study Treatment	Based on the corresponding "Reason for Medication" in CONCOMITANT MEDICATIONS – rhEPO form	SAC
Exposure and Treatment Compliance					
1.031	Safety	POP_T26	Summary of Extent of Exposure to Study Treatment		SAC
1.032	Safety	POP_T27	Summary of Study Treatment Compliance Categories		SAC
1.033	Safety	POP_T28	Summary of Study Treatment Compliance		SAC
COVID-19 Related Tables					
1.034	All Randomized (ITT)	COVID19 Shell 6.1	Summary of Subject Status and Reasons for Study Withdrawal by Relationship to COVID-19 Pandemic		SAC
1.035	All Randomized (ITT)	COVID19 Shell 6.2	Summary of Study Treatment Status and Reasons for Discontinuation of Study Treatment by Relationship to COVID-19 Pandemic		SAC
1.036	All Randomized (ITT)	COVID19 Shell 6.5	Summary of Significant Protocol Deviations by Relationship to COVID-19 Pandemic		SAC
1.037	All Randomized (ITT)	PAN 4	Summary of Visits Impacted by COVID-19 Pandemic		SAC

14.10.5. Study Population Figures

Study Population: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.001	All Randomized (ITT)	POP_F1.1	Kaplan-Meier Plot of Time to Withdrawal from the Study	Note: Change y-axis label to "Cumulative Proportion"	SAC
1.002	All Randomized (ITT)	POP_F1.1	Kaplan-Meier Plot of Time to Early Treatment Discontinuation	On-treatment death is counted as an event.	SAC
1.003	All Randomized (ITT)	POP_F1.1	Kaplan-Meier Plot of Time to Early Treatment Discontinuation for Subjects Who Did Not Die While Taking Study Treatment	On-treatment death will be censored See Section 6.2.1 and 14.6.2.2 for details.	SAC
1.004	All Randomized (ITT)	PAN8	Proportion of Subject Visits Impacted by COVID-19 Pandemic		SAC

14.10.6. Efficacy Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Primary Endpoint Point					
Primary Analyses of the Primary Efficacy Endpoint					
2.001	All Randomized (ITT)	EFF_T1	Summary of Post-randomization Hemoglobin (g/dL) Data	Observed Hgb used to calculate the summary statistics may include imputed HemoCue Hgb	SAC
2.002	All Randomized (ITT)	EFF_T1	Summary of Post-randomization HemoCue Hemoglobin (g/dL) Data		SAC
2.003	All Randomized (ITT)	EFF_T1	Summary of Post-randomization Central Laboratory Hemoglobin (g/dL) Data		SAC
2.004	All Randomized (ITT)	EFF_T2	Summary of Post-randomization Hemoglobin (g/dL) Change from Baseline Data	Change from based line derived based on observed data	SAC
2.005	All Randomized (ITT)	EFF_T45	Summary of Post-randomization Observed and Imputed Hemoglobin (g/dL) Data	Using the data used for the primary Hgb Analysis	SAC
2.006	All Randomized (ITT)	EFF_T46	Summary of Post-randomization Observed and Imputed Hemoglobin (g/dL) Change from Baseline Data	Using the data used for the primary Hgb Analysis	SAC
2.007	All Randomized (ITT)	EFF_T3	Summary of Primary Analysis of Post-randomization Hemoglobin Change from Baseline to the Evaluation Period		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.008	All Randomized (ITT)	EFF_T36	Summary of Imputed Data in the Primary Post-randomization Hemoglobin Analysis		SAC
Supportive Analysis of While On-Treatment Evaluable Hemoglobin Data					
2.009	All Randomized (ITT)	EFF_T1	Summary of Evaluable Hemoglobin (g/dL) Data		SAC
2.010	All Randomized (ITT)	EFF_T2	Summary of Evaluable Hemoglobin (g/dL) Change from Baseline Data		SAC
2.011	All Randomized (ITT)	EFF_T37	Summary of Missing Data in the Evaluable Hemoglobin Analysis		SAC
2.012	All Randomized (ITT)	EFF_T3	Supportive Analysis: Summary of Analysis of Evaluable Hemoglobin (g/dL) Change from Baseline to the Evaluation Period		SAC
2.013	All Randomized (ITT)	EFF_T44	Summary of Evaluable Hgb Exclusion by Visit		SAC
Per Protocol Population Analysis					
2.014	Per Protocol	EFF_T1	Summary of Evaluable Hemoglobin (g/dL) Data for Subjects in the Per Protocol Population		SAC
2.015	Per Protocol	EFF_T2	Summary of Evaluable Hemoglobin (g/dL) Change from Baseline Data for Subjects in the Per Protocol Population		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.016	Per Protocol	EFF_T3	Supportive Analysis: Summary of Analysis of Evaluable Hemoglobin (g/dL) Change from Baseline to the Evaluation Period for Subjects in the Per Protocol Population		SAC
Tipping Point (Multiple Imputation) Analysis of the Primary Efficacy Endpoint					
2.017	All Randomized (ITT)	EFF_T5	Sensitivity Analysis: Multiple Imputation Tipping Point Analysis of Post-randomization Hemoglobin (g/dL) Change from Baseline to the Evaluation Period		SAC
2.018	All Randomized (ITT)	EFF_T5	Supportive Analyses: Multiple Imputation Tipping Point Analysis of Evaluable Hemoglobin (g/dL) Change from Baseline During the Evaluation Period		SAC
Alternative EP (Week 28 to 36) Analysis					
2.019	All Randomized (ITT)	EFF_T3	Supportive Analysis: Summary of Analysis of Post-randomization Hemoglobin (g/dL) Change from Baseline to the Alternative Evaluation Period		SAC
2.020	All Randomized (ITT)	EFF_T3	Supportive Analysis: Summary of Analysis of Evaluable Hemoglobin (g/dL) Change from Baseline to the Alternative Evaluation Period		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Subgroup Analysis					
2.021	All Randomized (ITT)	EFF_T4	Summary of Analysis of Post-randomization Hemoglobin Change from Baseline to the Evaluation Period by Subgroup	In addition, a nominal one-sided non-inferiority p-value using a non-inferiority margin of -0.75 g/dL and a nominal one-sided superiority p-value will be generated for the difference between treatment groups for each level of the hyporesponder subgroup analyses of the primary Hgb endpoint, and will be added to shell EFF_T4	SAC
2.022	All Randomized (ITT)	EFF_T4	Summary of Analysis of Evaluable Hemoglobin Change from Baseline to the Evaluation Period by Subgroup	In addition, a nominal one-sided non-inferiority p-value using a non-inferiority margin of -0.75 g/dL and a nominal one-sided superiority p-value will be generated for the difference between treatment groups for each level of the hyporesponder subgroup analyses of the primary Hgb endpoint, and will be added to shell EFF_T4	SAC
Principal Secondary Endpoint					
Analysis of the Principal Secondary Endpoint					
2.023	All Randomized (ITT)	EFF_T7	Summary of On-treatment Average Monthly IV Iron Dose to Week 52		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.024	All Randomized (ITT)	EFF_T8	Summary of Analysis of On-treatment Average Monthly IV Iron Dose During Day 1 to Week 52		SAC
Subgroup Analysis					
2.025	All Randomized (ITT)	EFF_T9	Summary of Analysis of On-treatment Average Monthly IV Iron Dose During Day 1 to Week 52 by Subgroup		SAC
Supportive Analysis					
2.026	All Randomized (ITT)	EFF_T7	Summary of Post-randomization Average Monthly IV Iron Dose to Week 52		SAC
2.027	All Randomized (ITT)	EFF_T8	Supportive Analysis: Summary of Analysis of Post-Randomization Average Monthly IV Iron Dose During Day 1 to Week 52		SAC
Secondary Endpoints					
Analysis of Secondary Endpoints					
2.028	All Randomized (ITT)	EFF_T10	Summary of Analysis of Post-randomization Hemoglobin Change from Baseline at Week 52		SAC
2.029	All Randomized (ITT)	EFF_T10	Summary of Analysis of Evaluable Hemoglobin Change from Baseline at Week 52		SAC
2.030	All Randomized (ITT)	EFF_T11	Summary of Analysis of Post-randomization Hemoglobin Change from Baseline to Week 52 by Subgroup	By region and hyporesponder	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.031	All Randomized (ITT)	EFF_T11	Summary of Analysis of Evaluable Hemoglobin Change from Baseline at Week 52 by Subgroup	By region and hyporesponder	SAC
2.032	All Randomized (ITT)	EFF_T14	Summary of Percentage of Time Hemoglobin Below, Within and Above the Analysis Range During the Evaluation Period using Evaluable Hemoglobin Values	"m": Subjects who have at least one evaluable Hgb value during the evaluation period. "n" is a subset of "m", because there are additional rules to be included in the summary stat calculations. Three "m"s corresponding to the three categories should be the same value. Three "n"s corresponding to the three categories should also be the same value, because each subject contributes a % of time to each category.	SAC
2.033	All Randomized (ITT)	EFF_T15	Summary of Analysis of Percentage of Time Hemoglobin Within the Analysis Range During the Evaluation Period using Evaluable Hemoglobin Values		SAC
2.034	All Randomized (ITT)	EFF_T16	Summary of Percentage of Time Hemoglobin Below, Within and Above the Analysis Range During the Evaluation Period using Evaluable Hemoglobin Values by Subgroup	By region and hyporesponder	SAC
2.035	All Randomized (ITT)	EFF_T17	Summary of Analysis of Percentage of Time Hemoglobin Within the Analysis Range During the Evaluation Period using Evaluable Hemoglobin Values by Subgroup	By region and hyporesponder	SAC
2.036	All Randomized (ITT)	EFF_T39	Summary of Subjects with Mean Evaluation Period and End of Treatment Hemoglobin Below, Within and Above the Analysis Range using Evaluable Hemoglobin Values		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.037	All Randomized (ITT)	EFF_T12	Summary of Analysis of Hemoglobin Responders During the Evaluation Period using Evaluable Hemoglobin Values		SAC
2.038	All Randomized (ITT)	EFF_T13	Summary of Analysis of Hemoglobin Responders During the Evaluation Period using Evaluable Hemoglobin Values by Subgroup	By region and hyporesponder	SAC
2.039	All Randomized (ITT)	EFF_T18	Summary of Subjects Meeting Rescue Evaluation Criteria and Subjects Rescued		SAC
2.040	All Randomized (ITT)	EFF_T19	Summary of Analysis of Time to Permanently Stopping Study Treatment Due to Meeting Rescue Criteria		SAC
2.041	All Randomized (ITT)	EFF_T38	Summary of Analysis of Time to Permanently Stopping Study Treatment Due to Meeting Rescue Criteria by Hyporesponder Subgroup		SAC
Exploratory Endpoints					
2.042	All Randomized (ITT)	EFF_T20	Summary of Hemoglobin Values <7.5 or >=12.0 g/dL During the Evaluation Period Using Evaluable Central Laboratory Hemoglobin Values		SAC
2.043	All Randomized (ITT)	EFF_T20	Summary of Hemoglobin Values <7.5 or >=12.0 g/dL During the Evaluation Period Using Evaluable HemoCue Hemoglobin Values		SAC
2.044	All Randomized (ITT)	EFF_T21	Summary of Hemoglobin Increases Using Evaluable Central Laboratory Hemoglobin Values		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.045	All Randomized (ITT)	EFF_T21	Summary of Hemoglobin Increases Using Evaluable HemoCue Hemoglobin Values		SAC
2.046	All Randomized (ITT)	EFF_T21	Summary of Hemoglobin Decreases Using Evaluable Central Laboratory Hemoglobin Values		SAC
2.047	All Randomized (ITT)	EFF_T21	Summary of Hemoglobin Decreases Using Evaluable HemoCue Hemoglobin Values		SAC
2.048	All Randomized (ITT)	EFF_T22	Summary of On-treatment Transferrin Saturation, Total Iron Binding Capacity, and Unsaturated Iron Binding Capacity by Visit		SAC
2.049	All Randomized (ITT)	EFF_T23	Summary of On-treatment Change from Baseline in Transferrin Saturation, Total Iron Binding Capacity, and Unsaturated Iron Binding Capacity by Visit		SAC
2.050	All Randomized (ITT)	EFF_T40	Summary of On-treatment Hepcidin, Ferritin, and Iron by Visit		SAC
2.051	All Randomized (ITT)	EFF_T41	Summary of On-treatment Percent Change from Baseline in Hepcidin, Ferritin, and Iron by Visit		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.052	All Randomized (ITT)	EFF_T24	Summary of On-treatment Average Quarterly IV Iron Dose (mg/month)	Subjects who are not using IV iron will be included, but with a 0mg dose. (1) calculate the total iron use for each quarter; (2) convert to monthly dose for each subject; (3) calculate summary statistics.	SAC
2.053	All Randomized (ITT)	EFF_T24	Summary of On-treatment Average Quarterly IV Iron Dose (mg/month) for Subjects Using IV Iron	Only include subjects that are using IV iron (1) calculate the total iron use for each quarter; (2) convert to monthly dose for each subject; (3) calculate summary statistics.	SAC
2.054	All Randomized (ITT)	EFF_T42	Summary of On-treatment Iron Use by Quarter		SAC
2.055	All Randomized (ITT)	EFF_T24	Summary of On-treatment Average Quarterly TSAT (%)		SAC
2.056	All Randomized (ITT)	EFF_T24a	Summary of On-treatment Average Quarterly Ferritin (ug/L)		SAC
2.057	All Randomized (ITT)	EFF_T25	Summary of Subjects Meeting Iron Management Criteria		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.058	All Randomized (ITT)	EFF_T26	Summary of Subjects who Reduced On-treatment Monthly IV Iron During the Evaluation Period Relative to Baseline	Subjects who discontinued study treatment before EP will be excluded	SAC
2.059	All Randomized (ITT)	EFF_T27a	Summary of On-treatment RBC or Whole Blood Transfusions During the Evaluation Period and by Week 52		SAC
2.060	All Randomized (ITT)	EFF_T27a	Summary of On-treatment RBC or Whole Blood Transfusions During the Evaluation Period and by Week 52 and by Hyporesponder Status		SAC
2.061	All Randomized (ITT)	EFF_T19	Summary of Analysis of Time to First Occurrence of On-Treatment RBC or Whole Blood Transfusion		SAC
2.062	All Randomized (ITT)	EFF_T29	Summary of Assigned Dose by Visit		SAC
2.063	All Randomized (ITT)	EFF_T30	Summary of Categories of Assigned Dose by Visit for Daprodustat		SAC
2.064	All Randomized (ITT)	EFF_T31	Summary of Categories of Assigned Dose by Visit for rhEPO		SAC
2.065	All Randomized (ITT)	EFF_T33	Summary of Subjects with Dose Adjustments		SAC
2.066	All Randomized (ITT)	EFF_T33.1	Summary of Subjects with Dose Adjustments by Day 1 HemoCue Hemoglobin Category		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.067	All Randomized (ITT)	EFF_T34	Summary of Number of Dose Adjustments per Subject		SAC
2.068	All Randomized (ITT)	EFF_T35	Summary of Time Dose Held for HemoCue Hemoglobin >=12 g/dL		SAC
2.069	All Randomized (ITT)	EFF_T29	Summary of Assigned Dose by Visit by Hyporesponder Status		SAC
2.070	All Randomized (ITT)	EFF_T30	Summary of Categories of Assigned Dose by Visit for Daprodustat by Hyporesponder Status		SAC
2.071	All Randomized (ITT)	EFF_T31	Summary of Categories of Assigned Dose by Visit for rhEPO by Hyporesponder Status		SAC
2.072	All Randomized (ITT)	EFF_T33	Summary of Subjects with Dose Adjustments by Hyporesponder Status		SAC
2.073	All Randomized (ITT)	EFF_T34	Summary of Number of Dose Adjustments per Subject by Hyporesponder Status		SAC
2.074	All Randomized (ITT)	EFF_T35	Summary of Time Dose Held for HemoCue Hemoglobin >=12 g/dL by Hyporesponder Status		SAC
2.075	All Randomized (ITT)	EFF_T29	Summary of Assigned Dose by Visit by Region		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.076	All Randomized (ITT)	EFF_T30	Summary of Categories of Assigned Dose by Visit for Daprodustat by Region		SAC
2.077	All Randomized (ITT)	EFF_T31	Summary of Categories of Assigned Dose by Visit for rhEPO by Region		SAC
2.078	All Randomized (ITT)	EFF_T33	Summary of Subjects with Dose Adjustments by Region		SAC
2.079	All Randomized (ITT)	EFF_T34	Summary of Number of Dose Adjustments per Subject by Region		SAC
2.080	All Randomized (ITT)	EFF_T35	Summary of Time Dose Held for HemoCue Hemoglobin >=12 g/dL by Region		SAC
2.081	All Randomized (ITT)	EFF_T29	Summary of Assigned Dose by Visit by Race Group		SAC
2.082	All Randomized (ITT)	EFF_T30	Summary of Categories of Assigned Dose by Visit for Daprodustat by Race Group		SAC
2.083	All Randomized (ITT)	EFF_T31	Summary of Categories of Assigned Dose by Visit for rhEPO by Race Group		SAC
2.084	All Randomized (ITT)	EFF_T33	Summary of Subjects with Dose Adjustments by Race Group		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.085	All Randomized (ITT)	EFF_T34	Summary of Number of Dose Adjustments per Subject by Race Group		SAC
2.086	All Randomized (ITT)	EFF_T35	Summary of Time Dose Held for HemoCue Hemoglobin >=12 g/dL by Race Group		SAC
2.087	All Randomized (ITT)	EFF_T29	Summary of Assigned Dose by Visit by Baseline Weight Quartile		SAC
2.088	All Randomized (ITT)	EFF_T30	Summary of Categories of Assigned Dose by Visit for Daprodustat by Baseline Weight Quartile		SAC
2.089	All Randomized (ITT)	EFF_T31	Summary of Categories of Assigned Dose by Visit for rhEPO by Baseline Weight Quartile		SAC
2.090	All Randomized (ITT)	EFF_T33	Summary of Subjects with Dose Adjustments by Baseline Weight Quartile		SAC
2.091	All Randomized (ITT)	EFF_T34	Summary of Number of Dose Adjustments per Subject by Baseline Weight Quartile		SAC
2.092	All Randomized (ITT)	EFF_T35	Summary of Time Dose Held for HemoCue Hemoglobin >=12 g/dL by Baseline Weight Quartile		SAC
2.093	All Randomized (ITT)	EFF_T33	Summary of Subjects with Dose Adjustments Excluding Periods of Dose Hold		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
2.094	All Randomized (ITT)	EFF_T34	Summary of Number of Dose Adjustments per Subject Excluding Periods of Dose Hold		SAC
2.095	Pharmacokinetic	EFF_TED1	Summarized Daprodustat Efficacy Dose Parameters for PK Population		
2.096	Pharmacokinetic	EFF_TES1	Summarized Daprodustat Efficacy Special Parameters for Full PK Population		

14.10.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy Endpoint					
2.001	All Randomized (ITT)	EFF_F2.1	Line Plot of Post-Randomization Hemoglobin Data by Visit		SAC
2.002	All Randomized (ITT)	EFF_F2.1	Line Plot of Post-Randomization Hemoglobin Change from Baseline by Visit		SAC
2.003	All Randomized (ITT)	EFF_F2.2	Forest Plot of Adjusted Mean Difference in Hemoglobin Change from Baseline to the Evaluation Period	Excluding tipping point; including on-drug analysis, PP analysis and alternative EP (on and off treatment as well as evaluable). Display LS mean difference, associated two-sided 95% CI and one-sided non-inferiority p-value	SAC
2.004	All Randomized (ITT)	EFF_F2.1	Line Plot of Evaluable Hemoglobin Data by Visit		SAC
2.005	All Randomized (ITT)	EFF_F2.1	Line Plot of Evaluable Hemoglobin Change from Baseline by Visit		SAC
2.006	Per Protocol	EFF_F2.1	Line Plot of Evaluable Hemoglobin Data by Visit for the Per-Protocol Population		SAC
2.007	Per Protocol	EFF_F2.1	Line Plot of Evaluable Hemoglobin Change from Baseline by Visit for the Per-Protocol Population		SAC
2.008	All Randomized (ITT)	EFF_F2.3	Sensitivity Analysis: Tipping Point Analysis of Post-Randomization Hemoglobin Change from Baseline to the Evaluation Period		SAC

2.009	All Randomized (ITT)	EFF_F2.3	Supportive Analysis: Tipping Point Analysis of Evaluable Hemoglobin Change from Baseline to the Evaluation Period		SAC
2.010	All Randomized (ITT)	EFF_F2.4	Forest Plot of Adjusted Means from the Analysis of Post-Randomization Hemoglobin Change from Baseline to the Evaluation Period by Subgroup		SAC
2.011	All Randomized (ITT)	EFF_F2.4	Forest Plot of Adjusted Means from the Analysis of Evaluable Hemoglobin Change from Baseline to the Evaluation Period by Subgroup		SAC
Principal Secondary Endpoint					
2.012	All Randomized (ITT)	POP_F1.2	Box Plot of Summary of On-treatment Average Monthly IV Iron Dose to Week 52	POP_F1.2 is a shell for Study Population	SAC
2.013	All Randomized (ITT)	POP_F1.2	Box Plot of Summary of Post-randomization Average Monthly IV Iron Dose to Week 52	POP_F1.2 is a shell for Study Population	SAC
2.014	All Randomized (ITT)	EFF_F2.4	Forest Plot of Adjusted Treatment Differences of On-treatment Average Monthly IV Iron Dose (mg) to Week 52 by Subgroup		SAC
Secondary Efficacy Endpoints					
2.015	All Randomized (ITT)	POP_F1.1	Kaplan-Meier Plot of Time to Stopping Study Treatment Due to Meeting Rescue Criteria	POP_F1.1 is a shell for Study Population	SAC
2.016	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Transferrin Saturation by Visit		SAC
2.017	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Total Iron Binding Capacity by Visit		SAC

2.018	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Hepcidin by Visit	Log-transformed parameters	SAC
2.019	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Ferritin by Visit	Log-transformed parameters	SAC
2.020	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Total Iron by Visit	Log-transformed parameters	SAC
2.021	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Change from Baseline in Transferrin Saturation by Visit		SAC
2.022	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Change from Baseline in Total Iron Binding Capacity by Visit		SAC
2.023	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Percent Change from Baseline in Hepcidin by Visit	Log-transformed parameters	SAC
2.024	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Percent Change from Baseline in Ferritin by Visit	Log-transformed parameters	SAC
2.025	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Percent Change from Baseline in Total Iron by Visit	Log-transformed parameters	SAC
2.026	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Average Quarterly IV Iron Dose		SAC
2.027	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Average Quarterly IV Iron Dose for Subjects Receiving IV Iron		SAC

2.028	All Randomized (ITT)	EFF_F2.6	Stacked Bar Chart of On-treatment Iron Use by Quarter		SAC
2.029	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Average Quartely TSAT		SAC
2.030	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Average Quartely Ferritin		SAC
2.031	All Randomized (ITT)	EFF_F2.1	Line Plot of Median Assigned Dose by Visit: Dapro and rhEPO	Plot median dose with two Y-axes, Y1 for Dapro median dose and Y2 for rhEPO median dose.	SAC
2.032	All Randomized (ITT)	EFF_F2.7	Line Plot of Mean Evaluable Hemoglobin and Median Most Recent Dose by Visit: Dapro and rhEPO		SAC
2.033	All Randomized (ITT)	EFF_F2.5	Stacked Bar Chart of Assigned Daprodustat Dose by Visit		SAC
2.034	All Randomized (ITT)	EFF_F2.5	Stacked Bar Chart of Assigned rhEPO Dose by Visit		SAC
Exploratory Efficacy Endpoints					
2.035	All Randomized (ITT)	POP_F1.1	Kaplan-Meier Plot of Time to First Occurrence of RBC or Whole Blood Transfusion During the Time Period for On-Treatment Cardiovascular Events	POP_F1.1 is a shell for Study Population	SAC
2.036	Pharmacokinetic	EF_FSP1	Scatter plot of % Time Evaluable Hgb in Range during EP vs. Cmax/Avg Dose EP TIR		SAC
2.037	Pharmacokinetic	EFF_FSP2	Scatter plot of Mean Evaluable Hgb Change from Baseline during EP vs. Cmax/Avg Dose EP		SAC

2.038	Pharmacokinetic	EFF_FSP3	Scatter plot of % Time Evaluable Hgb in Range during EP vs. Avg Dose EP TIR		SAC
2.039	Pharmacokinetic	EFF_FSP4	Scatter plot of Mean Evaluable Hgb Change from Baseline during EP vs. Avg Dose 52		SAC

14.10.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Safety Statistical Analyses: Blood Pressure					
3.001	All Randomized (ITT)	SAFE_T15	Summary of On-Treatment Pre-Dialysis Blood Pressure Parameters by Visit		SAC
3.002	All Randomized (ITT)	SAFE_T15	Summary of On-Treatment Post-Dialysis Blood Pressure Parameters by Visit		SAC
3.003	All Randomized (ITT)	SAFE_T15	Summary of Post-Randomization Pre-Dialysis Blood Pressure Parameters by Visit	On- and off-treatment BP values	SAC
3.004	All Randomized (ITT)	SAFE_T15	Summary of Post-Randomization Post-Dialysis Blood Pressure Parameters by Visit	On- and off-treatment BP values	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.005	All Randomized (ITT)	SAFE_T16	Summary of Change from Baseline in On-Treatment Pre-Dialysis Blood Pressure Parameters by Visit		SAC
3.006	All Randomized (ITT)	SAFE_T16	Summary of Change from Baseline in On-Treatment Post-Dialysis Blood Pressure Parameters by Visit		SAC
3.007	All Randomized (ITT)	SAFE_T16	Summary of Change from Baseline in Post-Randomization Pre-Dialysis Blood Pressure Parameters by Visit	On- and off-treatment BP values	SAC
3.008	All Randomized (ITT)	SAFE_T16	Summary of Change from Baseline in Post-Randomization Post-Dialysis Blood Pressure Parameters by Visit	On- and off-treatment BP values	SAC
3.009	All Randomized (ITT)	SAFE_T17	Summary of Analysis of Change from Baseline to Week 52 in On-Treatment Blood Pressure Parameters Excluding the Stabilization Period	MMRM Per RAP Section 8.1 the post-dialysis BP values will be used.	SAC
3.010	All Randomized (ITT)	SAFE_T17	Summary of Analysis of Change from Baseline to Week 52 in On-Treatment Blood Pressure Parameters Including the Stabilization Period	MMRM Per RAP Section 8.1 the post-dialysis BP values will be used.	SAC
3.011	All Randomized (ITT)	SAFE_T17	Summary of Analysis of Change from Baseline to Week 52 in Post-Randomization Blood Pressure Parameters Excluding the Stabilization Period	MMRM On- and off-treatment BP values Per RAP Section 8.1 the post-dialysis BP values will be used.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.012	All Randomized (ITT)	SAFE_T17	Summary of Analysis of Change from Baseline to Week 52 in Post-Randomization Blood Pressure Parameters Including the Stabilization Period	MMRM On- and off-treatment BP values Per RAP Section 8.1 the post-dialysis BP values will be used.	SAC
3.013	All Randomized (ITT)	SAFE_T18	Summary of Analysis of Change from Baseline to End of Treatment in On-Treatment Blood Pressure Parameters	ANCOVA Per RAP Section 8.1 the post-dialysis BP values will be used.	SAC
3.014	All Randomized (ITT)	SAFE_T19	Summary of Analysis of On-Treatment Blood Pressure Exacerbation Events	Based on post-dialysis BP	SAC
3.015	All Randomized (ITT)	SAFE_T21	Summary of On-Treatment Blood Pressure Exacerbation Event		SAC
Exploratory Cardiovascular Safety Analyses					
3.016	All Randomized (ITT)	SAFE_T1	Summary of First Occurrence of Adjudicated MACE during the Time Period for Follow-up of Cardiovascular Events		SAC
3.017	All Randomized (ITT)	SAFE_T2aa	Summary of Analysis of First Occurrence of Adjudicated MACE during the Time Period for Follow-up of Cardiovascular Events		SAC
3.018	All Randomized (ITT)	SAFE_T3	Summary of All Adjudicated MACE during the Time Period for Follow-up of Cardiovascular Events		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.019	All Randomized (ITT)	SAFE_T1	Summary of First Occurrence of Adjudicated MACE or Thromboembolic Events during the Time Period for Follow-up of Cardiovascular Events		SAC
3.020	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of First Occurrence of Adjudicated MACE or Thromboembolic Events during the Time Period for Follow-up of Cardiovascular Events		SAC
3.021	All Randomized (ITT)	SAFE_T1	Summary of First Occurrence of Adjudicated MACE or Hospitalization for Heart Failure during the Time Period for Follow-up of Cardiovascular Events		SAC
3.022	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of First Occurrence of Adjudicated MACE or Hospitalization for Heart Failure during the Time Period for Follow-up of Cardiovascular Events		SAC
3.023	All Randomized (ITT)	SAFE_T1	Summary of First Occurrence of Adjudicated MACE or Thromboembolic Events or Hospitalization for CHF during the Time Period for Follow-up of Cardiovascular Events		SAC
3.024	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of First Occurrence of Adjudicated MACE or Thromboembolic Events or Hospitalization for CHF during the Time Period for Follow-up of Cardiovascular Events		SAC
3.025	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of Adjudicated All-Cause Mortality during the Time Period for Vital Status		SAC
3.026	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of Adjudicated CV Mortality during the Time Period for Follow-up of Cardiovascular Events		SAC
3.027	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of First Occurrence of Adjudicated Myocardial Infarction (Fatal and Non-Fatal) during the Time Period for Follow-up of Cardiovascular Events		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.028	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of First Occurrence of Adjudicated Stroke (Fatal and Non-Fatal) during the Time Period for Follow-up of Cardiovascular Events		SAC
3.029	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of First Occurrence of Adjudicated CV Mortality or Non-fatal Myocardial Infarction during the Time Period for Follow-up of Cardiovascular Events		SAC
3.030	All Randomized (ITT)	SAFE_T7a	Summary of All Adjudicated and Supportive Cardiovascular Safety Endpoints during the Time Period for Follow-up of Cardiovascular Events		SAC
3.031	All Randomized (ITT)	SAFE_T10	Summary of All-cause Hospitalization during the Time Period for Follow-up of Cardiovascular Events		SAC
3.032	All Randomized (ITT)	SAFE_T58	Summary of Primary Diagnosis at Discharge by System Organ Class and Lower Level Term for All-Cause Hospitalization During the Time Period for Follow-Up of Cardiovascular Events		SAC
3.033	All Randomized (ITT)	SAFE_T2ba	Summary of Analysis of First Occurrence of All-cause Hospitalization during the Time Period for Follow-up of Cardiovascular Events		SAC
3.034	All Randomized (ITT)	SAFE_T42	Summary of Adjudication Details of All-Cause Mortality During the Time Period for Vital Status	Cause of Death: collected from DEATH form Based on the data from DCRI adjudication data transfer	SAC
3.035	All Randomized (ITT)	SAFE_T43	Summary of Adjudication Details of All Myocardial Infarction Events During the Time Period for Follow-up of Cardiovascular Events	Based on the data from DCRI adjudication data transfer	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.036	All Randomized (ITT)	SAFE_T44	Summary of Adjudication Details of All Stroke Events During the Time Period for Follow-up of Cardiovascular Events	Based on the data from DCRI adjudication data transfer	SAC
3.037	All Randomized (ITT)	SAFE_T45	Summary of Adjudication Details of All Heart Failure Events During the Time Period for Follow-up of Cardiovascular Events	Based on the data from DCRI adjudication data transfer	SAC
3.038	All Randomized (ITT)	SAFE_T46	Summary of Adjudication Details of All Thromboembolic Events During the Time Period for Follow-up of Cardiovascular Events	Based on the data from DCRI adjudication data transfer	SAC
3.039	All Randomized (ITT)	SAFE_T13	Summary of Concordance Between Events Referred for Adjudication and Adjudicated Endpoint Events During the Time Period for Follow-up of Cardiovascular Events		SAC
Exploratory Safety Analyses: Relationship between Daprodustat C_{max}/Dosing and MACE/Combined MACE-related Endpoint					
3.040	Pharmacokinetic	SAFE_TSS1	Summarized Daprodustat Safety Special Parameters for PK Population	Please see RAP Section 8.2	SAC
3.041	Pharmacokinetic	SAFE_TSD1	Summarized Daprodustat Safety Dose Parameters for PK Population	Please see RAP Section 8.2	SAC
3.042	Pharmacokinetic	SAEF_TATD1	Summary of Average TIW Daprodustat Dose by Subjects with and without On-treatment MACE	Please see RAP Section 8.2	SAC
3.043	Pharmacokinetic	SAEF_TATD1	Summary of Average TIW Daprodustat Dose by Subjects with and without On-treatment MACE + Thromboembolic Events + Hospitalization for CHF	Please see RAP Section 8.2	SAC
Exploratory Safety Analyses: BP and BP Medication Changes					

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.044	All Randomized (ITT)	SAFE_T22	Summary of On-Treatment Blood Pressure Parameters Change from Baseline to Last Record Prior to First Change in Blood Pressure Medications	Based on Post-dialysis BP	SAC
3.045	All Randomized (ITT)	SAFE_T23	Summary of Number of On-Treatment Blood Pressure Medications per Subject per Visit	See Section 8.2 for details about calculation of number of BP medications at baseline, end of treatment and other nominal visits.	SAC
3.046	All Randomized (ITT)	SAFE_T24	Summary of Change from Baseline in Number of On-Treatment Blood Pressure Medications per Subject per Visit		SAC
3.047	All Randomized (ITT)	SAFE_T25	Summary of Subjects with Changes from Baseline in On-Treatment Blood Pressure Medications by Visit		SAC
3.048	All Randomized (ITT)	SAFE_T48	Summary of Cumulative Changes in On-treatment Blood Pressure Medications at Week 52		SAC
3.049	All Randomized (ITT)	SAFE_T50	Summary of Subjects with at Least One PRN Record of On-Treatment Blood Pressure Medication Until Week 52		SAC
3.050	All Randomized (ITT)	SAFE_T 51	Summary of Subjects on Any On-treatment Blood Pressure Medication at Any Time Until Week 52		SAC
Exploratory Safety Analyses: Lipid Parameters					
3.051	All Randomized (ITT)	SAFE_T26	Summary of On-treatment Lipid Parameters by Visit	Lipid parameters: Total Cholesterol, LDL-C, and HDL-C.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.052	All Randomized (ITT)	SAFE_T27	Summary of Percent Change from Baseline in On-treatment Lipid Parameters by Visit	Lipid parameters: Total Cholesterol, LDL-C, and HDL-C.	SAC
Adverse Events (AEs)					
AESI					
3.053	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Death, Myocardial Infarction, Stroke, Heart Failure, Thromboembolic Events, and Thrombosis of Vascular Access		SAC
3.054	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis		SAC
3.055	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Cardiomyopathy		SAC
3.056	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Pulmonary Artery Hypertension		SAC
3.057	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Cancer-related Mortality and Tumor Progression and Recurrence		SAC
3.058	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Esophageal and Gastric Erosions		SAC
3.059	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Proliferative Retinopathy, Macular Edema, Choroidal Neovascularization		SAC
3.060	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Exacerbation of Rheumatoid Arthritis		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.061	Safety	SAFE_T29	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Worsening of Hypertension		SAC
3.062	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Death, Myocardial Infarction, Stroke, Heart Failure, Thromboembolic Events, and Thrombosis of Vascular Access during the Follow-up Period		SAC
3.063	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis during the Follow-up Period		SAC
3.064	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Cardiomyopathy during the Follow-up Period		SAC
3.065	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Pulmonary Artery Hypertension during the Follow-up Period		SAC
3.066	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Cancer-related Mortality and Tumor Progression and Recurrence during the Follow-up Period		SAC
3.067	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Esophageal and Gastric Erosions during the Follow-up Period		SAC
3.068	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Proliferative Retinopathy, Macular Edema, Choroidal Neovascularization during the Follow-up Period		SAC
3.069	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Exacerbation of Rheumatoid Arthritis during the Follow-up Period		SAC
3.070	Safety	SAFE_T29	Summary of Characteristics of Adverse Event of Special Interest of Worsening of Hypertension during the Follow-up Period		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.071	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Death, Myocardial Infarction, Stroke, Heart Failure, Thromboembolic Events, and Thrombosis of Vascular Access		SAC
3.072	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis		SAC
3.073	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Cardiomyopathy		SAC
3.074	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Pulmonary Artery Hypertension		SAC
3.075	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Cancer-related Mortality and Tumor Progression and Recurrence		SAC
3.076	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Esophageal and Gastric Erosions		SAC
3.077	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Proliferative Retinopathy, Macular Edema, Choroidal Neovascularization		SAC
3.078	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Exacerbation of Rheumatoid Arthritis		SAC
3.079	Safety	SAFE_T29	Summary of Characteristics of Post-Randomization Adverse Event of Special Interest of Worsening of Hypertension		SAC
3.080	Safety	SAFE_T49	Summary of Treatment Emergent Adverse Events of Special Interest by Preferred Term		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.081	Safety	SAFE_T32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term		SAC
3.082	Safety	SAFE_T32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Age Group	< 65 years, 65-<75 years, ≥75 years. Add row on top of table to indicate subgroup level	SAC
3.083	Safety	SAFE_T32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Gender	Add row on top of table to indicate subgroup level	SAC
3.084	Safety	SAFE_T32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Race Group	American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race Add row on top of table to indicate subgroup level	SAC
3.085	Safety	SAFE_T32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Weight Quartiles		SAC
3.086	Safety	SAFE_T33	Summary of All Treatment Emergent Adverse Events by Overall Frequency by Age Group	< 65 years, 65-<75 years, ≥75 years. Add row on top of table to indicate subgroup level	SAC
3.087	Safety	SAFE_T33	Summary of All Treatment Emergent Adverse Events by Overall Frequency by Gender	Add row on top of table to indicate subgroup level	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.088	Safety	SAFE_T 33	Summary of All Treatment Emergent Adverse Events by Overall Frequency by Race Group	American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race Add row on top of table to indicate subgroup level	SAC
3.089	Safety	SAFE_T33	Summary of All Treatment Emergent Adverse Events by Overall Frequency by Weight Quartiles		SAC
3.090	Safety	SAFE_T32	Summary of All Post-Randomization Adverse Events by System Organ Class and Preferred Term		SAC
3.091	Safety	SAFE_T32	Summary of All Adverse Events during the Follow-up Period by System Organ Class and Preferred Term		SAC
3.092	Safety	SAFE_T33	Summary of Common (>=5%) Treatment Emergent Adverse Events by Overall Frequency		SAC
3.093	Safety	SAFE_T32	Summary of All Treatment Emergent Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
3.094	Safety	SAFE_T33	Summary of All Treatment Emergent Drug-Related Adverse Events by Overall Frequency		SAC
3.095	Safety	SAFE_T33	Summary of Common (>=5%) Non-serious Treatment Emergent Adverse Events by Overall Frequency		SAC
3.096	Safety	SAFE_T34	Summary of Common (>=5%) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.097	Safety	SAFE_T32.1	Summary of All Treatment Emergent Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.098	Safety	SAFE_T32.1	Summary of All Treatment Emergent Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		SAC
Serious and Other Significant Adverse Events					
3.099	Screened	SAFE_T34	Summary of Pre-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.100	Safety	SAFE_T34	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.101	Safety	SAFE_T33	Summary of Treatment Emergent Serious Adverse Events by Overall Frequency		SAC
3.102	Safety	SAFE_T34	Summary of Serious Adverse Events during the Follow-up Period by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.103	Safety	SAFE_T34	Summary of Post-Randomization Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.104	Safety	SAFE_T34	Summary of Treatment Emergent Drug-Related Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.105	Safety	SAFE_T33	Summary of Treatment Emergent Drug-Related Serious Adverse Events by Overall Frequency		SAC
3.106	Safety	SAFE_T34	Summary of Treatment Emergent Drug-Related Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.107	Safety	SAFE_T33	Summary of Treatment Emergent Drug-Related Non-Serious Adverse Events by Overall Frequency		SAC
3.108	Safety	SAFE_T32	Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study by System Organ Class and Preferred Term		SAC
3.109	Safety	SAFE_T33	Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study by Overall Frequency		SAC
3.110	Safety	SAFE_T34	Summary of Treatment Emergent Fatal Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.111	Safety	SAFE_T33	Summary of Treatment Emergent Fatal Serious Adverse Events by Overall Frequency		SAC
3.112	Safety	SAFE_T34	Summary of Treatment Emergent Non-fatal Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.113	Safety	SAFE_T33	Summary of Treatment Emergent Non-fatal Serious Adverse Events by Overall Frequency		SAC
3.114	Safety	SAFE_T34	Summary of Treatment Emergent Drug-Related Fatal Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.115	Safety	SAFE_T60	Summary of Treatment Emergent Serious Fatal and Non-Fatal Drug-Related Adverse Events by Overall Frequency		SAC
3.116	Safety	SAFE_T57	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.117	Safety	SAFE_T39	Summary of On-Treatment Blood Pressure Related Events		
3.118	Safety	SAFE_T32	Summary of Treatment Emergent Blood Pressure Related Serious Adverse Events		SAC
Laboratory: Chemistry					
3.119	Safety	SAFE_T15	Summary of On-Treatment Chemistry Values by Visit		SAC
3.120	Safety	SAFE_T16	Summary of On-Treatment Change from Baseline Chemistry Values by Visit		SAC
3.121	Safety	SAFE_T35	Summary of Worst Case On-treatment Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC
3.122	Safety	SAFE_T36	Summary of Worst Case On-treatment Chemistry Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		SAC
Laboratory: Hematology					
3.123	Safety	SAFE_T15	Summary of On-Treatment Hematology Values by Visit		
3.124	Safety	SAFE_T16	Summary of On-Treatment Change from Baseline Hematology Values by Visit		SAC
3.125	Safety	SAFE_T35	Summary of Worst Case On-treatment Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC
3.126	Safety	SAFE_T36	Summary of Worst Case On-treatment Hematology Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		SAC
Laboratory: Other Laboratory Tests					
3.127	Safety	SAFE_T15	Summary of On-treatment Other Laboratory Values by Visit		

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.128	Safety	SAFE_T16	Summary of On-treatment Change from Baseline Other Laboratory Values by Visit		SAC
3.129	Safety	SAFE_T35	Summary of Worst Case On-treatment Other Laboratory Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC
3.130	Safety	SAFE_T36	Summary of Worst Case On-treatment Other Laboratory Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		SAC
3.131	Safety	SAFE_T36	Summary of Worst Case On-treatment Iron Parameter Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	PCI for Ferritin and TSAT are provided in Section 14.8.1	SAC
3.132	Safety	SAFE_T36	Summary of Worst Case Post-treatment Iron Parameter Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	PCI for Ferritin and TSAT are provided in Section 14.8.1	SAC
3.133	Safety	SAFE_T26	Summary of On-treatment hsCRP by Visit		SAC
3.134	Safety	SAFE_T27	Summary of Percent Change from Baseline in On-treatment hsCRP Parameters by Visit		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hepatobiliary (Liver)					
3.135	Safety	SAFE_T37	Summary of Post-randomization Liver Monitoring/Stopping criteria Event		SAC
3.136	Safety	SAFE_T38	Summary of Post-randomization Hepatobiliary Laboratory Abnormalities		SAC
ECG					
3.137	Safety	SAFE_TEG1	Summary of ECG Findings	"Clinically significant change from baseline" will be derived from eCRF ECG form	SAC
3.138	Safety	SAFE_TEG2	Summary of Change from Baseline in ECG Values by Visit	For all ECG parameters	SAC
3.139	Safety	SAFE_TEG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	Remove "QTcF Interval, Aggregate (msec)" if not reported	SAC
3.140	Safety	SAFE_TEG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	Remove "QTcF Interval, Aggregate (msec)" if not reported	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.141	Safety	SAFE_T15	Summary of Post-randomization Vital Signs by Visit	Included both on-treatment and off-treatment vital signs. Add “pre-dialysis” or “post-dialysis” for each vital sign parameter. For example: Weight (kg) (pre-dialysis)	SAC
3.142	Safety	SAFE_T16	Summary of Change from Baseline in Post-randomization Vital Signs by Visit	Included both on-treatment and off-treatment vital signs. Add “pre-dialysis” or “post-dialysis” for each vital sign parameter. For example: Weight (kg) (pre-dialysis)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.143	Safety	SAFE_T36	Summary of Worst Case On-treatment Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	See IDSL Vital Sign Statistical Display Standards for programming notes. (Shell SAFE_T36 is equivalent to IDSL VS7) Based on post-dialysis vital signs. Add “post-dialysis” for each vital sign parameter. For example: SBP (mmHg) (post-dialysis)	SAC
3.144	Safety	SAFE_T36	Summary of Worst Case Post-treatment Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	See IDSL Vital Sign Statistical Display Standards for programming notes. (Shell SAFE_T36 is equivalent to IDSL VS7) Based on post-dialysis vital signs. Add “post-dialysis” for each vital sign parameter. For example: SBP (mmHg) (post-dialysis)	SAC
3.145	All Randomized (ITT)	SAFE_T15	Summary of Difference Between On-treatment Post-Dialysis Weight and Estimated Dry Weight by Visit		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
COVID-19 Impact on Safety Assessment					
3.146	Safety	PAN1	Summary of COVID-19 Assessments for Subjects with COVID-19 Adverse Events		SAC
3.147	Safety	PAN11	Summary of Exposure Adjusted Incidence Rate for Common (>=5%) Adverse Events		SAC
3.148	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time		SAC
3.149	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time by Region		SAC
3.150	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time by Country		SAC
3.151	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time by Sex		SAC
3.152	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time by Age		SAC
3.153	All Randomized (ITT)	SAFE_T1	Summary of First Occurrence of Adjudicated COVID-19 MACE During the Time Period for Follow-Up of Cardiovascular Events		SAC

14.10.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Safety Analyses					

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.001	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Pre-Dialysis Blood Pressure Parameters by Visit	SBP, DPB, MAP EFF_F2.1 is a shell for efficacy	SAC
3.002	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Post-Dialysis Blood Pressure Parameters by Visit	SBP, DPB, MAP EFF_F2.1 is a shell for efficacy	SAC
3.003	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Pre-dialysis Blood Pressure Parameters Change from Baseline by Visit	SBP, DPB, MAP EFF_F2.1 is a shell for efficacy	SAC
3.004	All Randomized (ITT)	EFF_F2.1	Line Plot of On-treatment Post-dialysis Blood Pressure Parameters Change from Baseline by Visit	SBP, DPB, MAP EFF_F2.1 is a shell for efficacy	SAC
Exploratory Safety Analyses					
3.005	All Randomized (ITT)	POP_F1.1	Kaplan-Meier Plot of Time to First Occurrence of Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events	Please see Section 14.6.4.1 CV Safety Endpoints, Time Period for Follow-up of Cardiovascular Endpoints, regarding deaths reported after this time period POP_F1.1 is a shell for Study Population.	SAC
3.006	Safety	POP_F1.1	Kaplan Meier Plot of Time to First Occurrence of Treatment Emergent Death, Myocardial Infarction, Stroke, Heart Failure, Thromboembolic Events, and Thrombosis of Vascular Access	POP_F1.1 is a shell for Study Population	SAC
3.007	Pharmacokinetic	SAFE_FBOX1	Boxplot of Cmax/Dose at on-treatment MACE by subjects with or without on-treatment MACE		SAC

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.008	Pharmacokinetic	SAFE_FBOX1	Boxplot of Cmax/Dose at on-treatment MACE + thromboembolic event + hospitalization for CHF by subjects with or without on-treatment MACE + thromboembolic event + hospitalization for CHF		SAC
3.009	Pharmacokinetic	SAFE_FBOX2	Boxplot of Average TIW Dose at on-treatment MACE by subjects with or without on-treatment MACE		SAC
3.010	Pharmacokinetic	SAFE_FBOX2	Boxplot of Average TIW Dose at on-treatment MACE + thromboembolic event + hospitalization for CHF by subjects with or without on-treatment MACE + thromboembolic event + hospitalization for CHF		SAC
Adverse Events					
3.011	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis		SAC
3.012	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Cardiomyopathy		SAC
3.013	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Pulmonary Artery Hypertension		SAC
3.014	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Cancer-related Mortality and Tumor Progression and Recurrence		SAC
3.015	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Esophageal and Gastric Erosions		SAC

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.016	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Proliferative Retinopathy, Macular Edema, Choroidal Neovascularization		SAC
3.017	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Exacerbation of Rheumatoid Arthritis		SAC
3.018	Safety	SAFE_F3.3	Cumulative Incidence Function Plot of Time to First Occurrence of Treatment Emergent Worsening of Hypertension		SAC

3.019	Safety	SAFE_F3.4	Dot Plot for Treatment Emergent Adverse Events of Special Interest	o The AESI table and corresponding plot should be consistent within a study and across the studies o Please use the order that we're using for our individual AESI displays: 0. Death, myocardial infarction, stroke, heart failure, thromboembolic events, and thrombosis of vascular access 1. Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis 2. Cardiomyopathy 3. Pulmonary artery hypertension 4. Cancer-related mortality and tumor progression and recurrence 5. Esophageal and gastric erosions 6. Proliferative retinopathy, macular edema, choroidal neovascularization 7. Exacerbation of rheumatoid arthritis 8. Worsening of hypertension Relative Risk (RR) is unadjusted raw RR.	SAC

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.020	Safety	SAFE_F3.4	Dot Plot of Most Common (>=5%) Treatment Emergent Adverse Events		SAC
Laboratory					
3.021	Safety	SAFE_F3.6	Scatter Plot of On-treatment Maximum vs. Baseline ALT		
3.022	Safety	SAFE_F3.7	Scatter Plot of On-treatment Maximum ALT vs. Maximum Total Bilirubin		SAC
Vital Signs					
3.023	Safety	EFF_F2.1	Line Plot of Difference Between On-treatment Post-dialysis Weight and Estimated Dry Weight by Visit	EFF_F2.1 is a shell for efficacy	SAC

14.10.10. Patient Reported Outcome Tables

Patient Reported Outcome: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Patient Reported Outcome					
4.001	All Randomized (ITT)	PRO_T7	Summary Statistics for On-Treatment PGI-S Scores		SAC
4.002	All Randomized (ITT)	PRO_T8	Summary Statistics for the Change from Baseline in On-Treatment PGI-S Scores		SAC
4.003	All Randomized (ITT)	PRO_T9	Summary of Analysis of Change from Baseline in On-Treatment PGI-S Scores		SAC
4.004	All Randomized (ITT)	PRO_T10	Summary of Shifts from Baseline in On-Treatment PGI-S Categories		SAC
4.005	All Randomized (ITT)	PRO_T11	Summary of On-Treatment PGI-C Categories		SAC

14.10.11. Patient Reported Outcome Figures

Patient Reported Outcome:: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Patient Reported Outcome					
4.001	All Randomized (ITT)	PRO_F5.3	Stacked Bar Chart of the Percentage of Patients Reporting Each PGI-S Response at Baseline and On-treatment at Week 8		SAC
4.002	All Randomized (ITT)	PRO_F5.3	Stacked Bar Chart of the Percentage of Patients Reporting Each PGI-S Response at Baseline and On-treatment at Week 12		SAC
4.003	All Randomized (ITT)	PRO_F5.3	Stacked Bar Chart of the Percentage of Patients Reporting Each PGI-S Response at Baseline and On-treatment at Week 28		SAC
4.004	All Randomized (ITT)	PRO_F5.3	Stacked Bar Chart of the Percentage of Patients Reporting Each PGI-S Response at Baseline and On-treatment Week 52		SAC

14.10.12. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Analysis: Drug Concentration Measures and PK Parameters					
5.001	Pharmacokinetic	PK_T1	Summary of GSK1278863 and Metabolites Plasma Pharmacokinetic Concentration Time Data (ng/ml) by Dose Level		SAC
5.002	Pharmacokinetic	PK_T2	Summary of GSK1278863 and Metabolites Plasma Pharmacokinetic Parameters by Dose Level		SAC

14.10.13. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.001	All Randomized (ITT)	PD_T1	Summary of Observed Erythropoietin (unit) by Visit and Sample Time		SAC
6.002	All Randomized (ITT)	PD_T2	Summary of Erythropoietin (unit) Change from Baseline by Visit and Sample Time		SAC
6.003	All Randomized (ITT)	PD_T3	Summary of Erythropoietin (unit) Maximum Observed Change from Baseline		SAC
6.004	All Randomized (ITT)	PD_T4	Summary of Observed VEGF (unit) by Visit and Sample Time		SAC
6.005	All Randomized (ITT)	PD_T5	Summary of VEGF (unit) Percent Change from Baseline by Visit and Sample Time		SAC
6.006	All Randomized (ITT)	PD_T6	Summary of VEGF (unit) Maximum Observed Percent Change from Baseline		SAC

14.10.14. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.001	Screened	POP_L1	Listing of Reasons for Screen Failure	Including the "specify" text, if any, associated with the reason term for SF	SAC
1.002	All Randomize (ITT)	POP_L3	Listing of Reasons for Study Withdrawal	Note that this listing should not include reasons for screen failure	SAC
1.003	All Randomize (ITT)	POP_L4	Listing of Reasons for Study Treatment Discontinuation		SAC
1.004	All Randomize (ITT)	POP_L14	Listing of Subjects for Whom the Treatment Blind was Broken	If the reason for breaking the treatment blind is 'Other', then the listing should display 'Other: *text*', where *text* is the reason entered on the eCRF page.	SAC
1.005	All Randomize (ITT)	POP_L5	Listing of Planned and Actual Treatments	Data will be sorted and displayed by country, site ID then subject number. Investigator name will appear in the page header along with site ID. Please print one site per page for this listing so that the pages can be sent to each site	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Protocol Deviations					
1.006	All Randomized (ITT)	POP_L6	Listing of Important Protocol Deviations		SAC
1.007	All Randomized (ITT)	POP_L7	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
1.008	All Randomized (ITT)	POP_L2	Listing of Subjects Excluded from Per Protocol and Safety Populations		SAC
Demographic and Baseline Characteristics					
1.009	All Randomized (ITT)	POP_L8	Listing of Selected Demographic and Baseline Characteristics		SAC
1.010	All Randomized (ITT)	POP_L 9	Listing of Race		SAC
Prior and Concomitant Medications					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.011	All Randomized (ITT)	POP_L10	Listing of Concomitant Medications	This listing displays all data captured in the concomitant medications dataset, including medications used pre-, on- and post-treatment. Including anti-hypertensive, iron therapy, and rhEPO, which are collected in special conmed form	SAC
Exposure and Treatment Compliance					
1.012	All Randomized (ITT)	POP_L11	Listing of Exposure Data		SAC
1.013	All Randomized (ITT)	POP_L11	Listing of Exposure Data from Unblinded eCRF		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.001	Safety	SAFE_L3	Listing of All Adverse Events		SAC
3.002	Safety	SAFE_L4	Listing of Subject Numbers for Individual Adverse Events		SAC
3.003	Safety	SAFE_L5	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Term		SAC
3.004	Screened	SAFE_L3	Listing of Pre-treatment Adverse Events		SAC
Serious and Other Significant Adverse Events					
3.005	Safety	SAFE_L6	Listing of Reasons for Considering as a Serious AE		SAC
3.006	Safety	SAFE_L3	Listing of AEs Leading to Premature Withdrawal from Study		SAC
3.007	Safety	SAFE_L3	Listing of AEs Leading to Permanent Discontinuation of Study Treatment		SAC
3.008	Safety	SAFE_L3	Listing of Fatal Serious AEs		SAC
3.009	Safety	SAFE_L3	Listing of Non-fatal Serious AEs		SAC
3.010	Safety	SAFE_L3	Listing of Other Significant AEs	Please include the following footnote: Other significant AEs are non-fatal non-serious AEs resulting in an action taken with study treatment of either ‘dose interrupted/delayed’ or ‘dose reduced’.	SAC
Hepatobiliary (Liver)					
3.011	Safety	SAFE_L7	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.012	Safety	SAFE_L8	Listing of Substance Use for Subjects with Liver Stopping Events	AESI shown under "Visit" is the eCRF form from which the substance use data are collected. For example, from the ESOPHAGEAL AND GASTRIC EROSIONS form, we can get the data on Average Number of Cigarettes/Day and Average Number of Units of Alcohol/week	SAC
All Laboratory					
3.013	Safety	SAFE_L9	Listing of All Chemistry Data for Subjects with Abnormalities of Potential Clinical Concern	Display "ALL" (pre-, on-, and post-treatment) labs for a subject who experienced an value of potential clinical importance	SAC
3.014	Safety	SAFE_L9	Listing of All Hematology Data for Subjects with Abnormalities of Potential Clinical Concern	Display "ALL" (pre-, on-, and post-treatment) labs for a subject who experienced an value of potential clinical importance	SAC
3.015	Safety	SAFE_L9	Listing of All Other Laboratory Data for Subjects with Abnormalities of Potential Clinical Concern	Display "ALL" (pre-, on-, and post-treatment) labs for a subject who experienced an value of potential clinical importance	SAC
3.016	Safety	SAFE_L9	Listing of All Chemistry Data		SAC
3.017	Safety	SAFE_L9	Listing of All Hematology Data		SAC
3.018	Safety	SAFE_L9	Listing of All Other Laboratory Data		SAC
3.019	Safety	IDSL LB14	Listing of Laboratory Data with Character Results		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.020	Safety	SAFE_L10	Listing of All Vital Signs for Subjects with Post-Dialysis Values of Potential Clinical Importance	Use post-dialysis vital signs to identify the subject with PCI, but the listing will include all vital signs (pre- on- or post-treatment, and both pre-dialysis and post-dialysis signs)	SAC

14.10.15. Non-ICH Listing

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
1.014	All Randomized (ITT)	POP_L12	Listing of Prior and Concomitant ESA Medications	Include all ESAs, prior and concomitant ESA,	SAC
Subject Disposition					
1.015	Screened	POP_L13	Listing of Subjects Who Were Rescreened		SAC
COVID-19 Impacted Visits					
1.016	All Randomized (ITT)	PAN7	Listing of Visits Impacted by COVID-19 Pandemic		SAC
Efficacy					
2.001	All Randomized (ITT)	EFF_L1	Listing of Hemoglobin Data		SAC
2.002	All Randomized (ITT)	EFF_L2	Listing of On-treatment Average Monthly IV Iron Dose to Week 52		SAC
2.003	Pharmacokinetic	EFF_LED1	Listing of Daprodustat Efficacy Dose Parameters		SAC
2.004	Pharmacokinetic	EFF_LES1	Listing of Daprodustat Efficacy Special Parameters		SAC
Safety					
3.021	All Randomized (ITT)	SAFE_L1	Listing of All Adjudicated MACE Events		SAC
3.022	All Randomized (ITT)	SAFE_L2	Listing of Adjudicated All-Cause Mortality		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.023	All Randomized (ITT)	SAFE_L15	Listing of Subjects Who Became Pregnant During the Study		SAC
3.024	Pharmacokinetic	SAFE_LSD1	Listing of Daprodustat Safety Dose Parameters		SAC
3.025	Pharmacokinetic	SAFE_LSS1	Listing of Daprodustat Safety Special Parameters		SAC
Pharmacokinetic					
5.001	Pharmacokinetic	PK_L1	Listing of GSK1278863 and Metabolites Pharmacokinetic Plasma Concentration-Time Data		SAC
5.002	Pharmacokinetic	PK_L2	Listing of GS1278863 and Metabolites Plasma Pharmacokinetic Parameters		SAC