The GlaxoSmithKline group of companies 200807

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

Title	:	Reporting and Analysis Plan for A phase 3, randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoiesis-stimulating agents.
Compound Number	:	GSK1278863
Effective Date	:	Refer to Document Date

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for the study Protocol: GlaxoSmithKline Document Number 2015N226659_07.

RAP Author(s):
(Method: E-mail)

Author	Date
Lead PPD Principal Statistician (Specialty Biostatistics)	N/A
Co-Authors PPD Director Clinical Statistics (Specialty Biostatistics)	02-March-2021
PPD Statistics Leader (Specialty Biostatistics)	02-March-2021
PPD Statistician (Specialty Biostatistics)	03-March-2021
PPD Director Clinical Pharmacology Modelling and Simulation (Clinical Pharmacology and Experimental Medicine)	02-March-2021

RAP Team Reviews:

RAP Team Review Confirmations

(Method: E-mail)

Reviewer	Date
PPD Sr. Director Clinical Development Lead (Clinical Sciences Respiratory and Specialty)	03-March-2021
PPD Programming Leader (Specialty Biostatistics)	02-March-2021

Clinical Statistics and Clinical Programming Line Approvals:

Clinical Statistics & Clinical Programming Line Approvals

(Method: Pharma TMF eSignature)

Approver	Date	Approval Method
PPD Statistics Director (Specialty Clinical Statistics)	Refer to Document Date	E-signature, eTMF
PPD Programming Leader (Specialty Clinical Programming)	Refer to Document Date	E-signature, eTMF

CONFIDENTIAL

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP describes the planned analyses and outputs required for the final Clinical Study Report (CSR) for study 200807.
Protocol	• This RAP is based on the fifth protocol amendment of study 200807 [GlaxoSmithKline Document Number 2015N226659_07, 30JUL2020]. While there is also a France-specific fifth protocol amendment [GlaxoSmithKline Document Number 2015N226659_08, 30JUL2020], the analyses described in the France-specific amendment are consistent with the analyses described in the global protocol amendment.
Co-Primary Objectives	• To compare daprodustat to rhEPO for hemoglobin (Hgb) efficacy (non-inferiority) • To compare daprodustat to rhEPO for cardiovascular (CV) safety (non-inferiority)
Co-Primary Endpoints	• Mean change in Hgb between baseline and evaluation period (EP, mean over Weeks 28 to 52) • Time to first occurrence of adjudicated major adverse cardiovascular event (MACE); [composite of all-cause mortality, non-fatal myocardial infarction (MI) or non-fatal stroke]
Study Design	• This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center, event-driven study in dialysis subjects with anemia associated with chronic kidney disease (CKD) who are currently treated with erythropoiesis stimulating agents (ESAs). ESAs refer to any rhEPO or methoxy PEG-epoetin beta. • This study will comprise 4 study periods: a 4-week screening period, a 4-week placebo run-in period, a treatment period, and a follow-up period. Prior ESA therapy continues during the screening and run-in periods. • The total duration of the study is dependent upon the accumulation of at least 664 adjudicated first MACE (i.e., it is event-driven) unless review of interim data by the Independent Data Monitoring Committee (IDMC) recommends bringing the study to an earlier close. • Subjects will be stratified by dialysis type, by region and by participation in the ambulatory blood pressure monitoring (ABPM) sub-study. Dialysis type and region are considered to be stratification factors that are potentially prognostically important, i.e., predictive of study endpoints while participation in the ABPM sub-study is an administrative stratification factor intended solely to ensure a similar number of sub-study subjects in each of the two randomized groups. • Following stratification, subjects will be randomized 1:1 to receive oral daprodustat or rhEPO [intravenous (IV) epoetin alfa or subcutaneous (SC) darbepoetin alfa].

Overview	Key Elements of the RAP
	• Both treatment arms (daprodustat and rhEPO) will follow a protocol-specified randomized treatment dose adjustment algorithm to achieve and/or maintain Hgb within the target range of 10-11 g/dL inclusive. Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both randomized treatment arms.
Planned Analyses	• It is planned that study unblinding will occur after at least 664 first MACE have occurred (see Section 3.2). Planned final analyses will be performed after study unblinding. • An IDMC will review safety and efficacy data periodically from ongoing clinical trials in the daprodustat clinical development program for the treatment of subjects with anemia associated with chronic kidney disease. • In addition, an interim analysis is planned for this study which will assess whether the daprodustat program has met criteria for futility or harm and whether the study should be stopped. The IDMC will review the interim analysis results and will provide a recommendation regarding early stopping to the sponsor.
Key Analysis Populations	• The primary population for the Hgb efficacy and MACE safety analyses will be the All Randomized Intent-to-Treat (ITT) population. Subjects will be analyzed according to the treatment to which they were randomized.

Co-Primary Hypotheses	• The co-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 -rhEPO), 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 -rhEPO), is greater than -0.75 g/dL.
	• The co-primary CV safety objective will assess the estimand of time to first occurrence (in days) of adjudicated MACE from randomization to the end of study in all randomized subjects regardless of what treatment(s) they go on to receive. The primary analysis will test for non-inferiority of treatment with daprodustat relative to rhEPO, expressed by the following statistical hypotheses:
	  • Null: daprodustat is inferior to rhEPO, with at least a 25% increased relative risk of first MACE (i.e. the hazard ratio is ≥1.25).

Overview	Key Elements of the RAP
	• Alternative: daprodustat is non-inferior to rhEPO (i.e. the hazard ratio is <1.25).
Co-Primary Analyses	• For the Hgb efficacy analysis, an analysis of covariance (ANCOVA) model including prognostic randomization stratification factors (dialysis type and region), baseline Hgb 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. 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. • For the CV safety analysis, a Cox-Proportional Hazards regression model, adjusting for treatment and prognostic randomization stratification factors (dialysis type and region), will be used to estimate the hazard-ratio, its two-sided 95% CI and to generate the p-value for the non-inferiority test for the MACE endpoint. Non-inferiority will be achieved if the upper limit of the two-sided 95% CI is below the margin of 1.25.

Key Secondary Analyses	Principal Secondary Endpoints (multiplicity adjusted endpoints, tested for superiority; for other endpoints see Section 2.2)
	• Time to first occurrence of adjudicated
	  • MACE
	  • MACE or an adjudicated thromboembolic event (vascular access thrombosis, deep vein thrombosis or pulmonary embolism)
	  • MACE or an adjudicated hospitalization for heart failure (HF)
	• Average monthly IV iron dose (mg)/subject to Week 52

Safety Endpoints	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest (AESI) • Reasons for discontinuation of randomized treatment • Absolute values and changes from baseline in laboratory parameters, blood pressure (BP) and heart rate (HR)

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes to the originally planned statistical analysis specified in the fourth protocol amendment (Dated: 30JUL2020) are detailed as follows:

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
• None	• Number of RBC whole blood and transfusion event is included in the exploratory efficacy analysis of RBC and Whole Blood Transfusions	• Number of RBC whole blood and transfusion event has been defined and included in the exploratory endpoints
• None	• Time to first RBC and whole blood transfusion is included in the exploratory efficacy analysis of RBC and Whole Blood Transfusions	• Time to first RBC and whole blood transfusion has been included in the exploratory endpoints
• None	• Phosphate Binder analyses have been added	• Assessing the effect of Phosphate Binder co-administration.
• None	• Clopidogrel analyses have been added	• Assessing the effect of Clopidogrel co-administration.
PK Sub-study Statistical Analysis Plan	**PK Sub-study Statistical Analysis Plan**	**Rationale for Changes**
• PK sub-study endpoints described as dose normalized	• PK sub-study endpoints described as dose extrapolated	• Terminology clarification following discussion with regulatory agencies
PK sub-study endpoints include: • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP. • Scatter plots of average daprodustat dose during EP vs. percent time in range during EP. • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP vs. percent time in range during EP.	PK sub-study endpoints modified as follows: • *Endpoints removed:* Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP. • Scatter plots of average daprodustat dose during EP **while in target Hgb range** vs. percent time in range during EP.	• Removed as these endpoints do not provide additional information for efficacy explorations than what will be available from remaining endpoints.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. change from baseline of Hgb during EP. • Boxplots of daprodustat PK parameters (Ctau and Cmax) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint	• Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP **while in target Hgb range** vs. percent time in range during EP. • *Endpoints removed:* Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. change from baseline of Hgb during EP. • *Endpoints removed:* Boxplots of daprodustat PK parameters (Ctau and Cmax) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint	
ABPM Sub-study Statistical Analysis Plan	**ABPM Sub-study Statistical Analysis Plan**	**Rationale for Changes**
• Statistical analyses planned.	• No statistical analysis will be conducted for this sub-study due to the small number of subjects recruited. Instead all data will either be summarized or listed.	• Small number of subjects recruited.

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

Objectives	Endpoints
Co-Primary Objectives	**Co-Primary Endpoints**
• To compare daprodustat to rhEPO for CV safety (non-inferiority)	• Time to first occurrence of **adjudicated** MACE (composite of all-cause mortality, non-fatal MI and non-fatal stroke)
• To compare daprodustat to rhEPO for Hgb efficacy(non-inferiority)	• Mean change in Hgb between baseline and EP (mean over Weeks 28 to 52)
Principal Secondary Objectives	**Principal Secondary Endpoints (tested for superiority, adjusted for multiplicity)**

• To compare daprodustat to rhEPO on CV safety endpoints	• Time to first occurrence of adjudicated
	  • MACE
	  • MACE or a thromboembolic event (vascular access thrombosis, symptomatic deep vein thrombosis or symptomatic pulmonary embolism)
	  • MACE or a hospitalization for heart failure (HF)

Objectives	Endpoints
• To compare daprodustat to rhEPO on the use of intravenous (IV) iron	• Average monthly IV iron dose (mg)/subject to Week 52
Secondary Objectives	**Secondary Endpoints (tested for superiority[1], no multiplicity adjustment)**
• To compare daprodustat to rhEPO on additional CV safety endpoints	• All-cause mortality, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke[2] • MACE or hospitalization for HF[2] (recurrent events analysis) • CV mortality or non-fatal MI[2] • All-cause hospitalization • All cause hospital re-admission within 30 days • MACE or hospitalization for HF or thromboembolic events[2] • Hospitalization for HF[2] • Thromboembolic events[2]
• To compare daprodustat to rhEPO on Hgb variability	• Hgb change from baseline to Week 52[1] • N (%) responders, defined as mean Hgb within the Hgb analysis range 10-11.5 g/dL during EP • % time Hgb in analysis range (10-11.5 g/dL) during the evaluation period (EP, Week 28 to 52) and during the maintenance period (MP; Week 28 to end of trial) *(non-inferiority analysis that will use a margin of 15% less time in range)* [1]
• To compare daprodustat to rhEPO on BP	• Change from baseline in SBP, DBP and MAP at Week 52 and at end of treatment • Number of BP exacerbation events per 100 patient years • N (%) with at least one BP exacerbation event during study
• To compare daprodustat to rhEPO on the time to rescue (defined as permanently stopping randomized treatment due to meeting rescue criteria).	• Time to stopping randomized treatment due to meeting rescue criteria
• To compare daprodustat to rhEPO on HRQoL and Utility score	• Mean change in SF-36 HRQOL scores (Physical Component Score (PCS), Mental Component Score (MCS) and 8 health domains) between baseline and Weeks 8, 12, 28, 52, of particular interest are the changes from baseline in the vitality and physical functioning domains at Wk 28 and 52 • Change from baseline in Health Utility (EQ-5D-5L) score at Week 52 • Change from baseline in EQ VAS at Week 52
• To compare daprodustat to rhEPO on the symptom severity and change	• Change from Baseline at Wk 8,12, 28, 52 in PGI-S
Exploratory Objectives	**Exploratory Endpoints (statistical testing not planned)**
• To further compare daprodustat and rhEPO on Hgb variability	• Hgb observed and change from baseline across all visits to end of treatment • % of time Hgb is above, within and below the range of

Objectives	Endpoints
	10-11.5 g/dL during EP and MP • Number (%) of subjects with mean Hgb above, within and below the Hgb analysis range during EP and at the end of treatment • Number (%) of subjects with a Hgb <7.5 g/dL during the EP and MP • Number of times Hgb < 7.5 g/dL during the EP and MP • Number (%) of subjects with a >1g/dL increase in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL increase in Hgb within any 4 week period from Week 4 to Week 52 • Number (%) of subjects with a >1g/dL decrease in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL decrease in Hgb within any 4 week period from Week 4 to Week 52 • N (%) of subjects with a Hgb value ≥ 12 g/dL during the EP and MP • Number of times Hgb ≥ 12 g/dL during the EP and MP • % of time Hgb ≥ 12 g/dL during the EP and MP
• To compare daprodustat to rhEPO on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, TSAT, total iron, TIBC across all visits to end of treatment • Average quarterly ferritin • Average quarterly TSAT • Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria • N (%) of subjects 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 further compare daprodustat to rhEPO on BP and BP medication changes	• Observed and change from baseline in SBP, DBP and MAP by visit • Number of BP medications per subject by visit • Change from baseline in the number of BP medications per subject by visit • N (%) of subjects who had no change, an increase or a decrease in the dosage or number of BP medications from baseline by visit
• To compare daprodustat to rhEPO on the need for RBC and whole blood transfusions	• Number (%) of subjects who receive at least one RBC or whole blood transfusions by Week 52 and by end of treatment • Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years
• To compare daprodustat to rhEPO 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)]

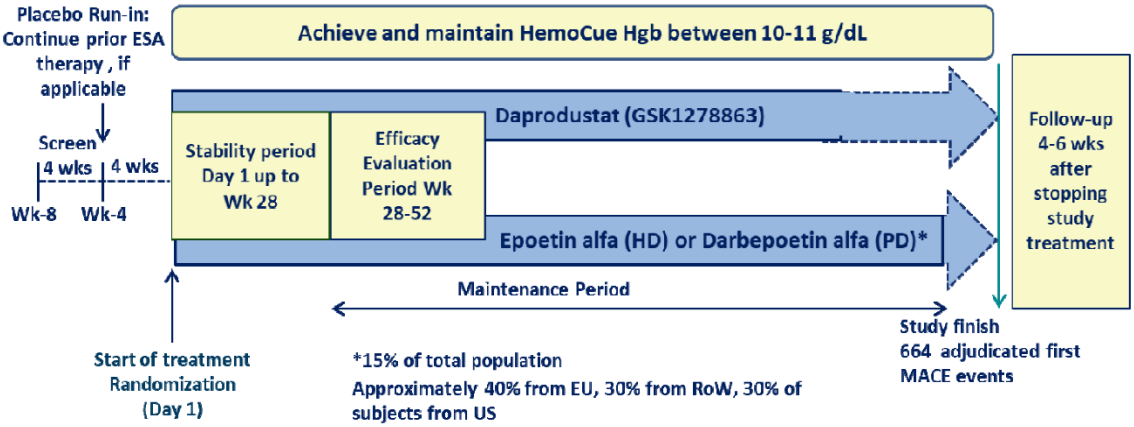
Objectives	Endpoints
• To compare the effect of daprodustat to rhEPO on delayed graft function (DGF) after deceased donor kidney transplantation	• Number (%) of subjects experiencing DGF after deceased donor kidney transplantation (where DGF is defined as the use of dialysis within 7 days of the transplant) • Length of time that subjects experience DGF after deceased donor kidney transplantation
• Evaluate the dose adjustment schemes	• Assigned dose by visit and at Day 1, Week 28, Week 52, and yearly • Most recent dose prior to Week 28, Week 52, yearly and End of Treatment • Number (%) of patients with 0, 1, 2, or >2 dose adjustments during the following periods: o Day 1 - < Week 28 o Week 28 - < Week 52 o Day 1 - < End of Treatment • Number of dose adjustments during the following periods: o Day 1 - < Week 28 o Week 28 - < Week 52 o Day 1 - < End of Treatment • Number of dose adjustments per year during Day 1 - < End of Treatment • Time dose held for Hgb≥12 g/dL
• To further compare daprodustat to rhEPO on HRQoL and Utility score	• Change from baseline in Health Utility I (EQ-5D-5L) score at Weeks 8,12, 28, 52, yearly, EOS • Change from baseline in EQ VAS at Weeks 8, 12, 28, 52, yearly, EOS
• To further compare daprodustat to rhEPO on the symptom severity and change	• 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.
Safety Objective	**Safety Endpoints**
• To compare the safety and tolerability of daprodustat to rhEPO	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest[3] • Reasons for discontinuation of randomized treatment • Absolute values and changes from baseline in laboratory parameters, BP and heart rate (HR)

Conversion from g/dL to g/L is 1:10 and from g/dL to mmol/L is 0.6206. For example, Hgb of 10 to 11.g/dL is equivalent to 100-110g/L or 6.2 to 6.8 mmol/L.

1. Hgb change from baseline to Wk 52 is tested for non-inferiority, using the -0.75 g/dL margin used in the co-primary analysis. % time in range is tested first for non-inferiority, then for superiority.
2. Events adjudicated.
3. Defined as thrombosis and/or tissue ischemia secondary to excessive erythropoiesis; worsening of hypertension;cardiomyopathy; pulmonary artery hypertension; cancer-related mortality and tumor progression and recurrence; esophageal and gastric erosions; proliferative retinopathy, macular edema, choroidal neovascularization; and exacerbation of rheumatoid arthritis

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center, event-driven study in dialysis subjects with anemia associated with CKD who are currently treated with ESAs.
Dosing and Randomized Treatment Assignment	• A central randomization approach will be used to protect against potential selection bias due to the open-label design. The randomization schedule will be generated by PPD, and PPD's IRT system will be used for treatment allocation. • Subjects will be stratified by dialysis type [hemodialysis (HD*) or peritoneal dialysis (PD)], by region (see Section 10.9.1) and by participation in the ABPM sub-study. Dialysis type and region are stratification factors considered to be potentially prognostically important, i.e., predictive of study endpoints, while participation in the ABPM sub-study is an administrative stratification factor intended solely to ensure a similar number of sub-study subjects in each of the two randomized groups. ** In addition to HD this group also includes combination methods such as hemodiafiltration (HDF) or hemofiltration (HF).* • Following stratification, subjects will be randomized 1:1 to receive oral daprodustat or rhEPO (IV epoetin alfa or SC darbepoetin alfa). • Please refer to the protocol for starting doses, dose steps and elements of the dose adjustment scheme.
Interim Analysis	• An IDMC will review safety and efficacy data periodically from ongoing clinical trials in the daprodustat clinical development program for the treatment of subjects with anemia of chronic kidney disease. • In addition, a formal interim analysis is planned for this study which will assess whether the daprodustat program has met criteria for

Overview of Study Design and Key Features	
	futility or harm and should be stopped. The IDMC will review the interim analysis results and will provide a recommendation regarding early stopping to the sponsor. See Section 3.1 for further details.

2.4. Statistical Hypotheses

2.4.1. Hgb efficacy Co-Primary Hypothesis

The co-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 -rhEPO), 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 -rhEPO), is greater than -0.75 g/dL

The non-inferiority margin is pre-defined as -0.75 g/dL; 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 ANCOVA model including prognostic randomization stratification factors (dialysis type and region), baseline Hgb and treatment will be used to obtain a point estimate and two-sided 95% 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.

2.4.2. CV Safety (MACE) Co-Primary Hypothesis

The co-primary CV safety objective will assess the estimand of time to first occurrence (in days) of adjudicated MACE from randomization to the end of study in all randomized subjects regardless of what treatment(s) they go on to receive. The primary analysis will test for non-inferiority of treatment with daprodustat relative to rhEPO, expressed by the following statistical hypotheses:

- **Null:** daprodustat is inferior to rhEPO, with at least a 25% increased relative risk of first MACE (i.e. the hazard ratio is ≥1.25)
- **Alternative:** daprodustat is non-inferior to rhEPO (i.e. the hazard ratio is <1.25)

The non-inferiority margin is pre-defined as the hazard ratio of 1.25; supported by a review of evidence reported in historical randomized trials of rhEPO in dialysis and non-

dialysis CKD subjects and after consideration of the largest point estimate that, by design, would meet the statistical criterion for non-inferiority.

Statistical significance of non-inferiority will be assessed at the one-sided 2.5% level. A Cox-Proportional Hazards-Regression model, adjusting for treatment and prognostic randomization stratification factors (dialysis type and region), will be used to estimate the hazard-ratio, its two-sided 95% CI and to generate the p-value for the non-inferiority test. Non-inferiority will be achieved if the upper limit of the two-sided 95% CI is below the margin of 1.25.

The co-primary endpoints will be tested first. Non-inferiority needs to be established for both co-primaries to proceed to evaluate MACE for superiority as well as the principal secondary endpoints for superiority. Principal secondary endpoints include prioritized composites for MACE (including thromboembolic events and hospitalizations for HF) and IV iron utilization (defined as the average monthly IV iron dose used to Week 52). Statistical testing of MACE for superiority as well as the principal secondary endpoints will be adjusted for multiplicity (Section 10.11.1).

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.

In addition, the IDMC will evaluate the co-primary MACE endpoint to assess for futility of achieving non-inferiority at study completion. Pre-specified guidelines governing the decision to continue or stop the study will consider signals for harm, the predictive probability of achieving at least non-inferiority at trial end and the risk of incorrectly stopping for futility. In addition to MACE, any decisions regarding futility will take into account data related to: 1) components of MACE, 2) endpoints describing blood pressure, 3) efficacy in rhEPO hyporesponders, 4) other safety and efficacy data across the daprodustat clinical program and 5) emerging data in the public domain pertaining to safety or efficacy of HIF-prolyl hydroxylase inhibitors, and 6) any other data considered to be relevant by the IDMC. The IDMC will make a recommendation to GSK and the ESC chair as outlined in the IDMC charter regarding whether the study should continue unchanged, be modified or be terminated.

There are no prospectively defined interim analyses planned to stop the study early for benefit. While the planned futility analysis will have a small impact on reducing study-wise Type I error rate, there are no plans to adjust the alpha level used for the final analysis.

Further details of futility rules and analysis timings will be provided in the IDMC Charter.

3.1.1. Additional Considerations at the Interim Analysis Not Specified in the Protocol

If the study stops because of results of an interim analysis, subjects will be brought to the investigational sites for the final study visits (end of study visit and follow-up visit) as soon as possible.

If the trial is stopped for increased MACE risk, futility or other safety concerns, point estimates, two-sided 95% confidence intervals, and one-sided p-values will be generated for the primary and principal secondary endpoints. One-sided p-values will be compared to 0.025 to assess nominal significance, and will be provided for descriptive purposes only.

3.2. Final Analyses

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

1. It is projected that the target number of events has been attained as defined in the protocol, and final study clinic visits have occurred.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by PPD Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to GSK and PPD procedures.

4. ANALYSIS POPULATIONS

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

Population	Definition / Criteria	Analyses Evaluated
Screened	• All screened subjects.	• Study Population • Safety
Intent-To-Treat (ITT)	• All randomized subjects. • Subjects will be analyzed according to the treatment to which they were randomized.	• Study Population • Efficacy • Safety
Enrolled	• All randomized subjects. • Subjects will be analyzed according to the treatment to which they were randomized. • Use of the enrolled population is required for some displays; for this study, the enrolled and ITT populations will be identical.	• Study Population
Per-Protocol (PP)	• All ITT subjects without PP population exclusions. • Exclusions from the PP population are defined	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
	in Section 4.1 (Protocol Deviations and Study Population Exclusions) and Section 10.1 (Protocol Deviation Management and Definition for Per-Protocol Population). • Subjects will be analyzed according to the treatment received.[1]	
Safety	• All randomized subjects who receive at least one dose of randomized treatment. • Subjects will be analyzed according to the treatment received.[1]	• Safety
Sub-study Populations		
Please see sub-study analysis plans for definitions of sub-study analysis populations.		

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

4.1. Protocol Deviations and Study Population Exclusions

- Significant protocol deviations will be summarized and listed.
- Exclusions from the main study populations described above will also be summarized and listed. Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per-Protocol Population for further details of Per-Protocol population exclusions.
- Protocol deviations and study population exclusions will be tracked by the study team throughout the conduct of the study in accordance with PPD's Deviation Management Plan and Study Deviation Rules Document.
    - Data will be reviewed prior to unblinding the database to ensure all significant deviations and deviations which may lead to exclusion from the analysis are captured and categorized on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

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

Table 2 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per-Protocol Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance
10.9	Appendix 9: Multicenter Studies
10.10	Appendix 10: Examination of Covariates, Subgroups & Other Strata
10.11	Appendix 11: Multiple Comparisons & Multiplicity
10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the ITT population and will include a total column, unless otherwise specified.

Table 3 provides an overview of the planned study population analyses.

Table 3 Overview of Planned Study Population Analyses

Parameter	Analysis Population	Data Displays Generated		
		Table	Figure	Listing
Populations Analyzed				
Study Populations	Screened	Y		
Screening Status and Reasons for Screen Failure	Screened	Y		Y
Screening Attempts	Screened	Y		
Exclusions from Study Populations	ITT	Y		Y
Subject Disposition				
Subjects Who Were Rescreened	Screened			Y

Parameter	Analysis Population	Data Displays Generated		
		Table	Figure	Listing
Subject Status and Reasons for Study Withdrawal at Wk28, Wk52 and End of Study	ITT	Y	Y	Y
Subject Status and Reasons for Study Withdrawal at Wk28, Wk52 and End of Study by Region	ITT	Y		
Subject Status and Reasons for Study Withdrawal at Wk28, Wk52 and End of Study by Country	ITT	Y		
Treatment Status and Reasons for Discontinuation of Randomized Treatment at Wk28, Wk52 and End of Study	ITT	Y	Y	Y
Treatment Status and Reasons for Discontinuation of Randomized Treatment at Wk28, Wk52 and End of Study by Region	ITT	Y		
Treatment Status and Reasons for Discontinuation of Randomized Treatment at Wk28, Wk52 and End of Study by Country	ITT	Y		
Number of Subjects by Region, Country and Site ID	Enrolled	Y		
Type of Subject Contact at Wk28, Wk52 and End of Study	ITT	Y		
End of Study Contact	ITT	Y		
Subject Follow-up Time	ITT	Y		
Subject Completion Status	ITT	Y		
Subject Survival Status	ITT	Y		
Planned and Actual Treatments	ITT			Y
Protocol Deviations				
Significant Protocol Deviations	ITT	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations	ITT	Y		Y
Demographic & Baseline Characteristics				
Demographic & Baseline Characteristics	ITT & Safety	Y		Y
Demographic & Baseline Characteristics for Hyporesponders	ITT	Y		
Demographic & Baseline Characteristics by Baseline Dialysis Type	ITT	Y		
Age Ranges	Enrolled	Y		
Race and Racial Combinations	ITT	Y		Y
Smoking History	ITT	Y		
Medical Conditions	ITT	Y		
Dialysis Modality and Frequency	ITT	Y		
Dialysis Modality Changes	ITT	Y		
Prior and Concomitant Medications				
Pre-Treatment Medications	ITT	Y		
On-Treatment Medications	ITT	Y		Y
Post-Treatment Medications	ITT	Y		
Non-randomized ESA Use During Treatment Period	Safety	Y		Y

Parameter	Analysis Population	Data Displays Generated		
		Table	Figure	Listing
Exposure and Randomized Treatment Compliance				
Extent of Exposure to Randomized Treatment	Safety	Y		Y
Randomized Treatment Compliance Categories	Safety	Y		
Randomized Treatment Compliance	Safety	Y		
IRT and eCRF Dose and Frequency Discrepancies	Safety	Y		

NOTES:

- Y = Yes display generated.

6.2. Display Details

6.2.1. Populations Analyzed

The number of subjects in the Screened, Safety, ITT, Enrolled, PP and relevant sub-study populations will be summarized by treatment group and overall.

The number and percentage of subjects by screening status (enrolled/randomized, screen failed) and associated reasons for screen failure will be summarized for the screened population.

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 screen failure records will be provided for all subjects who failed screening, including site ID, unique subject ID, date of screen failure, and reason(s) for screen failure.

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, date of deviation, study day of deviation, category, coded term, criteria which lead to exclusion, and the populations from which the subject was excluded.

6.2.2. Subject Disposition

The summary of subject status and reasons for study withdrawal will include:

- the number and percentage of subjects ongoing at the Week 28 visit and Week 52 visit, the associated randomized treatment status (on randomized treatment or in follow-up), the number and percentage of subjects withdrawing early before the Week 28 visit and the Week 52 visit, the associated reasons/subreasons for withdrawal, and the number and percentage of subjects that died before the Week 28 visit and Week 52 visit, summarized by treatment group and overall. For

subjects with an adverse event leading to withdrawal of consent, the outcome (fatal, non-fatal) of the adverse event will be summarized.

- the overall number and percentage of subjects who completed the study, the overall number and percentage of subjects withdrawing early from the study and the associated reasons/subreasons for withdrawal summarized by treatment group and overall. For subjects with an adverse event leading to withdrawal of consent, the outcome (fatal, non-fatal) of the adverse event will be summarized.

The summary of subject status and reasons for study withdrawal will be repeated by region and by country. The overall only summary of subject status and reasons for study withdrawal will be repeated by relationship to 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, date of withdrawal, study day of withdrawal, primary reason for withdrawal, subreason for withdrawal, was a follow-up phone contact attempted 3 times, and was a follow-up certified letter mailed.

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.

The summary of treatment status and reasons for discontinuation of randomized treatment will include:

- the number and percentage of subjects who never received randomized treatment at the Week 28 and Week 52 visits, the number and percentage of subjects ongoing on randomized treatment at the Week 28 and Week 52 visits, and the number and percentage of subjects who discontinued randomized treatment, including the breakdown of the number and percentage of subjects who died while taking randomized treatment and those that did not die while taking randomized treatment, and the associated reasons/subreasons for randomized treatment discontinuation overall and separately for subjects who did not die while taking randomized treatment and for subjects who died while taking randomized treatment at the Week 28 and Week 52 visits summarized by treatment group and overall.

- the overall number and percentage of subjects who never received randomized treatment, the overall number and percentage of subjects who prematurely discontinued randomized treatment during the study, including the breakdown of the number and percentage of subjects who died while taking randomized treatment and those that did not die while taking randomized treatment, and a summary of the reasons and subreasons for randomized treatment discontinuation overall and separately for subjects who died while taking randomized treatment and for subjects who did not die while taking randomized treatment, and the overall number and percentage of subjects who did not prematurely discontinue

randomized treatment during the study summarized by treatment group and overall.

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

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

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 randomized treatment discontinuation by treatment group will be produced. For both of the plots, the risk set will include all subjects who started taking randomized treatment. The first plot will consider an event as subjects who discontinued randomized treatment and the second plot will consider an event as subjects who discontinued randomized treatment and did not die while on treatment. If a subject discontinued treatment due to death, that subject will not count towards the event, and will be censored instead.

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.

The type of subject contact at the Week 28, Week 52 visit and End of Study visit will be provided by treatment group and overall.

A summary of the timing of the end of study contact will be provided by subject status, type of contact, treatment group and overall.

A summary of the total follow-up time and percentage of total possible follow-up time during time periods of the study (i.e., time period for follow-up of CV endpoints, time period for vital status, and time period for on-treatment CV endpoints) will be provided by treatment group and overall (see Section 10.6.2 and Section 10.6.4 for definitions). Cardiovascular Endpoint Follow-up Among All Randomized Subjects will be presented by a figure.

A summary of the subject completion status, including the number and percentage of subjects included in the co-primary Hgb analysis, by CV endpoint status (known and unknown at the end of study) and by vital status (known and unknown at the end of study) 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.

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

6.2.3. Protocol Deviations

The number and percentage of subjects who had significant protocol deviations (defined in PPD's Study Deviation Rules Document) will be summarized by category and by treatment group and overall. It will be repeated by relationship to COVID-19 pandemic.

A listing of significant protocol deviations will be provided. The listing will include treatment, site ID, unique 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, inclusion/exclusion type, and criteria description.

6.2.4. Demographic & Baseline Characteristics

The number and percentage of subjects or summary statistics will be provided by treatment group and overall for the demographic and baseline characteristics listed in Section 10.10. This table will be repeated for the primary definition of a hyporesponder outlined in Section 10.6.2 and by baseline dialysis type (HD/PD).

A listing of demographic characteristics will be produced. This listing will include treatment, site ID, unique subject ID, year of birth, age, sex, and ethnicity and may include additional demographic characteristics.

The number and percentage of subjects in the following age ranges: Adult (18-64 years), ≥ 65 – 84 years, and ≥ 85 years will be provided by treatment group and overall.

A summary of race and racial combinations will be provided by treatment group and overall.

A listing of race will be provided. This listing will include treatment, site ID, unique subject ID, race, and race detail.

A summary of smoking history will be provided by treatment group and overall.

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

A summary of dialysis modality and frequency at randomization, Week 28, Week 52 and End of Study 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 for subjects on hemodialysis and peritoneal dialysis separately.

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. Prior and Concomitant Medications

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 post-treatment medication will be provided separately. See Section 10.4.1 for a summary of treatment states for concomitant medications.

A listing of on-treatment concomitant medication records will be provided with details of the on-treatment concomitant medication use.

The number and percentage of subjects with any non-randomized ESA use in addition to randomized treatment during the treatment period (see Section 10.6.2) will be provided by treatment group and overall. Similarly, the number and percentage of subjects with any non-randomized ESA used instead of randomized treatment during the treatment period (see Section 10.6.2) 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 subjects who have non-randomized ESA use will be provided with details of the ESA use.

6.2.6. Exposure and Randomized Treatment Compliance

Months of exposure (see Section 10.6.2) 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 in each 6-monthly exposure category (≤ 6 months, >6 - ≤ 12 months, > 12 - ≤ 18 months, etc.) 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, dose start date, dose stop date, duration of time on dose, dose, dose units, dose form, route of administration, and dosing frequency.

The number and percentage of subjects in each randomized treatment compliance category (see Section 10.6.2) during the study will be summarized by treatment group for the following time periods: Day 1 < Week 28, Week 28 - < Week 52, Week 28 - < End of Treatment, and Day 1 - < End of Treatment (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 by treatment group for the following time periods: Day 1 < Week 28, Week 28 - < Week 52, Week 28 - < End of Treatment, and Day 1 - < End of Treatment (Overall Compliance).

The number and percentage of subjects with no dose discrepancy, and at least one dose any discrepancy and the number of discrepancies between the IRT-assigned dose and the dose recorded in the eCRF will be summarized by treatment group for the following time periods: Day 1 < Week 28, Week 28 - < Week 52, Week 28 - < End of Treatment, and Day 1 - < End of Treatment (Overall Compliance). For subjects with at least one dose discrepancy, the number and percentage of subjects with 1, 2-3, 4-5 and ≥6 discrepancies will be summarized by treatment group for the same time periods.

A visit schedule will be produced that will be utilized in merging eCRF data with IRT data. This Visit schedule will generally be based on the actual visits and dates found in the IRT. Supplemental information (to account for items such as skipped visits, unscheduled visits, and kit replacements) will be provided by means of a protocol-defined visit schedule, whereby scheduled visit dates and visit windowing will be based on the intervals from randomization to each scheduled visit, as specified in the protocol.

6.2.7. COVID-19 Impacted Visits

A summary of the number and percentage of subjects with any visit impacted by COVID-19 pandemic and each visit impacted by 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. PRIMARY STATISTICAL ANALYSES

7.1. Hgb Efficacy Co-Primary Analysis

7.1.1. Overview of Planned Hgb Efficacy Co-Primary and Supportive Analyses

Table 4 provides an overview of the planned Hgb efficacy co-primary and supportive analyses.

Table 4 Overview of Planned Hgb Efficacy Co-Primary and Supportive Analyses

Endpoint	Analysis Population	Absolute				Change from Baseline						
		Summary		Individual		Stats Analysis			Summary		Individual	
		T	F	F	L	T	F	L	T	F	F	L
Mean Change in Hgb between Baseline and EP												
Co-Primary Analysis	ITT *[all available observed and imputed (on and off treatment) Hgb values]*	Y	Y			Y	Y		Y	Y		Y
Supportive While On Treatment Analysis	ITT *[evaluable Hgb values only]*	Y	Y			Y	Y		Y	Y		
Supportive Analysis PP	PP *[evaluable Hgb values only]*	Y	Y			Y	Y		Y	Y		
Sensitivity & Supportive Tipping Point Analyses[1]	ITT					Y	Y					
Supportive Analyses Alternative EP[1]	ITT	Y				Y	Y		Y			
By Subgroup[1]	ITT					Y	Y		Y			
Supportive Analysis: Observed Values only	ITT *[all available observed (on and off treatment) Hgb values]*	Y	Y			Y	Y		Y	Y		

NOTES:

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

[1] Analysis will be performed using all available observed and imputed (on and off-treatment) Hgb values and separately using evaluable Hgb values only (see Section 10.6.3).

7.1.2. Planned Hgb Efficacy Co-Primary Statistical Analyses

The co-primary efficacy estimand is the effect of daprodustat 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.

7.1.2.1. Endpoint / Variables

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

7.1.2.2. Summary Measure

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

7.1.2.3. Population of Interest

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

The analysis population included in the co-primary efficacy analyses will be based on the ITT population, unless otherwise specified.

7.1.2.4. Strategy for Intercurrent (Post-Randomization) Events

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

- Death prior to the end of the EP (i.e. before Week 52 visit)
- Randomized 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 death 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 co-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 7.1.2.5.

The following are causes of missing Hgb data affecting the co-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 the end of the EP
- Intermittent missing Hgb values at one or more visits with the EP

Missing data will be imputed as described in Section 7.1.2.5.

7.1.2.5. Statistical Analyses/Methods

Hgb Efficacy Co-Primary Statistical Analyses
Endpoint(s)
• Mean change in Hgb between baseline and EP
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 10.5.2)
  ○ Dialysis type (as randomized, see Section 10.10.2)
  ○ Region (as randomized, see Section 10.9 & Section 10.10.2)

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 10.6.3).
  ○ 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 200807. The imputations will be done by randomized treatment, dialysis type, 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, dialysis type, and region. The monotone regression will have baseline Hgb, prior scheduled (possibly imputed) Hgb values, and may include dialysis type and region as covariates (see Model Checking & Diagnostics, below). The seed for reproducibility is set to 200807.
  ○ 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 co-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
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
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 MP, mean EP, mean Alt EP, and end of treatment values will be included (see Section 10.6.3). This summary is repeated by dialysis type at randomization.   ○ This summary of Hgb will also be repeated for visits up to and including Week 52,

Hgb Efficacy Co-Primary Statistical Analyses

using the data used for the primary Hgb analysis (i.e., including imputed values). (see Section 10.6.3)), and by dialysis type at randomization.

- 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 MP, mean EP, mean Alt EP, and end of treatment values (see Section 10.6.3). This summary is repeated by dialysis type at randomization.
    - This summary of Hgb 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). (see Section 10.6.3)), and by dialysis type at randomization.
- 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 co-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 observed Hgb values (on and off-treatment (see Section 10.6.3)) 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 horizontal reference lines to depict the Hgb 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. The plot will be repeated by dialysis type at randomization.
    - This figure 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). (see Section 10.6.3)).
- All available observed Hgb change from baseline values (on and off-treatment (see Section 10.6.3)) will be displayed graphically for each scheduled study visit using a line plot. The line

Hgb Efficacy Co-Primary Statistical Analyses

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. The plot will be repeated by dialysis type at randomization.

- This figure 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). (see Section 10.6.3)).

- A listing of all hemoglobin values will be provided, including treatment, most recent dose, site ID, unique subject ID, visit, assessment date, select 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 for the co-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 200807. The imputations will be done by randomized treatment, baseline dialysis type, 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, baseline dialysis type, and region. The monotone regression will include baseline Hgb, prior scheduled (possibly imputed) Hgb values, and may have region, and baseline dialysis type as covariates (see Model Checking & Diagnostics, below). The seed for reproducibility is set to 200807.
  - 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-week interval, the imputed Hgb value would shift an additional delta. For example, the first missed visit will use delta, the second missed visit will use 2*delta, etc. The deltas explored for each treatment arm will range from -4 g/dL to 4 g/dL per 4-week interval with a 0.1 g/dL increment respectively. Delta scenarios which are known ahead of time to not 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

Sensitivity Statistical Analyses
imputed Hgb values. ○ EP Hgb values will be computed for each pair of deltas and compared across treatment groups using the co-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 will be calculated.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• 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. Colored 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
• This estimand utilizes the same endpoint, summary measure and target population as the co-primary Hgb estimand. For the intercurrent events of death, randomized 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 co-primary Hgb analyses and summaries described above will be performed using evaluable Hgb values (see Section 10.6.3). • No data will be imputed in this analysis, so a summary of missing data will be provided. • The LS mean treatment difference and associated two-sided 95% CI from this analysis will be included on a forest plot with the co-primary Hgb analysis results. • The number and percentage of subjects meeting each evaluable Hgb (see Section 10.6.3) exclusion criterion 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 10.6.3). • The LS mean treatment difference and associated two-sided 95% CI from this analysis will be included on a forest plot with the co-primary Hgb analysis results.

Supportive Statistical Analyses
Alternative EP (Week 28-36) Analysis

• The following analyses will be repeated using an alternative EP from Week 28-36:
  ○ The co-primary analysis and summaries (using on- and off-treatment, observed and imputed Hgb values (see Section 10.6.3))
  ○ Supportive analysis 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 co-primary Hgb analysis results.

Subgroup Analysis
• Subgroup analysis will be performed 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. • Subgroup analysis will also be performed separately using evaluable Hgb values only (see Section 10.6.3). • Subgroup analysis details are discussed in Section 10.10.1.
Observed Values Only Analysis
• The co-primary analysis will be performed using available observed Hgb values (on and off-treatment) only for post-randomization hemoglobin. There will be no imputation in this approach. • The LS mean treatment difference and associated two-sided 95% CI from this analysis will be included on a forest plot with the co-primary Hgb analysis results.

7.2. CV Safety (MACE) Co-Primary Analysis

7.2.1. Overview of Planned CV Safety (MACE) Co-Primary and Supportive Analyses

Table 5 provides an overview of the planned CV safety (MACE) co-primary, and supportive analyses.

Table 5 Overview of Planned CV Safety (MACE) Co-Primary and Supportive Analyses

Endpoint	Analysis Population	Absolute						
		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L
Time to First Occurrence of Adjudicated MACE								
Co-Primary Analysis	ITT	Y	Y		Y			Y
Supportive Analysis While On-treatment	ITT	Y	Y		Y			
Sensitivity Analysis Tipping Point	ITT	Y	Y					
COVID-19 Supportive Analyses	ITT	Y	Y		Y			
Events Until 664th MACE Supportive	ITT	Y	Y		Y			

Endpoint	Analysis Population	Absolute						
		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L
Analysis								
By Subgroup	ITT	Y	Y		Y			

NOTES:

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

7.2.2. Planned CV Safety (MACE) Co-Primary Statistical Analyses

CV Safety (MACE) Co-Primary Statistical Analyses
Endpoint(s)
• Time to first occurrence of adjudicated MACE
Model Specification

• The Cox Proportional Hazards model will adjust for the following baseline categorical values:
  ○ Treatment
  ○ Dialysis type (as randomized, see Section 10.10.2)
  ○ Region (as randomized, see Section 10.9 & Section 10.10.2)
• 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].
• The co-primary analysis will use only adjudicated safety endpoints as determined by the clinical endpoint committee (CEC) within the time period for follow-up of CV endpoints defined in Section 10.6.4.
• Calculation of time-to-event or censoring is described in further detail in Section 10.6.4.
• First occurrence of adjudicated MACE for a subject is defined as the first adjudicated event, determined by the event date, that is indicated as all-cause mortality, non-fatal MI or non-fatal stroke with further details in Section 10.6.4.

Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
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. • 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. Subjects experiencing MACE will be further broken down into subjects who experienced exactly one MACE, subjects who experienced exactly two MACE, and subjects who experienced more than two MACE. The number and percentage of subjects in each of these categories by event type combinations will be provided by treatment group. • The hazard ratio, two-sided 95% CI, one-sided p-value for the statistical non-inferiority test,

CV Safety (MACE) Co-Primary Statistical Analyses

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. The number and percentage of subjects with a MACE event and the number censored at the end of the study, the MACE incidence rate per 100 person-years, and the absolute rate difference per 100 person-years and associated two-sided 95% CI will be displayed with the results of the Cox proportional hazards regression model.

- To inform on the validity of the adjusted Cox proportional hazards model, the proportional hazards assumption will be assessed by plotting the logarithm of the negative logarithm of the estimated survivor function against the logarithm of time, for each treatment group. If the hazards are proportional, the lines should be approximately parallel.
- The hazard ratio, two-sided 95% CIs and one-sided non-inferiority and superiority p-values will be displayed on a forest plot together with supportive analysis results (i.e., excluding the Tipping Point Analysis).
- Time from Randomization to first 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.
- A listing of all MACE events occurring during the study will be provided and will include treatment, site ID, unique subject ID, select demographic information, event type, event date, and study day.

Model Results Interpretation

- Non-inferiority will be achieved if the upper limit of the two-sided 95% CI for the hazard ratio is below the pre-specified non-inferiority margin of 1.25. For evaluation of MACE superiority, a principal secondary analysis, see Section 10.11.1.

Sensitivity Statistical Analyses

Tipping Point (Multiple Imputation) Analysis

- Tipping point sensitivity analyses will be conducted under a range of missing data assumptions to determine how extreme assumptions need to be for non-inferiority conclusions to change. Assumptions about missing outcomes 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. Missing data that occurs before the end of the study (i.e., due to withdrawal from the study) will be imputed across a range of scenarios using multiple imputation with treatment, dialysis type (as randomized, see Section 10.10.2) and region (as randomized, see Section 10.9 & Section 10.10.2) as strata in the imputation model and to generate the bootstrap samples. For each treatment arm separately, the assumed event rates will range from assuming that all prematurely censored subjects have a MACE at the time of censoring (corresponding to an infinite event rate for subjects who drop out), to assuming that all prematurely censored subjects complete the study without experiencing the event (corresponding to zero event rate for subjects who drop out). Event rates between the 0 and infinite scenarios, including a censored at random scenario, will be explored by varying the log-hazard rate [Jackson, 2014]. The resulting time to first occurrence of MACE data will be compared across treatment groups using the co-primary Cox proportional hazards model described above, and Rubin's rules [Rubin,1987] will be used to combine results of the imputed datasets.
    - Graphics depicting hazard ratio and one-sided NI p-value surfaces will be produced using an enhanced tipping point approach [Liublinska, 2014].

Supportive Statistical Analyses

While On-Treatment Analysis

- The while on-treatment MACE analysis will use a structure identical to that described for the co-primary MACE analysis and will use the time to the first occurrence of while on-treatment adjudicated MACE endpoint (excluding those MACE occurring after subjects permanently discontinued IP). This analysis will use the time period for on-treatment CV endpoints as described in Section 10.6.4.
- The HR, associated two-sided 95% CI, and one-sided non-inferiority and superiority p-values from this supportive analysis will be included on a forest plot with the co-primary MACE results.
- Cumulative time from Randomization to first adjudicated while on-treatment MACE event or end of trial will be evaluated using KM methodology and displayed graphically for the comparison of daprodustat vs. rhEPO.

COVID-19 Supportive Analyses

- COVID-19 MACE are identified by the CEC through one of the following statements:
  - Definitive death due to COVID-19
  - Possible death due to COVID-19
  - Definite COVID-19 related hospitalization (for MIs and strokes)
  - Possible COVID-19 related hospitalization (for MIs and strokes)
- 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.
- The additional supportive analysis of MACE excluding adjudicated COVID-19 MACE, will use a structure identical to that described for the co-primary MACE analysis and will exclude those adjudicated COVID-19 MACE. This analysis will use the time period for follow-up of CV endpoints defined in (see Section 10.6.4).
- The HR, associated two-sided 95% CI, and one-sided non-inferiority and superiority p-values from this supportive analysis will be included on a forest plot with the co-primary MACE results.
- Cumulative first adjudicated MACE hazard ratio and the upper bound of the 95%CI (Dapro vs Darbe) will be estimated using the same Cox Proportional Hazards model specified in the co-primary MACE analysis (See Section 7.2.2). They will be displayed graphically by calendar date, at every half year mark, starting from Jan2018 or later when the Cox Proportional Hazards model could converge. At each half year mark, subjects who have not had their first MACE will be censored at the date of the half year mark. The graph will also show the cumulative number of first adjudicated MACE by calendar date. A vertical reference line will be used to represent the date the pandemic measures begin in the majority of the countries.

Events Until Date of 664th MACE Supportive Analysis

- The fourth protocol amendment changed the target number of adjudicated first MACE from 945 to 664. At the time of protocol amendment approval, the new target 664th adjudicated first MACE had already occurred. The additional MACE that occur before study closeout will be included in the co-primary MACE analysis. This supportive analysis will only include adjudicated first MACE that occurred on or before the date of the 664th adjudicated first MACE.
- A summary of the number and percentage of subjects having first-occurrence adjudicated MACE on or before the date of the 664th adjudicated first MACE will be provided by treatment group. The number and percentage of the types of events that make up the first occurrence of adjudicated MACE will also be provided by treatment group.
- This supportive analysis of adjudicated first MACE occurring on or before the date of the 664th

Sensitivity Statistical Analyses
adjudicated first MACE will use a structure identical to that described for the co-primary MACE analysis and will use the earlier of (the date of the 664th MACE, and the end of the time period for follow-up of CV endpoints as described in Section 10.6.4) for censoring. • The HR, associated two-sided 95% CI, and one-sided non-inferiority and superiority p-values from this supportive analysis will be included on a forest plot with the co-primary MACE results. • Cumulative time from Randomization to first adjudicated MACE event or end of trial will be evaluated using KM methodology and displayed graphically for the comparison of daprodustat vs. rhEPO.
Subgroup Analysis
• Subgroup analysis details are discussed in Section 10.10.1.

8. OTHER STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Principal Secondary Efficacy Analyses

8.1.1.1. Overview of Planned Principal Secondary Efficacy Analyses

Table 6 provides an overview of the planned principal secondary efficacy analyses.

Table 6 Overview of Planned Principal Secondary Efficacy Analyses

Endpoint	Analysis Population	Absolute						
		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L
Iron Use								
Average monthly IV iron dose (mg)/subject to Week 52	ITT	Y			Y	Y		Y
Supportive analysis: Average monthly IV iron dose (mg)/subject to Week 52 using on and off-treatment IV iron records	ITT	Y			Y	Y		
By subgroup	ITT	Y	Y					

NOTES:

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

8.1.1.2. Planned Principal Secondary Efficacy Statistical Analyses

Principal Secondary Efficacy Statistical Analyses: Average Monthly IV Iron Dose
Endpoint(s)
• Average monthly IV iron dose (mg)/subject to Week 52
Model Specification
• Average monthly IV iron dose (mg)/subject from baseline to Week 52 will be determined by calculating the total IV iron dose per subject from treatment start date + 1 to the earliest of (Week 52 visit date, first blood (RBC or whole blood) transfusion date, and treatment stop date + 1 day) which corresponds to the time while the subject was on randomized treatment and before receiving a blood transfusion. This total IV iron dose will be divided by (the number of days from treatment start date + 1 to the earliest of (Week 52 visit date, first blood transfusion date (RBC or whole blood), and treatment stop date +1) /30.4375 days). See Section 10.4.1 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 subject between arms, adjusting for: ○ Treatment ○ Baseline monthly IV iron dose (see Section 10.5.2) ○ Dialysis type (as randomized, see Section 10.10.2) ○ Region (as randomized, see Section 10.9 & Section 10.10.2)

Principal Secondary Efficacy Statistical Analyses: Average Monthly IV Iron Dose
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. • 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, time period, and average monthly IV iron dose at Week 52.
Model Results Interpretation
• See Section 10.11.1.

Supportive Statistical Analyses
Average monthly IV iron dose (mg)/subject to Week 52 using on and off treatment IV iron records, regardless of transfusion
• 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 or transfusion. • 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 the earliest of Week 52 visit date, study completion/withdrawal date) and dividing by (earliest of the (Week 52 visit date, study completion/withdrawal date) – Randomization date + 1 day/30.4375 days).
Subgroup Analysis
• Subgroup analysis details are discussed in Section 10.10.1.

8.1.2. Additional Secondary Efficacy Analyses

8.1.2.1. Overview of Planned Additional Secondary Efficacy Analyses

Table 7 provides an overview of the planned additional secondary efficacy analyses.

Table 7 Overview of Planned Additional Secondary Efficacy Analyses

Endpoint	Analysis Population	Absolute							Change from Baseline						
		Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L	T	F	L	T	F	F	L
Hgb Variability															
Hgb change from baseline to Week 52[1, 2]	ITT								Y	Y		Y			
Hgb change from baseline to Week 52 by subgroup[1,2,3]	ITT								Y	Y					
Hgb responders[2]	ITT	Y			Y										
Hgb responders by subgroup[2,3]	ITT	Y	Y												
% of time Hgb in analysis range[2]	ITT	Y			Y										
% of time Hgb in analysis range by subgroup[2,3]	ITT	Y	Y												
Time to Rescue															
Time to stopping randomized treatment due to meeting rescue criteria	ITT	Y	Y		Y										
Time to stopping randomized treatment due to meeting rescue criteria by hyporesponder subgroup	ITT	Y													

NOTES:

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

[1] Analysis will be performed using all available (on and off-treatment) Hgb values.
[2] Analysis will be performed using evaluable Hgb values only (see Section 10.6.3).
[3] Subgroup analysis will only use the region and hyporesponder subgroups defined in Section 10.10.1.

8.1.2.2. Planned Secondary Efficacy Statistical Analyses

Hgb Variability

Secondary Efficacy Statistical Analyses: Hgb Variability
Endpoint(s)
• Hgb change from baseline to Week 52 • N (%) responders, defined as mean Hgb within the Hgb analysis range 10-11.5 g/dL during EP • % time Hgb in analysis range (10-11.5 g/dL) during the evaluation period (EP, Week 28 to 52) and during the maintenance period (MP; Week 28 to end of trial) *(non-inferiority analysis that will use a margin of 15 percentage points less time in range)*
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 (Randomization date + 1 day to <Week 28). The model will include factors for treatment, time, prognostic randomization stratification factors (as randomized, see Section 10.10.2), 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 10.6.3). 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 randomized treatment before Week 52 are assumed to be missing at random. • For the Hgb responder analysis, mean Hgb during the EP will be defined as in the while on-treatment supportive analysis (Section 10.6.3). 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 factors (as randomized, see Section 10.10.2), will be used to compare the number and % of responders between the treatment groups. • For the analysis of % time in range, the method by Rosendaal [Rosendall, 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) and separately during the MP (Week 28 – end of study) (See Section 10.6.3). 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 factors (see Section 10.10.2). 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.
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, mean MP Hgb, and end of treatment Hgb above, within and below the Hgb analysis range will be

Secondary Efficacy Statistical Analyses: Hgb Variability
summarized by treatment group. • For the responder analysis, the number and % of responders by treatment group, difference in response rate (daprodustat vs – rhEPO) and two-sided 95% CI using Wald method will be provided along with the one-sided CMH p-value for the treatment group comparison. If the CMH adjusted treatment difference is positive, then the one-sided p-value is p/2, and if the adjusted treatment difference is negative, then the one-sided p-value is 1-p/2, where p is the two-sided p-value from the CMH test. • The % time Hgb is above, in and below the Hgb analysis range (10-11.5 g/dL) during the MP and the EP will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. • The percent time in 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 co-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 the one-sided p-value is < 0.025.

Supportive Statistical Analyses
Subgroup Analysis
• Subgroup analyses will be performed for all Hgb variability endpoints, using the region and hyporesponder subgroups only (described in Section 10.9.1 & Section 10.10), in a method similar to that described for the subgroup analyses of the co-primary and principal secondary analyses.

Time to Rescue

Secondary Efficacy Statistical Analyses: Time to Rescue
Endpoint(s)
• Time to stopping randomized treatment due to meeting rescue criteria
Model Specification
• Analysis of the endpoint above will be performed using an analysis model identical to that described for the co-primary MACE analysis. • 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 10.6.3. • 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

Secondary Efficacy Statistical Analyses: Time to Rescue
meeting criteria for rescue.
Model Results Presentation
• Summaries will include (see Section 10.6.3): ○ 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 will be identical to the co-primary MACE model results, with the following exceptions: ○ The one-sided p-value presented will be for the test of superiority of daprodustat vs. rhEPO. ○ The forest plot figure will not be created for the time to stopping study medication due to meeting rescue criteria endpoint.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance.

Supportive Statistical Analyses
Subgroup Analysis
• Subgroup analyses will be performed for the time to rescue endpoint using the hyporesponder subgroup only (described in Section 10.10), in a method similar to that described for the subgroup analyses of the co-primary MACE analysis.

8.1.3. Exploratory Efficacy Analyses

8.1.3.1. Overview of Planned Exploratory Efficacy Analyses

Table 8 provides an overview of the planned exploratory efficacy analyses.

Table 8 Overview of Planned Exploratory Efficacy Analyses

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	L	T	F	F	L
Hgb Variability									
Hgb observed (including imputed) and change from baseline (CFB) at all visits	ITT	Included with Hgb co-primary and supportive analyses (Section 7.1)							
% of time Hgb is above, within and below Hgb analysis range during EP and MP	ITT	Included with Hgb secondary analyses (Section 8.1.2)							
Number (%) of subjects with mean Hgb above, within and below Hgb analysis range during EP and at the end of treatment	ITT	Included with Hgb secondary analyses (Section 8.1.2)							

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	L	T	F	F	L
Number (%) of subjects with Hgb < 7.5 g/dL during EP and MP[1]	ITT	Y							
Number of times Hgb < 7.5 g/dL during EP and MP[1]	ITT	Y							
Number (%) of subjects with a >1g/dL increase in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL increase in Hgb within any 4 week period from Week 4 to Week 52[1]	ITT	Y							
Number (%) of subjects with a >1g/dL decrease in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL decrease in Hgb within any 4 week period from Week 4 to Week 52[1]	ITT	Y							
N (%) of subjects with a Hgb value ≥ 12 g/dL during the EP and MP[1]	ITT	Y							
Number of times Hgb ≥ 12 g/dL during the EP and MP[1]	ITT	Y							
% of time Hgb ≥ 12 g/dL during the EP and MP[1]	ITT	Y							
Iron Parameters									
Hepcidin, ferritin, TSAT, total iron, TIBC observed and CFB at all visits	ITT	Y	Y			Y	Y		
Average quarterly IV iron dose/subject	ITT	Y	Y						
Average quarterly TSAT	ITT	Y	Y						
Average quarterly ferritin	ITT	Y	Y						
Subjects who met iron management criteria	ITT	Y							
Subjects who reduced IV iron during EP	ITT	Y							

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	L	T	F	F	L
relative to Baseline									
RBC and Whole Blood Transfusions									
Number (%) of subjects receiving at least one RBC or whole blood transfusion by Week 52 and by end of treatment	ITT	Y							
Number of RBC and whole blood transfusion events per 100 patient years	ITT	Y							
Number of RBC and whole blood transfusions per 100 patient years	ITT	Y							
Number of RBC and whole blood units per 100 patient years	ITT	Y							
Time to first RBC or whole blood transfusion	ITT	Y	Y						
DGF									
Number (%) of subjects experiencing DGF	ITT	Y							
Duration of DGF	ITT	Y							
Dose Adjustment Scheme Evaluation									
Assigned dose by visit	ITT	Y	Y						
Most recent dose by visit	ITT		Y						Y
Number (%) of patients with 0,1,2…, 10, or >10 dose adjustments during the following periods: Day 1 - <Week 28, Week 28 – <Week 52, Day 1 – < end of treatment	ITT	Y							
Number of dose adjustments during the following periods: Day 1 - <Week 28, Week 28 – <Week 52, Day 1 – < end of treatment	ITT	Y							
Time dose held for Hgb ≥ 12 g/dL	ITT	Y							
Dosing algorithm update[1]	ITT	Y[2]	Y[2]						

NOTES:

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

[1] Summaries will be presented using evaluable Hgb values only (see Section 10.6.3).
[2] Summary tables and figures will contain the results of a statistical model.

8.1.3.2. Planned Exploratory Efficacy Display Details

Hgb Variability

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 and the MP 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 10.6.3). 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 and Week 4) or a >2 g/dL increase in Hgb within any 4-week period from Week 4 to Week 52 will be summarized by visit and overall at Week 52 by treatment group using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).

The number and percentage of subjects with a >2 g/dL increase in Hgb within any 4-week period from Week 4 to Week 52 will be summarized by visit and overall at Week 52 by treatment group using central laboratory Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3). 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 and Week 4) or a >2 g/dL increase in Hgb within any 4-week period from Week 4 to Week 52 will be summarized by visit and overall at Week 52 by treatment group using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).

The number and percentage of subjects with a >2 g/dL decrease in Hgb within any 4-week period from Week 4 to Week 52 will be summarized by visit and overall at Week 52 by treatment group using central laboratory Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3). 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 and the MP 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 10.6.3). The central laboratory summary will be considered the primary summary of this data.

The percentage of time Hgb is ≥ 12 g/dL and the percentage of time Hgb is ≥ 12 g/dL for subjects with at least one Hgb ≥ 12 g/dL during the MP and the EP will be calculated using the Rosendaal method as described in Section 8.1.2. The percentage of time Hgb is ≥ 12 g/dL during the MP and 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 10.6.3).

Iron Parameters

Hepcidin, ferritin, and total iron on-treatment values will be log-transformed (see Section 10.5.2) 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 and TIBC 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.

Percent change from baseline in log-transformed (see Section 10.5.2) hepcidin , ferritin, and total iron 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. Graphical summaries will be provided.

Change from baseline in TSAT and TIBC 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.

Average quarterly IV iron dose/subject while on treatment will be summarized by presenting average monthly IV iron dose by quarter (see Section 10.6.3). Summaries will include mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. Graphical summaries will be provided.

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 10.6.3). 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 10.6.3). 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, the first year 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 10.6.3). 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 Time and Events table (see Section 10.2.1). 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 10.6.3) 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 10.6.3).

RBC and Whole Blood Transfusions

Summary and analysis tables will use the 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 10.6.3.

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 transfusions 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, Week 52 and End of Treatment.

An analysis of time to first RBC or whole blood transfusion will be performed as described in Section 10.6.3, including a Kaplan-Meier plot.

All transfusion summaries will be repeated for the primary definition of ESA hyporesponder subgroups (see Section 10.6.2).

DGF

Delayed graft function after deceased donor kidney transplantation is defined in Section 10.6.3.

The number and percentage of patients experiencing DGF after deceased donor kidney transplantation will be summarized by treatment group.

The length of time in days that subjects experience DGF after deceased donor kidney transplantation will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group.

Dose Adjustment Scheme

See Section 10.6.3 for additional details of dose adjustment scheme endpoints.

For exploratory summaries of dose levels, subjects in the rhEPO arm will be further divided into subjects receiving epoetin alfa and subjects receiving darbepoetin alfa. The total weekly dose of epoetin alfa will be summarized and the total 4-weekly dose of darbepoetin alfa will be summarized (see Section 10.6.3). Since it is possible for subjects to switch from epoetin alfa to darbepoetin alfa during the study, subjects who receive both treatments during the study will be counted in each group.

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 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 following summaries of dose adjustments will be produced twice – the first time counting all dose adjustments, including adjustments related to periods of dose holds (i.e., IRT assignment of a 0-dose), the second time excluding dose adjustments related to periods of dose hold.

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 – < end of treatment.

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 – < end of treatment. For the period of time from Day 1 - < end of treatment, the number of dose adjustments per year will be summarized as well.

The time (in days) that study treatment was withheld for 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, Day 1 – < end of treatment, Week 28 - < end of treatment.

Summary tables for the dose adjustment scheme endpoints will also be repeated for the following subgroups (see Section 10.10.1 for subgroup definitions):

- rhEPO hyporesponders (primary definition)
- Region
- Race group
- Dialysis type at randomization
- 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 separately for subjects receiving epoetin alfa and darbepoetin alfa and these plots will also be overlaid on a graph of corresponding Hgb values by visit.

Protocol Amendment 3 updated the dosing algorithm used to assign doses of randomized treatment to subjects in both treatment arms. In order to assess the impact of the dosing algorithm update, Hgb profiles will be created by dosing algorithm category (original algorithm, updated algorithm) and by treatment group. Subjects who were randomized under the original algorithm but switched to the updated algorithm will only have their original dosing algorithm Hgb values included. Hgb values from subjects who were randomized under the updated algorithm will be included in the updated algorithm group (see Section 10.6.3). Only evaluable Hgb values will be used.

Evaluable Hgb data will be fit in an MMRM model with an unstructured covariance matrix using the Kenward-Roger option for PROC MIXED in SAS to estimate denominator degrees of freedom and standard errors. The model will adjust for dialysis type, region, baseline Hgb, baseline Hgb by time, and algorithm by treatment by time. The model will be run without main effects (treatment, time, and algorithm) and without two-way interaction terms (algorithm by time, treatment by time, and algorithm 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 results. In the event of model convergence issues, the steps outlined in Section 10.10.1 will be followed.

A summary of adjusted mean evaluable Hgb values, standard errors, 95% confidence intervals, and 95% predictions intervals (see Section 10.6.3) for each scheduled study

visit will be provided for each algorithm (original, updated) overall and by treatment group. A corresponding figure will plot the adjusted mean Hgb values in a line plot and the 95% confidence intervals and 95% prediction intervals with shaded regions for each visit for each algorithm group by treatment (including overall), as long as the algorithm/treatment group combination contains at least 20 subjects at the visit.

8.1.4. Other Efficacy Analyses

Phosphate Binder Analyses

The following analyses will be conducted to confirm the effect of phosphate binder co-administration.

Evaluable Hgb values will be summarized using mean, standard deviation, minimum, P25, median, P75 and maximum at week 4 by treatment group and by baseline phosphate binder use (see Section 10.6.3).

The number and percentage of subjects with evaluable Hgb above, within and below the Hgb analysis range (10-11.5g/dL) at week 28 and week 52 will be summarized by treatment group and by phosphate binder use at week 28 and week 52 respectively(see Section 10.6.3).

The assigned dose by visit will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at week 28 and week 52 by treatment group and by baseline phosphate binder use (see Section 10.6.3).

The median assigned dose by treatment, by baseline phosphate binder use (see Section 10.6.3) will be displayed graphically for each scheduled study visit from day 1 to week 52 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. This plot will be created by treatment group separately for subjects receiving epoetin alfa and darbepoetin alfa and these plots will also be overlaid on a graph of corresponding mean evaluable Hgb values by visit. Since it is possible for subjects to switch from epoetin alfa to darbepoetin alfa during the study, subjects who receive both treatments during the study will be counted in each group.

8.2. Safety Analyses

8.2.1. Principal Secondary Safety Analyses

8.2.1.1. Overview of Planned Principal Secondary Safety Analyses

Table 9 provides an overview of the planned principal secondary safety analyses.

Table 9 Overview of Planned Principal Secondary Safety Analyses

Endpoint	Analysis Population	Absolute						
		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L
CV Safety Endpoints								
Time to First Occurrence of [1] • MACE[2] • MACE + thromboembolic events (vascular access thrombosis, deep vein thrombosis, pulmonary embolism) • MACE + hospitalization for HF	ITT	Y	Y		Y			
Supportive Analysis While On-treatment	ITT	Y	Y					
By subgroup	ITT	Y	Y					

NOTES:

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

[1] Separate displays produced for each event - adjudicated events used.

[2] Displays to assess MACE superiority will be included with the co-primary MACE displays.

8.2.1.2. Planned Principal Secondary Safety Statistical Analyses

Principal Secondary Safety Statistical Analyses: Additional Cardiovascular Safety Endpoints
Endpoint(s)

• Time to first occurrence of
  • MACE
  • MACE or a thromboembolic event (vascular access thrombosis, deep vein thrombosis or pulmonary embolism)
  • MACE or hospitalization for HF

Model Specification
• Analysis of each of the endpoints above will be performed individually using an analysis model identical to that described for the co-primary MACE analysis (Section 7.2.2) for the evaluation of superiority. • Analysis will include only those safety endpoints occurring within the time period for follow-up of CV endpoints as described in Section 10.6.4. • For those endpoints or components of endpoints intended to go through the adjudication process, only the adjudicated results will be used.
Model Results Presentation
• The summary displays of time-to-event endpoints will include a summary of the number and percentage of subjects having events. The number and percentage of the type of first occurrence will also be provided for the composite endpoints by treatment group. • A summary of all MACE or thromboembolic events including the number and percentage of

Principal Secondary Safety Statistical Analyses: Additional Cardiovascular Safety Endpoints
subjects and number of events (including first and subsequent MACE or thromboembolic event) by type of event will be provided by treatment group. • A summary of all MACE or hospitalization for HF events including the number and percentage of subjects and number of events (including first and subsequent MACE or hospitalization for HF) by type of event will be provided by treatment group. Subjects experiencing MACE or hospitalization for HF events will be further classified into subjects who experienced exactly one MACE or hospitalization for HF event, subjects who experienced exactly two MACE or hospitalization for HF events, and subjects who experienced more than two MACE or hospitalization for HF events. The number and percentage of subjects in each of these categories by event type combinations will be provided by treatment group. • The model results presentation will be identical to the co-primary MACE model results, with the following exception: ○ A single one-sided p-value for the test of superiority of daprodustat vs. rhEPO will be presented (i.e. there will be no test for non-inferiority).
Model Results Interpretation
• See Section 10.11.1.

Supportive Statistical Analyses
While On-Treatment Analysis
• While on-treatment analyses will be produced for superiority comparisons of the principal secondary CV safety endpoints in a method that is identical to the while on-treatment supportive analysis of the MACE co-primary endpoint described in Section 7.2.2, using events that occur during the time period for on-treatment CV endpoints (see Section 10.6.4).
Subgroup Analysis
• Subgroup analysis details are discussed in Section 10.10.1.

8.2.2. Additional Secondary Safety Analyses

8.2.2.1. Overview of Planned Additional Secondary Safety Analyses

Table 10 provides an overview of the planned additional secondary safety analyses.

Table 10 Overview of Planned Additional Secondary Safety Analyses

Endpoint	Analysis Popula-tion	Absolute							Change from Baseline						
		Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L	T	F	L	T	F	F	L
Additional CV Safety Endpoints[1]															
All-cause mortality	ITT	Y	Y		Y			Y							
CV mortality	ITT	Y	Y		Y										
MI (non-fatal and fatal)	ITT	Y	Y		Y										
Stroke (non-fatal and fatal)	ITT	Y	Y		Y										
MACE or	ITT	Y			Y										

Endpoint	Analysis Population	Absolute							Change from Baseline						
		Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L	T	F	L	T	F	F	L
hospitali-zation for HF (recurrent events)															
CV mortality or non-fatal MI	ITT	Y	Y		Y										
All-cause hospitalization	ITT	Y	Y		Y										
All-cause hospital re-admission within 30 days	ITT	Y	Y		Y										
MACE or hospitali-zation for HF or thrombo-embolic events	ITT	Y	Y		Y										
Hospitalization for HF	ITT	Y	Y		Y										
Thromboembolic events	ITT	Y	Y		Y										
Blood Pressure															
SBP, DBP and MAP changes from Baseline[2,3]	ITT				Y	Y			Y			Y	Y		
Number of BP exacerbation events per 100 patient years[3]	ITT	Y			Y										
Patients experiencing at least one BP exacerbation event during study[3]	ITT	Y			Y										

NOTES:

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

[1] Adjudicated events used where available.

[2] Analysis will be performed using all available (on and off treatment) BP values.

[3] Analysis will be performed using on-treatment BP values only.

8.2.2.2. Planned Additional Secondary Safety Statistical Analyses

Additional CV Safety Endpoints

Secondary Safety Statistical Analyses: Additional CV Safety Endpoints
Endpoint(s)
• All-cause mortality, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke • MACE or hospitalization for HF (recurrent events analysis) • CV mortality or non-fatal MI • All-cause hospitalization (see Section 10.6.4) • All-cause hospital re-admission within 30 days (see Section 10.6.4) • MACE or hospitalization for HF or thromboembolic events • Hospitalization for HF • Thromboembolic events
Model Specification
• Analysis of the endpoints above (except the recurrent event analysis) will be performed individually using an analysis model identical to that described for the co-primary MACE analysis for the evaluation of superiority, using the event dates defined in Section 10.6.4. Additionally, supportive summaries and analyses for the following endpoints will be generated including fatal events which are identified only through the death endpoint page and do not have a corresponding positively adjudicated endpoint event (see Section 10.6.4): ○ MI ○ Stroke ○ Thromboembolic events: Pulmonary Embolism • For purposes of time-to-event models, subjects who have never been hospitalized will be right-censored (i.e., are still considered to be at-risk) for an all-cause hospital re-admission within 30 days. • The recurrent event analysis of MACE or hospitalization for HF events will use the Prentice, Williams, Peterson (PWP) model [Prentice, 1981], based on the Cox proportional hazards model, to analyze the multiple event data. This model analyzes the time to first, second, etc. events while accounting for the correlation of events within an individual subject. Subjects are at risk for a k^{th} event only if they survived a $(k-1)^{st}$ event. For the models described below, if there are not at least 15 k^{th} events per arm, the treatment effect associated with the k^{th}, $(k+1)^{th}$, etc. events will not be estimated. All event times will be relative to randomization, as opposed to intra-event time (i.e. total times rather than gap times will be used). Three models will be used. The first model will estimate a common treatment effect, regardless of the number of events experienced by subjects. A second model will be run that allows the treatment effects to differ depending on the number of events experienced by subjects. A third model will be run that allows the treatment effect associated with the time to 1^{st} MACE or hospitalization for HF to differ from a common treatment effect estimated for time to 2^{nd}, 3^{rd}, 4^{th}, etc. MACE or hospitalization for HF. The common treatment effect associated with the time to 2^{nd}, 3^{rd}, 4^{th}, etc. in the third model would provide support for a treatment effect on time to subsequent MACE or hospitalization for HF. It is possible for a patient to die in conjunction with experiencing a series of events in a short time frame. Ultimately, the CEC will identify the primary cause of death. For the purposes of

Secondary Safety Statistical Analyses: Additional CV Safety Endpoints
analysis of time to first and subsequent MACE or hospitalization for HF, only those events occurring prior to and including the 'fatal' event will be included. For example, suppose a subject has an MI, followed by a stroke, and dies within a short time frame. If the CEC attributes the death to the MI, only the MI will be used in the analysis. If the CEC attributes the death to the stroke, both the MI and stroke would be used. If the CEC attributes the death to some cause other than the MI and stroke, all three events would be used. • Analyses will include only those safety endpoints occurring within the time period for follow-up of CV endpoints, with the exception of all-cause mortality, which will use the time period for vital status (see Section 10.6.4). • For those endpoints or components of endpoints intended to go through the adjudication process, only the adjudicated results will be used.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation

• The summary displays of time-to-event endpoints will include a summary of the number and percentage of subjects having events. Summaries of composite endpoints will include the number and percentage of the type of first occurrence by treatment group.
• A summary of all time-to-event endpoints including the number and percentage of subjects and number of events (including first and subsequent events) by type of event will 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 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).
  ○ Summaries of PEs will include outcome of PE (fatal or non-fatal).
  ○ 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).
• The model results presentation for the endpoints above (except the recurrent event analysis) will be identical to the co-primary MACE model results, with the single exception being the one-sided p-value presented will be for the test of superiority of daprodustat vs. rhEPO.
• For the recurrent events analysis, hazard ratios, two-sided 95% CIs and one-sided chi-squared p-values associated with treatment effects (daprodustat vs. rhEPO) will be presented for the

Secondary Safety Statistical Analyses: Additional CV Safety Endpoints
three models described above. • Summaries that partition the investigator-reported events as (adjudicated to the same event, adjudicated to a different event, adjudicated as a non-event) will be presented. Summaries of investigator/adjudicator agreement by type of event reported by investigators may also be reported. • 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.. • A summary of all-cause hospital re-admission within 30 days will be provided by treatment group including summaries of the number of re-admissions within 30 days per subject and the primary diagnosis at re-admission discharge by system organ class and lower level term. • 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.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance.

Blood Pressure

Secondary Safety Statistical Analyses: Blood Pressure
Endpoint(s)
• Change from baseline in SBP, DBP and MAP at Week 52 and at end of treatment • Number of BP exacerbation events per 100 patient years • N (%) of subjects with at least one BP exacerbation event during study
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. Models will be run two times: ○ On-treatment BP values only, excluding values collected during the stabilization period (Randomization date + 1 day to <Week 28). ○ On-treatment BP values only, including values collected during the stabilization period. • The models will include factors for treatment, time, prognostic randomization stratification factors (see Section 10.10.2), 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 randomized 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 10.6.4) will be analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors (see Section 10.10.2) and the corresponding baseline BP parameter. This analysis will be performed using on-treatment BP values only.

Secondary Safety Statistical Analyses: Blood Pressure

- The number of on-treatment BP exacerbation events per 100 patient years will be calculated (see Section 10.6.4). 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 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 10.6.4). Summaries of on-treatment BP values only and on- and off-treatment BP values together will be produced. A summary of on-treatment BP values by baseline dialysis type will be produced. 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 10.6.4). Summaries of on-treatment BP values only and on- and off-treatment BP values together will be produced. A summary of change from baseline in on-treatment BP parameter values by baseline dialysis type will be produced. 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 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.
- 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 10.6.4). The total treatment exposure in years and overall on-treatment BP exacerbation rate per 100 PY will be provided by treatment group.
    - The BP exacerbation summary above will be repeated for the following groups and BP values:
        - All subjects, on-treatment post-dialysis BP values only

Secondary Safety Statistical Analyses: Blood Pressure
▪ All subjects, on-treatment pre-dialysis BP values only ▪ Hemodialysis subjects, all on-treatment BP values ▪ Hemodialysis subjects, on-treatment post-dialysis BP values only ▪ Peritoneal dialysis subjects, on-treatment post-dialysis BP values only
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance.

8.2.3. Exploratory Safety Analyses

8.2.3.1. Overview of Planned Exploratory Safety Analyses

Table 11 provides an overview of the planned exploratory safety analyses.

Table 11 Overview of Planned Exploratory Safety Analyses

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	L	T	F	F	L
BP and BP Medication Changes									
SBP, DBP and MAP by visit	ITT	Included with BP secondary analyses (Section 8.2.2)							
SBP, DBP, and MAP change from baseline to last record prior to change in BP medications[1]	ITT					Y			
Number of BP medications per subject by visit[1]	ITT	Y							
CFB in number of BP medications per subject by visit[1]	ITT					Y			
Number (%) of subjects who had no change, an increase or a decrease in dosage or number of BP medications from baseline by visit[1]	ITT	Y							
Lipid Parameters									
Lipid parameters by visit (TC, LDL-C, HDL-C)	ITT	Y	Y			Y			

NOTES:

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

[1]: Summary will include on-treatment BP values or BP medications taken while the subject was on treatment only.

8.2.3.2. Planned Exploratory Safety Display Details

Blood Pressure

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 randomized 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 10.6.4 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 and End of Treatment 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 10.6.4 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 and End of Treatment for "Once only" records only will be

summarized using mean, standard deviation, minimum, P25, median, P75, and maximum (see Section 10.6.4 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 randomized treatment start date to Week 52 and End of Treatment will be displayed by treatment group.

Number and percentage of subjects with any BP medication taken at baseline (the day before randomized treatment start date) and any on-treatment BP medication during the period from randomized treatment start date to Week 52 and End of Treatment will be displayed by treatment group.

Lipid Parameters

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 Time and Events table (see Section 10.2.1). Lipid parameter values follow the derivation guidelines for laboratory values outlined in Section 10.6.4. 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 on-treatment 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.

8.2.4. Adverse Event Safety Analyses

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

The reporting of the CEC-adjudicated CV endpoint events has been described in Section 7.2, Section 8.2.1, and Section 8.2.2. However, AE summaries and analysis will also include the AEs and SAEs associated with the adjudicated events listed below:

- All-cause mortality (CV and non-CV mortality)
- Non-fatal MI
- Non-fatal stroke
- Hospitalization for HF
- Thromboembolic events (vascular access thrombosis, deep vein thrombosis, pulmonary embolism)

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

Adopting recommendations from the Pharmaceutical Research and Manufacturers of America (PhRMA) Safety Planning, Evaluation and Reporting Team (SPERT) [Crowe, 2009], the first two tiers of the three-tier system will be used for the evaluation of AEs to examine the level of statistical evidence for differences between treatment groups.

- Tier 1 events in this study are defined as treatment emergent AEs of special interest (AESI). Tier 1 events will include AEs which meet criteria for inclusion as an AESI (see Section 10.6.4). Statistical comparisons will be made to compare the number and % of AESIs between the treatment groups, using the CMH chi-square test. A nominal statistical association will be declared if the unadjusted two-sided p-value for an event is less than 0.05.

- Tier 2 events in this study are defined as the most common treatment emergent AEs (those occurring in ≥ 5% of subjects in any treatment group). Tier 2 events are mutually exclusive of the Tier 1 AESI events. Any statistical comparisons for Tier 2 events will be made to compare treatment groups with multiplicity adjustment, using a CMH chi-square test, and the double false discovery rate (FDR, see Section 10.6.4) [Mehrota, 2012]. The double FDR multiplicity procedure is designed to limit the number of false positive signals identified to no more than two-sided 10% (the false discovery rate).

Unless otherwise specified, all other AE and SAE summaries will include all AEs.

See Section 10.4.1 for AE treatment state definitions.

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

8.2.4.1. Overview of Planned Adverse Event Analyses

Table 12 provides an overview of the planned adverse event safety analyses.

Table 12 Overview of Planned Adverse Event Safety Analyses

Parameter	Absolute			
	Summary		Individual	
	T	F	F	L
AESIs & PhRMA SPERT Adverse Event Analyses				
Analysis of AESIs	Y	Y		
Analysis of Common (≥ 5%) AEs	Y	Y		
Adverse Events				
All AEs by System Organ Class (SOC) and Preferred Term	Y			Y
All AEs by System Organ Class (SOC) and Preferred Term (subjects and occurrences)	Y			
All AEs by SOC and Preferred Term by	Y			

Parameter	Absolute			
	Summary		Individual	
	T	F	F	L
Subgroups				
All AEs by Overall Frequency	Y			
Common AEs by Overall Frequency	Y	Y[1]		
All AEs by Maximum Intensity	Y			
All Drug-Related AEs by Maximum Intensity	Y			
All Drug-Related AEs by SOC and Preferred Term	Y			
Common Non-Serious AEs by SOC and Preferred Term (subjects and occurrences)	Y			
Subject Numbers for Individual AEs				Y
Relationship Between AE SOCs, Preferred Term & Verbatim Text				Y
Serious and Other Significant Adverse Events				
SAEs by SOC and Preferred Term (subjects and occurrences)	Y			
SAEs by Maximum Intensity	Y			
Reasons for Considering as a SAE				Y
Drug-Related SAEs by SOC and Preferred Term (subjects and occurrences)	Y			
Fatal SAEs by SOC and Preferred Term (subjects and occurrences)	Y			Y
Non-Fatal SAEs by SOC and Preferred Term (subjects and occurrences)	Y			Y
Drug-Related Fatal SAEs by SOC and Preferred Term (subjects and occurrences)	Y			
AEs Leading to Permanent Discontinuation of Randomized Treatment by SOC and Preferred Term	Y			Y
BP Exacerbation Events	Y			
BP Exacerbation SAEs	Y			
Other Significant AEs				Y
Other CV Events				
Other CV Events[2]				

NOTES:

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

[1]: Plot of common AEs and relative risk will be generated.
[2]: Electronically generated patient profiles will be produced and used in the preparation of SAE summaries as a part of the study report.

8.2.4.2. Planned Adverse Event Safety Statistical Analyses

AESIs & PhRMA SPERT Adverse Event Analyses

Adverse events of special interest are described in Section 10.6.4.

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.

Cumulative incidence function (CIF) plots may be produced for each AESI summarizing the time to first occurrence of the AESI by treatment group. 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

Additionally, as a part of the PhRMA SPERT analyses described in Section 8.2.4, treatment emergent AE of special interest are considered Tier 1 events. The relative risk, corresponding two-sided 95% confidence intervals and two-sided p-values comparing daprodustat vs. rhEPO for these Tier 1 AEs will be provided.

The number, percentage and rate per 100 person-years for subjects reporting Tier 2 AEs will be summarized by system organ class, preferred term and treatment group. Additionally, as a part of the PhRMA SPERT analyses described in Section 8.2.4, the most common treatment emergent AEs that are not Tier 1 AEs are considered to be Tier 2 AEs. The relative risk will be calculated for these Tier 2 AEs and a corresponding two-sided 95% confidence interval comparing daprodustat vs. rhEPO. Two two-sided p-values will be displayed: one that makes no adjustment for multiplicity and one that makes the double FDR adjustment.

Dot plots displaying the incidence of the event will be provided for the Tier 1 and Tier 2 events by AESI term (Tier 1)/ preferred term (Tier 2) 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.

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. Pre-treatment and treatment emergent AEs will be summarized separately.

The number and percentage of subjects and the number of occurrences of all treatment emergent AEs will be summarized by primary system organ class, and preferred term.

Summaries of all treatment emergent AEs will be produced for the age group, gender, race group, baseline dialysis type, 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. The max intensity will be presented as “Unknown” if Missing and/or N/A are the only available severity values. 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.

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.

Serious and Other Significant Adverse Events

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

Summaries of treatment emergent SAEs will be provided by maximum intensity.

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

The number and percentage of subjects and the number of occurrences of treatment emergent drug-related 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 treatment emergent fatal SAE records and a listing of treatment emergent non-fatal SAE records will be provided.

The number and percentage of subjects reporting treatment emergent AEs leading to discontinuation of randomized treatment will be summarized by treatment group, primary system organ class, and preferred term.

A listing of treatment emergent AEs leading to discontinuation of randomized treatment will be provided.

BP events and BP-related SAEs are defined in Section 10.6.4.

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 and any adverse events that led to an intervention, including withdrawal of drug treatment, 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'.

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
- Valvulopathy
- Revascularization

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

8.2.5. Clinical Laboratory Safety Analyses

Clinical chemistry, hematology and other laboratory tests are assessed in this study according to the schedule outlined in the Time and Events table (see Section 10.2.1). The following tests will be summarized in clinical laboratory displays:

Clinical Chemistry	Potassium (serum)	Aspartate aminotransferase (AST)	Albumin
	Calcium (albumin corrected)	Alanine amintotransferase (ALT)	Blood Urea Nitrogen (BUN)
	Phosphate	Bilirubin (total and direct/indirect)	

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)
	Reticulocyte count	Mean corpuscular hemoglobin (MCH)	Lymphocytes
	Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
		Erythrocytes (red cell) distribution width (RDW)	Eosinophils
			Basophils

Other laboratory tests	Intact parathyroid hormone (iPTH)	Hemoglobin A1c (HbA1c) in diabetic subjects	High-sensitivity C-reactive protein (hs-CRP)

Summaries of central laboratory Hgb values, HemoCue Hgb values, iron parameter values (serum iron, ferritin, hepcidin, TIBC, TSAT), and lipid parameter values (total cholesterol, direct LDL-C, HDL-C) are included in earlier efficacy and safety 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 Time and Events table (see Section 10.2.1), any of these assessments can be performed at an unscheduled/retest visit or at the follow-up visit at the discretion of the investigator. See Section 10.5.3 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 10.8.1.

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, albumin corrected calcium, phosphate, albumin, BUN, total cholesterol, LDL-C, and HDL-C. Conversions from SI units to conventional units are included in Section 10.6.4. 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).

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

8.2.5.1. Overview of Planned Clinical Laboratory Safety Analyses

Table 13 provides an overview of the planned clinical laboratory safety analyses.

Table 13 Overview of Planned Clinical Laboratory Safety Analyses

Parameter	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Chemistry								
Chemistry Values by Visit	Y				Y			
Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline	Y							

Parameter	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Hematology								
Hematology Values by Visit	Y				Y			
Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline	Y							
Other Laboratory Tests								
Other Laboratory Values by Visit	Y				Y			
Worst Case Other Laboratory Results by PCI Criteria Post-Baseline Relative to Baseline	Y							
Hepatobiliary (Liver)								
Liver Monitoring/Stopping Event Reporting	Y							
Hepatobiliary Laboratory Abnormalities	Y							
Medical Conditions for Subjects with Liver Stopping Events				Y				
Substance Use for Subjects with Liver Stopping Events				Y				
Scatter Plot of Maximum vs. Baseline for ALT		Y						
Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin		Y						
All Laboratory								
All Laboratory Data for Subjects with Any Value of PCI				Y				
All Laboratory Data				Y				
Iron								
Worst Case Iron Results by PCI Criteria Post-Baseline Relative to Baseline				Y				

NOTES:

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

8.2.5.2. Planned Clinical Laboratory Safety Display Details

Clinical Chemistry

Continuous on-treatment values (see Section 10.4.1) 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 10.6.4) 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 10.6.4) by treatment group.

The number and percentage of subjects with on-treatment or worst case laboratory results relative to PCI criteria (see Section 10.8.1) which are post-baseline relative to baseline will be summarized by laboratory test, category and treatment group. See Section 10.6.4 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 laboratory tests listed in Section 8.2.5.

Other Laboratory Tests

The displays presented for clinical chemistry laboratory values will also be presented for the other laboratory tests listed in Section 8.2.5.

On-treatment hsCRP values will be log-transformed (see Section 10.5.2) 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 10.5.2) 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 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 laboratory data for subjects with on-treatment laboratory values outside of PCI criteria will be provided.

A listing of all laboratory data will be provided.

Iron parameters

The number and percentage of subjects with on-treatment or post-treatment worst case laboratory results relative to PCI criteria (see Section 10.8.1) which are post-baseline relative to baseline will be summarized by laboratory test, category and treatment group. See Section 10.6.4 for additional information on worst case values and PCI categories.

8.2.6. Vital Signs Analyses

Vital signs are assessed in this study according to the schedule outlined in the Time and Events table (see Section 10.2.1) and include the following assessments:

- Height
- HR
- Weight
- Estimated Dry Weight

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.

8.2.6.1. Overview of Planned Vital Signs Analyses

Table 14 provides an overview of the planned vital signs analyses.

Table 14 Overview of Planned Vital Signs Analyses

Parameter	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Vital Signs								
Vital Signs by Visit	Y				Y			
Summary of Worst Case Vital Signs Results by PCI Criteria	Y							
All Vital Signs for Subjects with Any Value of Potential Clinical Importance				Y				

NOTES:

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

8.2.6.2. Planned Vital Signs Display Details

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.

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.

The number and percentage of subjects with on-treatment or post-treatment worst case vital sign results relative to PCI criteria (see Section 10.8.1) which are post-baseline relative to baseline will be summarized by test, category and treatment group. See Section 10.6.4 for additional information on worst case values and PCI categories. 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 on-treatment vital signs values outside of PCI criteria will be provided.

8.2.7. Electrocardiograms

Electrocardiograms (ECGs) will be read locally and ECG data will not be included in summary tables or individual subject listings.

8.2.8. Pregnancies

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

8.2.9. Other Safety Analyses

Clopidogrel Analyses

The following analyses will be conducted to confirm the effect of clopidogrel co-administration.

The treatment emergent AEs and SAEs will be summarized with the number, percentage and rate per 100 person-years, by clopidogrel co-administration, treatment group, and system organ class and preferred term. Clopidogrel co-administration is defined as subjects who use clopidogrel once or more during the on-treatment state for concomitant medications (see Section 10.4.1).

The number and percentage of subjects with a >1 g/dL increase in Hgb over 2 weeks (assessed at Week 2 and Week 4), or a >2 g/dL increase in Hgb within any 4-week period from Week 4 to Week 52, will be summarized by visit by clopidogrel co-administration, and by treatment group using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).

The number and percentage of subjects with a >2 g/dL increase in Hgb within any 4-week period from Week 4 to Week 52, will be summarized by visit by clopidogrel co-administration, and by treatment group using central laboratory Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).

For the above two tables, the Clopidogrel co-administration groups are baseline clopidogrel users, new clopidogrel users, and clopidogrel non-users during the first year of the study. Baseline clopidogrel users, defined as subjects who use clopidogrel at randomization, will be summarized only at Week 2 and Week 4 for the HemoCue Hgb table, and only at week 4 in the central laboratory Hgb table. New clopidogrel users are defined as subjects who started clopidogrel after randomization during the on-treatment state for concomitant medications (see Section 10.4.1) in the first year of the study. If they started clopidogrel within two weeks of a scheduled visit (i.e. visit date - 2w < clopidogrel start date ≤visit date + 2w), they will only be summarized in the following scheduled visit. Clopidogrel non-users are subjects who do not use clopidogrel neither at randomization nor anytime during the on-treatment state for concomitant medications (see Section 10.4.1) in the first year of the study.

The number and percentage of subjects with a Hgb value ≥ 12 g/dL during the study will be summarized by clopidogrel co-administration, and by treatment group using evaluable Hgb values (see Section 10.6.3). Clopidogrel co-administration is defined as subjects who use clopidogrel once or more either at randomization or during the on-treatment state for concomitant medications (see Section 10.4.1).

The number and percentage of subjects who had dose adjustments (decreases, increases, no change) will be summarized at Week 2 and Week 4 by baseline clopidogrel co-administration, and by treatment group. The number of dose decreases per subject will be summarized for baseline clopidogrel users, using mean, standard deviation, minimum, P25, median, P75, and maximum by baseline clopidogrel use, and by treatment group, for

Day 1 to Week 12. Baseline clopidogrel co-administration is defined as subjects who use clopidogrel at randomization.

The number and percentage of subjects had dose adjustments (decreases, increases, no change) will be summarized for new clopidogrel users, who started clopidogrel after randomization, during the on-treatment state for concomitant medications (see Section 10.4.1), by treatment group. If they started clopidogrel within two weeks of a scheduled visit (i.e. visit date - 2w < clopidogrel start date ≤ visit date + 2w), they will be summarized in the following scheduled visit. The number of dose decreases per subject will also be summarized for these new clopidogrel users using mean, standard deviation, minimum, P25, median, P75, and maximum by clopidogrel use, and by treatment group, for clopidogrel use start date to clopidogrel use + Week 12.

The median assigned dose by treatment, by clopidogrel co-administration, and visit will be displayed graphically for each scheduled study visit from day 1 to week 52 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. This plot will be created by treatment group separately for subjects receiving epoetin alfa and darbepoetin alfa and these plots will also be overlaid on a graph of corresponding mean evaluable Hgb values by visit. Since it is possible for subjects to switch from epoetin alfa to darbepoetin alfa during the study, subjects who receive both treatments during the study will be counted in each group. Clopidogrel co-administration here is defined as subjects who use clopidogrel once or more, at randomization, or during the on-treatment state for concomitant medications (see Section 10.4.1) in the first year of the study.

A box plot of evaluable Hgb change at Week 2 from baseline, by baseline clopidogrel co-administration and treatment group will be produced. Hemocue Hgb will be used in this figure, since only Hemocue Hgb is available at Week 2. Baseline clopidogrel co-administration is defined as subjects who use clopidogrel at randomization. This box plot will be repeated at Week 4 using evaluable Hgb, by baseline clopidogrel co-administration and treatment group.

A box plot of 4-week changes in evaluable Hgb after starting clopidogrel will also be produced by treatment for new clopidogrel users, who started clopidogrel after randomization, during the on-treatment state for concomitant medications (see Section 10.4.1). The 4-week change in evaluable Hgb will be estimated by calculating the change at the first visit after starting clopidogrel, from the previous visit at least 4 weeks before. The first visit after starting clopidogrel is defined as the first visit (scheduled or unscheduled) after clopidogrel start that was at least two weeks after the start date of clopidogrel.

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.

Summaries of characteristics of COVID-19 AEs will include the number, percentage of subjects having at least one occurrence, the outcome, maximum intensity, and the duration of the AE summarized by treatment group. For each count, a subject will be summarized as follows:

- 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.
- Duration of the occurrence (days): AE resolution date – AE onset date/AE worsening date + 1 for the occurrence

A summary of the number and percentage of subjects with COVID-19 symptoms will be produced.

A summary of exposure adjusted incidence rates over time (see Section 10.6.4) will be produced by treatment group for any treatment emergent AE, any treatment emergent SAE, and any treatment emergent 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 10.10.1). 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.

8.3. Patient Reported Outcomes Analyses

This study includes the following patient reported outcomes (PROs) that are assessed according to the schedule in the Time and Events table in Section 10.2.1:

- SF-36
- EQ-5D-5L & EQ-VAS
- PGI-S
- PGI-C

Additional details on these questionnaires can be found in Section 10.6.5. All analyses will use on-treatment values only unless otherwise specified.

8.3.1. Overview of Planned Patient Reported Outcomes Analyses

Table 15 provides an overview of the planned patient reported outcomes analyses.

Table 15 Overview of Planned Patient Reported Outcomes Analyses

Endpoint	Analysis Population	Absolute							Change from Baseline						
		Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L	T	F	L	T	F	F	L
HRQoL and Utility Scores															
SF-36 domain and component scores	ITT				Y				Y	Y		Y			
EQ-5D-5L & EQ-VAS	ITT				Y				Y	Y		Y			
Hyporesponder SF-36 subgroup analyses	ITT								Y						
Symptom Severity															
PGI-S score	ITT				Y				Y	Y		Y			
PGI-S categories	ITT											Y			
PGI-C categories	ITT				Y										

NOTES:

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

8.3.2. Planned Patient Reported Outcomes Statistical Analyses

8.3.2.1. HRQoL and Utility Score

Patient Reported Outcomes Statistical Analyses: HRQoL and Utility Score
Secondary Endpoints Endpoint(s)
• Mean change in SF-36 HRQoL scores (PCS, MCS and 8 health domains) between baseline and Wk 8, 12, 28, 52, of particular interest are the changes from baseline in the vitality and physical functioning domains at Wk 28 and 52. • Change from baseline in Health Utility (EQ-5D-5L) score at Week 52 • Change from baseline in EQ VAS at Week 52
Exploratory Endpoint(s)
• Change from baseline in Health Utility (EQ-5D-5L) score at Weeks 8, 12, 29, 52, yearly, EOS • Change from baseline in EQ VAS at Weeks 8, 12, 28, 52, yearly, EOS
Model Specification
• Scoring for the SF-36 parameters and EQ-5D parameters is outlined in Section 10.6.5. • The mean change from baseline in SF-36 HRQoL scores (PCS, MCS, and 8 health domains), EQ-5D-5L score, and EQ-VAS 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 QoL data collected after baseline up to Week 52. The model will include factors for treatment, time, prognostic randomization stratification factors, baseline QoL parameter

Patient Reported Outcomes Statistical Analyses: HRQoL and Utility Score
value and the baseline QoL 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.
Model Results Presentation
• SF-36 domain scores (PCS, MCS, and 8 health domains) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Change from baseline in SF-36 domain scores (PCS, MCS, and 8 health domains) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Bar graphs displaying mean change from baseline for the Week 8, 12, 28, and 52 visits for the SF-36 PCS, MCS, and 8 health domains will be provided by treatment group. • EQ-5D-5L responses will be summarized by dimension at all scheduled visits, including the derived end of treatment visit. • EQ-5D-5L and EQ-VAS scores will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits, including the derived end of treatment visit. • Change from baseline in EQ-5D-5L and EQ-VAS scores will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits, including the derived end of treatment visit. • Bar graphs displaying mean baseline and Week 52 visit scores for the EQ-5D-5L will be provided by treatment group. • For the MMRM analyses of change from baseline in HRQoL parameters, 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 for the SF-36 component scores and domains, and at Week 52 for the EQ-5D-5L and EQ VAS.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance. • Clinically meaningful effects for PRO assessments focused on metrics that would be needed for a reimbursement agency or health technology assessment agency will be specified in a separate reimbursement RAP.

Supportive Statistical Analyses
Subgroup Analysis
• Subgroup analyses will be performed for the change from baseline in the SF-36 PCS, MCS, vitality and physical functioning domains at Week 28 and 52 using the age, gender and hyporesponder subgroups only (described in Section 10.10), in a method similar to that described for the subgroup analysis of the secondary Hgb change from baseline analyses.

8.3.2.2. Symptom Severity & Change

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 10.6.5. • 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, prognostic randomization stratification factors, 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. • Clinically meaningful effects for PRO assessments will be specified in a separate reimbursement RAP.

8.4. Biomarker Analyses

Blood samples will be collected as outlined in the Time and Events Table in Section 10.2.1 for potential future analysis of CV risk, inflammation and iron metabolism. If biomarker analysis is pursued, details will be included in a separate RAP.

8.5. Pharmacogenetics Analyses

Blood samples will be collected as outline in the Time and Events Table in Section 10.2.1 for potential future pharmacogenetics (PGx) analysis of the response to daprodustat (GSK1278863). If PGx analysis is pursued, details will be included in a separate RAP.

8.6. Analyses Excluding Sites with Suspected Fraud

During the conduct of the study, 3 sites were closed due to GCP issues including suspected fraud at the site. The data from these sites will be included in the study displays, however in order to assess the impact of these sites on overall study conclusions, a subset of the displays created for the study will be repeated, excluding the data from these 3 sites with ID: PPD and PPD.

The list of displays to be repeated is below:

Display Type	Display Number	Display Title
Study Population Table	1.001	Summary of Study Populations
Study Population Table	1.005	Summary of Subject Status and Reasons for Study Withdrawal at Week 28, Week 52 and Overall
Study Population Table	1.008	Summary of Randomized Treatment Status and Discontinuation of Randomized Treatment at Week 28, Week 52, and Overall
Study Population Table	1.017	Summary of Subject Follow-up Time
Study Population Table	1.019	Summary of Subject Survival Status
Study Population Table	1.021	Summary of Demographic and Baseline Characteristics for the Intent-to-Treat Population
Study Population Table	1.035	Summary of Extent of Exposure to Study Treatment
Study Population Table	1.036	Summary of Randomized Treatment Compliance Categories
Study Population Table	1.037	Summary of Randomized Treatment Compliance
Study Population Table	1.038	Summary of IRT and eCRF Dose Comparison
Efficacy Table	2.001	Summary of Post-randomization Hemoglobin (g/dL) Data
Efficacy Table	2.003	Summary of Post-randomization Hemoglobin (g/dL) Change from Baseline Data
Efficacy Table	2.006	Summary of Co-primary Analysis of Post-randomization Hemoglobin Change from Baseline to the Evaluation Period
Safety Table	3.001	Summary of First Occurrence Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events
Safety Table	3.002	Summary of Analysis of Time to First Occurrence of Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events
Safety Table	3.003	Summary of All Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events

Display Type	Display Number	Display Title
Safety Table	3.004	Summary of First and Subsequent Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events
Safety Table	3.005	Supportive Analysis: Summary of First Occurrence of Adjudicated MACE During the Time Period for On-treatment Cardiovascular Events
Safety Table	3.006	Supportive Analysis: Summary of Analysis of Time to First Occurrence of Adjudicated MACE During the Time Period for On-treatment Cardiovascular Events
Safety Figure	3.002	Kaplan-Meier Plot of Time to First Occurrence of Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events
Safety Figure	3.003	Kaplan-Meier Plot of Time to First Occurrence of Adjudicated MACE During the Time Period for On-treatment Cardiovascular Events

9. REFERENCES

Agarwal RJ. Blood pressure and mortality among hemodialysis patients. *Hypertension*. 2010;55:762-768.

Anker SD et al. Development and validation of cardiovascular risk scores for haemodialysis patients. *International Journal of Cardiology*. 2016; 216:68–77.

Bakris GL, Townsend RR, Liu M *et al.,* Impact of Renal Denervation on 24-Hour Ambulatory Blood Pressure. *J Ame Coll Cardiol*. 2014; 64:1071-1078.

Crowe BJ, Xia HA, Berlin JA, Watson DJ, Shi H, Lin SL, *et al.* Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. *Clinical Trials*. 2009; 6 (5): 430-440.

Francq BG, Lin D, Hoyer W. Confidence, prediction, and tolerance in linear mixed models. *Statistics in Medicine*. 2019; 38 (30): 5603 – 5622.

Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*. 1999; 94:496–509.

GlaxoSmithKline Document Number 2015N226659_07, 200807, A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoietin-stimulating agents, 30JUL2020.

GlaxoSmithKline Document Number 2015N226659_08, 200807, A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoietin-stimulating agents, 30JUL2020.

Holm S. A simple sequential rejective multiple test procedure. *Scandinavian Journal of Statistics*. 1979; 6: 65-70.

Iverson C, Christiansen S, Flanagin A, et al. *AMA Manual of Style: A Guide for Authors and Editors*. 10th ed. New York, NY: Oxford University Press; 2007.

Jackson D, White IR, Seaman S, Evans H, Baisley K, Carpenter J. Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation. *Statistics in Medicine.* 2014; 33: 4681-4694.

Kawaguchi A, Koch GG, Wang X. Stratified multivariate Mann-Whitey estimators for the comparison of two treatments with randomization based covariance adjustment. *Statistics in Biopharmaceutical Research*. 2011; 3 (2): 217-231.

Liu GF, Wang J, Liu K, Snavely DB. Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. *Statistics in Medicine* 2006; 25: 1275-1286.

Liublinska V, Rubin DB. Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial. *Statistics in Medicine* 2014; 33(24): 4170-4185.

Mehrota DV, Adewale AJ. Flagging clinical adverse experiences: Reducing false discoveries without materially compromising power for detecting true signals. *Statistics in Medicine.* 2012; 31: 1918-1930.

Peters SA, Huxley RR, Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke*. 2013; 44 (9): 2394 – 2401.

Prentice RL, Williams BJ, Peterson AV. On the regression-analysis of multivariate failure time data. *Biometrika* 1981; 68: 373-379.

Rosendall FR, Cannegieter SC, Van der Meer, FJM, and Briet, E. A Method to Determine the Optimal Intensity of Oral Anticoagulant Therapy. *Thrombosis and Haemostasis.* 1993; 69 (3): 236 – 239.

Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons, 1987.

10. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per-Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Treatment States & Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.6	Appendix 6: Derived and Transformed Data • General • Study Population • Efficacy • Safety • Patient Reported Outcomes
Section 10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.8	Appendix 8: Values of Potential Clinical Importance • Laboratory Values • Vital Signs
Section 10.9	Appendix 9: Multicentre Studies
Section 10.10	Appendix 10: Examination of Covariates and Subgroups
Section 10.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Section 10.13	Appendix 13: Pharmacokinetic Sub-study Analysis Plan
Section 10.14	Appendix 14: ABPM Sub-study Analysis Plan
Other RAP Appendices	
Section 10.15	Appendix 15: Abbreviations & Trade Marks

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

10.1.1. 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. 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[1] Hgb values[2] from the EP
03	Non-compliance with randomized treatment (compliance category of under compliant or over compliant) during the EP, based on eCRF randomized medication exposure and compliance 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. See Section 10.6.3.
2. Based on central laboratory Hgb values. If central laboratory Hgb value is missing, a non-missing HemoCue Hgb value will be used.
3. Prohibited medications include strong inhibitors of CYP2C8 (e.g., gemfibrozil) and strong inducers of CYP2C8 (e.g., rifampin/rifampicin).

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

10.2.1.1. Schedule of Assessments Year 1 to End of Study

Protocol activity (visits ±1 week, except Weeks 2 and 4 which are ±3 days) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
Informed consent (main study)	X[22]							
IRT system transaction[17]	X	X	X	X	X	X	X	X
Subject reminder, inform site staff of changes in health[1]			X				X	
Check/confirm entry criteria	X		X					
History: medical, hospitalization, transfusion demography, height	X							
Weight (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; at study visits per standard of care for PD) and EDW	X	X	X	X	X	X	X	X
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; at study visits per standard of care for PD) (single readings unless otherwise indicated)	X	X	X (triplicate)	X	X	X	X (triplicate)	X
Kt/V_{urea} [18]			X		X		X	
ECG [2]			X[2]				X	
Ultrasound of kidneys and adrenal glands		X[16]						
Placebo run-in or randomized treatment dispensing (start administration on date treatment dispensed)[19]		X (placebo)	X	X[9]	X	X	X	X[9]
Placebo run-in or randomized treatment compliance[19]			X (placebo)	X[11]	X	X	X	X[11]
Iron therapy, transfusions[3]	X	X	X	X	X	X	X	X
Rescue medication(s) for Initial Intervention[3,4]					X	X	X	
Females only: estradiol and FSH (if required)	X							
FRP only: Serum pregnancy test [5,20]		X	X		X		X	

Protocol activity (visits ±1 week, except Weeks 2 and 4 which are ±3 days) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
HemoCue Hgb	X	X	X	X	X	X	X	X
Hematology[6]	X	X	X		X	Hgb only	X	X
Clinical chemistry[6]	X		X		X		X	X
Ferritin, total iron, UIBC [6]	X		X		X		X	
Hepcidin			X		X		X	
HbA1c[7], lipids (non-fasting)			X				X	
hsCRP, iPTH			X		Wk 28		X	
Storage biomarkers[21]			X		Wk 28		X	
Hospitalization [3], kidney transplant[3]				X	X	X	X	X
Non-serious AEs, SAEs, AEs of special interest, clinical events	X[8]	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X

Schedule of Assessments Year 1 to End of Study (Continued)

	Year 2				Year 3				Year 4							
Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Week 64**	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208[14]**	**Unscheduled[10,12]**	**End of Study[15]**	**Follow-up (4-6 weeks after stopping randomized treatment)**
IRT system transaction[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; at study visits per standard of care for PD) and EDW	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; at study visits per standard of care for PD) (single readings unless otherwise indicated)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (triplicate)	X
Kt/V_{urea} [18]	X		X		X		X		X		X		X			
ECG [2]				X				X					X			
Randomized treatment dispensing (start administration on day of dispensing)[17,19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]		
Randomized treatment compliance[17,19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	X	
Iron therapy, transfusions[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rescue medication(s) for Initial Intervention [3,4]	X	X	X	X	X	X	X	X	X	X	X	X	X			
FRP only: serum pregnancy test[5,20]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
HemoCue Hgb	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology[6]	X	Hgb only	X	Hgb only	X	Hgb only	X	Hgb only	X	Hgb only	X	Hgb only	X	X	X	X
Clinical chemistry[6]	X		X		X		X		X		X		X	X	X	X
Ferritin, total iron, UIBC[6]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Hepcidin, HbA1c[7], lipids (non-fasting), hsCRP				X												

CONFIDENTIAL

200807

	Year 2				Year 3				Year 4							
Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Week 64**	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208[14]**	**Unscheduled[10,12]**	**End of Study[15]**	**Follow-up (4-6 weeks after stopping randomized treatment)**
iPTH		X		X												
Hospitalization[3], kidney transplant[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-serious AEs, SAEs, AEs of special interest, clinical events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	x	X	X	X

iPTH, intact parathyroid hormone; FSH, follicle stimulating hormone; UIBC, unsaturated iron binding capacity; HbA1c, glycated hemoglobin; hsCRP, high sensitivity C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram; EDW, estimated dry weight

1. Health changes include new symptoms or medical problems (e.g., pregnancy, hospitalizations) and changes in medication.
2. Day 1 ECG may be performed as early as the Week -4 visit through the Day 1 visit on a dialysis day (if 3 times/week dialysis, cannot be done on the first dialysis session of the week). If performed on Day 1, it must be pre-dialysis and over-read prior to randomization. All other ECGs assessments may be recorded pre or post dialysis and require over-reading.
3. Record in eCRF, if applicable.
4. See details on Rescue in Protocol Section 6.12.
5. Repeat pregnancy test prior to placebo run in or randomized treatment re-administration if it is disrupted for >7 days and there was also a lapse in contraceptive use, regardless of the reason for the disruption. If a subject becomes post menopausal (as defined in Protocol Appendix 5) during the study pregnancy tests are no longer required.
6. See details on hematology and clinical chemistry in Protocol Section 7.4.11.
7. HbA1c assessment only in subjects with diabetes on Day 1 or diagnosed during the study.
8. Only SAEs assessed as related to study participation or a GSK product are collected at this visit. See Protocol Section 7.4.3.1 for additional details.
9. If dose does not change, then randomized treatment is returned to subject.
10. If a subject lost their placebo run-in or randomized treatment, it is not necessary to perform the unscheduled visit assessments other than dispensing placebo run-in or randomized treatment.
11. Required only if dose is changed or randomized treatment is dispensed. Compliance checking will be required when a dose of randomized treatment is changed.
12. Additional visits to check Hgb and dispense randomized treatment (where directed by the IRT system) are required under the circumstances described in Protocol Appendix 6. Hematology and chemistry samples are not required.
13. All assessments pre-dose.
14. Further visits every 12 weeks as required.
15. Investigator will inform subject when to attend this End of Study visit (Protocol Section 6.3.4).
16. Ultrasound of the kidneys and adrenal glands will be performed as early as 6 weeks prior to the Day 1 visit. If results of kidney and adrenal ultrasound require follow-up testing, then the run-in period can 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 7.4.10.

17. Treatment will be dispensed every 4±1 weeks; an IRT transaction will be required; perform randomized treatment compliance.
18. 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. Kt/Vurea and URR measurements are not required for daily HHD.
19. In circumstances where the new dose of randomized treatment cannot be dispensed on the day of the study visit, the new dose of randomized treatment can be dispensed at next HD treatment. For visits after Day 1, prior randomized treatment should be continued unless on dose hold, Hgb ≥12 g/dL. Compliance is deferred until randomized treatment is returned.
20. **For Argentina ONLY:** Pregnancy testing will be performed every 4 weeks for FRP as required by local law.
21. Biomarker samples will be stored for future analyses for all subjects, except if not permitted by IRB/EC or refused by subject.
22. Informed consent will be obtained prior to any study procedures.

10.2.1.2. Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies

Protocol Activity (visits ±1 week) (Note: All visit timings are relative to Day 1)	Screening		Day 1 through Week 208								End of Study
	Week -8	Week -4	Day 1	Week 4	Week 8 & 12	Week 16, 20 & 24	Week 28	Week 32, 36, 40, 44, 48	Week 52	Week 100, 148, 208	
Patient Global Impression of Severity (PGI-S)[1]	X		X		X		X		X		
Patient Global Impression of Change (PGI-C)[1]					X		X		X		
Short Form 36 (SF-36)[1]			X		X		X		X		
EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) and EuroQol Visual Analogue Scale (EQ-VAS)[1, 2]			X		X		X		X	X	X
Healthcare resource utilization (subject reported)				X	X	X	X		X	X	X (& Follow up)
Genetics sample[3]			X								
ABPM sub-study (Appendix 12): Informed Consent	X[4]	X[4]									
Atrial fibrillation/flutter screening		X[5]									
24 hour ABPM		X[6]				X (Week 16)					
Record awake and sleep times		X[7]				X[7] (Week 16)					
PK sub-study (Appendix 13): Informed Consent			X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]		
PK assessment				X[9]	X[9]	X[9]	X[9]	X[9]	X[9]		

1. Subjects who are unable to or require assistance to read must not complete the questionnaires.
2. Only in selected countries. See Protocol Appendix 3.
3. Informed consent for optional Genetic research should be obtained before collecting a sample. To minimize potential study bias, the genetic sample should be collected on Day 1.
4. Informed consent for ABPM sub-study can be obtained at Week -8 or at the Week -4 visit prior to conducting any ABPM sub-study assessments.
5. Heart rate will be assessed prior to ABPM, subjects with irregular heart beat will undergo an ECG to assess if atrial fibrillation/flutter is present (see Protocol Section 12.12.3.3)
6. Baseline ABPM will be performed at any mid-week dialysis visit starting at Week -4 until 1 week prior to randomization (Day 1); the device will be returned at the next visit, which ideally is no later than 1 week prior to randomization to allow for QC of the ABPM.
7. Subject will record sleep and awake times during the ABPM session.

8. Informed consent for PK sub-study can be obtained anytime from Day 1 (once the subjects is confirmed to have been randomized to daprodustat) till Week 52, i.e., last study visit where PK sampling can be obtained.
9. Blood samples will be collected at any single study visit from the Week 4 through Week 52 visit (i.e., PK is collected at one visit only, based on convenience for the subject/site).

10.2.1.3. Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)**	**Day 1 through Week 52[7]**	
		Week 4, 16, 28, 40, 52 ± 2 weeks	**Unscheduled**
IRT system transaction	X		
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; at study visits per standard of care for PD) (single readings unless otherwise indicated)	X (triplicate)	X	X
ECG	X		
Iron therapy, transfusions[1]	X	X	X
Serum pregnancy test (FRP only)	X[6]		
HemoCue Hgb	X	X	X
Hematology[3] ,	X	X	
Clinical chemistry[3]	X	X	
Ferritin, total iron, UIBC, hepcidin, lipids, iPTH	X		
Hospitalization[1], kidney transplant[1]	X	X	X
Non-serious AEs, AEs of special interest, SAEs, clinical events	X	X	X
Review concomitant medications	X	X	X
Healthcare resource utilization (subject reported)	X		
PGI-S, PGI-C[4, 9]	X		
SF-36[4, 9]	X		
EQ-5D-5L& EQ-VAS[4, 5, 9]	X		
ABPM sub-study (Appendix 12): 24 hour ABPM		X (Week 16)	
Record awake and sleep times		X (Week 16)[2]	

Note: see footnotes on next page

Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment (Continued)

Protocol activity (visits ± 2 week) (Note: All visit timings are relative to Day 1)	Year 2[7]				Year 3[7]				Year 4[7]					Unscheduled	End of Study[8]
	Week 64	Week 76	Week 88	Week 100	Week 112	Week 124	Week 136	Week 148	Week 160	Week 172	Week 184	Week 196	Week 208		
IRT system call															X
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects, between treatments for HHD and PD subjects) (single readings unless otherwise indicated)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HemoCue Hgb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[3]	X	Hgb only	X	Hgb only	X	Hgb only	X	Hgb only	X	Hgb only	X	Hgb only	X		X
Clinical chemistry[3]	X		X		X		X		X		X		X		X
Hospitalization[1], kidney transplant[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-serious AEs, SAEs, AEs of special interest, clinical events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Record in eCRF, if applicable.
2. Subject will record sleep and wake time during the ABPM session.
3. See details on hematology and clinical chemistry in Protocol Section 7.4.11.
4. Only completed at Early Treatment Discontinuation visit if the randomized treatment discontinuation occurs on or before Week 52
5. Only in selected countries. See Protocol Appendix 3.
6. Additional pregnancy test required at subsequent visit. Must be at least 4 weeks after the end of randomized treatment.
7. Phone visits are acceptable in exceptional circumstances.
8. Investigator will inform subject when to attend this End of Study visit.
9. Subjects who are unable to or require assistance to read must not complete the questionnaires.

10.3. 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 10.6.3 and BP endpoints described in Section 10.6.4).

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment States

Assessments and events will be classified according to time of occurrence relative to the treatment start and stop dates and last non-zero dose date (see Section 10.6.1).

10.4.1.1. Treatment States for Hgb, Iron Parameters, IV Iron Dose Endpoints, Iron Use Summaries, Transfusion and PRO Data

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

10.4.1.2. Treatment States for CV Endpoint Data

Treatment State	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
- Treatment state definitions use the imputed CV endpoint date

10.4.1.3. Treatment States for BP, Lipid Parameters, Clinical Chemistry, Hematology, Other Laboratory Tests, Hepatobiliary (Liver) and Vital Signs Data

Treatment State	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

10.4.1.4. Treatment States for AE Data

Non-serious AEs and serious AEs are to be recorded on the eCRF starting at the placebo run-in phase. Serious AEs assessed as related to study procedures or related to a GSK concomitant medication are to be recorded on the eCRF from the time a subject consents

to participation in the study. AE of worsening of an on-going event will be counted once in a particular treatment state.

Treatment State	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
Placebo Run-In	If AE onset date or AE worsening date is on or after placebo run-in treatment start date & on or before placebo run-in treatment stop date: Placebo Run-in Treatment Start Date ≤ AE Start Date ≤ Placebo Run-in Treatment Stop Date Placebo Run-in Treatment Start Date ≤ AE Worsening Date ≤ Placebo Run-in Treatment Stop Date AE worsening during placebo run-in will be defined relative to the maximum intensity of AE prior to placebo run-in start date. AE worsening date is the first date in the placebo run-in period, when AE intensity increased relative to the maximum intensity of the AE prior to placebo run-in 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 will be defined relative to the maximum intensity of AE prior to randomized 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 randomized 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 randomized 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 randomized 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

Treatment State	Definition
	Date 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 the AE resolution date is after the start of placebo run-in, the AE will also be considered a Placebo Run-in AE.
- 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.

10.4.1.5. Treatment States for Concomitant Medications (Other Than IV Iron Dose Endpoints and Iron Use Summaries)

Pre-treatment medications are those taken (i.e., started) before the start date of randomized treatment. On-treatment medications are those taken (i.e., started or continued) at any time between the randomized 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 randomized treatment, it will be assumed that the medication was taken after the subject started taking randomized 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

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
IVWRS		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Dapro	Dapro	1
B	rhEPO	rhEPO	2
--	--	Total	3

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints (except as noted) the baseline value will be the latest non-missing pre-dose assessment on or before the randomization date. This is generally expected to be the pre-dose value from the Day 1 visit, although such values may be missing.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screen Week -8	Run-in Week -4	Day 1 (Pre-Dose)	
Efficacy				
Hgb			X	Randomization Date
Monthly IV iron[1]			X	Randomization Date
Iron parameters			X	Randomization Date
Safety				
Subjects who have in-clinic HD: dry weight, pre-dialysis BP parameters, HR, and weight			X	Randomization Date
Subjects who have in-clinic HD: post-dialysis BP parameters, HR, and weight		X		Week -4/Randomization Date

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screen Week -8	Run-in Week -4	Day 1 (Pre-Dose)	
Subjects who do not have in-clinic HD: BP parameters, HR, weight and dry weight			X	Randomization Date
Lipid parameters, clinical chemistry, hematology, other laboratory, and hepatobiliary (liver) tests			X	Randomization Date
PRO				
SF-36 domain and component scores			X	Randomization Date
EQ-5D-5L & VAS			X	Randomization Date
PGI-S			X	Randomization Date

NOTES:

- 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 16 weeks prior to randomization. See Section 10.6.3.

[2]: Post-dialysis baseline values for subjects with in-clinic dialysis 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.

10.5.2.2. Derivations and Handling of Missing Baseline Data

Change from Baseline

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

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2 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 change from baseline using the log-transformed data
4. Exponentiate the mean, (if required, the mean – SE, the mean + SE), 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) as the percent change from baseline.

So, geometric mean for percent change from baseline =

$$[\ \text{Exp}(\sum \{\log(\text{value at specified time point\_i}) - \log(\text{baseline value\_i})\}/n) - 1\ ] \times 100,$$

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

To calculate a 95% CI of the 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 change from baseline using the log-transformed data
4. Calculate the lower and upper limits of the 95% CI of change from baseline using the log-transformed data using standardized normal distribution: Mean -/+ $z(1-\alpha/2)$*SE

(z for α=0.05 is obtained through PROBIT function in SAS that is specified as PROBIT(0.975))

5. Exponentiate the lower and upper limits of the 95% CI, back to the original scale and then subtract 1, then multiply everything by 100% in order to express the confidence interval (CI) as the percent change from baseline.

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 =

$$[\ \text{Exp}(\min\ \{\log(\text{value at specified time point\_i}) - \log(\text{baseline value\_i})\ \}) - 1\ ] \times 100,$$

Where i = subject.

Unless otherwise specified, the baseline definitions specified in Section 10.5.2 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.

10.5.3. Reporting Process & Standards

Reporting Process
Software
• The currently supported versions of SAS software, Version 9.4 (or higher) will be used for all analyses unless otherwise specified. Additionally, R Version 3.6.2 or higher may be used for analysis and the production of graphics.
Analysis Datasets
• Analysis datasets will be created according to clinical data interchange standards consortium (CDISC) standards: study data tabulation model (SDTM) implementation guide (IG) Version 3.1.3 with some updates from Version 3.2, Analysis data model (ADaM) IG Version 1.1, and GSK ADaM specification template. • 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
• Rich text format (RTF) files will be generated.

Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  - 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

Formats

- GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected.
- Numeric data will be reported at the precision collected on the eCRF.
- The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - Planned time relative to 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 10.6.1) 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.
- 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 10.6.3)
  - Some BP endpoints will include unscheduled BP values (see Section 10.6.4)
- 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 10.6.3)

Reporting Standards	
• Some BP endpoints will include unscheduled BP values (see Section 10.6.4) • 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.	
Adjusted Means	
• SAS option OBSMARGINS will be used to generate all adjusted mean values, e.g. LSMEANS statement in relevant SAS procedures will include the OBSMARGINS option (or OM as an abbreviation), to weight least square means coefficients of the categorical variables in the model to be proportional to those found in the input dataset.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. 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 10.2.1) • 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 randomized study treatment from the IP Discontinuation eCRF 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 do not receive randomized treatment for that period. Hence, it would be possible for a subject to complete the study, while still following the dosing algorithm, but not be actually taking any actual randomized treatment. The last non-zero dose date, then captures the latest date in the study that a subject physically took a dose of randomized treatment.
• The eCRF allows for the possibility of partial or missing dates to be recorded for the last actual dose of randomized study treatment on the IP Discontinuation form (i.e., missing day, or day and month, or day and month and year). In such a case, or in case of subjects who have a non-missing treatment start date, but are a missing an IP Discontinuation form, the following conventions will be applied in order to impute a last non-zero dose date:
  ○ Missing day:
  ▪ The last day of the month will be used, unless the treatment stop date also occurs in the same month; in this case, the treatment stop date will be used.
  ○ Missing day and month;
  ▪ '31' will be used for the day and 'Dec' will be used for the month, unless the treatment stop date also occurs in the same year; in this case the treatment stop date will be used.
  ○ Missing day, month, and year:
  ▪ Treatment stop date will be used only for subjects who have a non-missing treatment start date.

Treatment Stop Date

- Calculated as the latest randomized treatment dose stop date, for subjects who have a non-missing treatment start date. Note that this date could come from a randomized treatment exposure record with a missing or partial dose stop date if the associated dose start date for that exposure record is on or after the last non-missing randomized treatment dose stop date.
- The eCRF allows for the possibility of missing or partial dates to be recorded for the dose stop date on the study treatment form (i.e., missing day, or day and month, or day and month and year). In such a case, the following conventions will be applied in order to impute a treatment stop date:
    - Missing day:
        - The last day of the month will be used, unless the study completion or withdrawal date also occurs in the same month; in the case, the study completion or withdrawal date will be used.
    - Missing day and month:
        - '31' will be used for the day and 'Dec' will be used for the month, unless the study completion or withdrawal date also occurs in the same year; in this case, the study completion or withdrawal date will be used.
    - Missing day, month and year:
        - The study completion or withdrawal date will be used only for subjects who have a non-missing treatment start date.

End of Treatment Value

- Only defined for subjects with a non-missing treatment start date
- Hgb, iron, transfusion and PRO parameters: 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. If the date of study withdrawal entered in the eCRF is before the last study contact date, the last study contact date will be used as the study withdrawal date for analysis.

    - Note: Subjects who die while on study are considered as having completed the study
- The eCRF allows for the possibility of missing or partial dates to be recorded for the study completion/withdrawal date on the Study Conclusion form (i.e., missing day, or day and month, or day and month and year). In such a case, or in case of subjects who are missing a Study Conclusion form, the following conventions will be applied in order to impute a study completion/withdrawal date:
    - Missing day:
        - The last day of the month will be used, unless the last study contact date also occurs in the same month; in the case, the last study contact date will be used.

○ Missing day and month: ▪ '31' will be used for the day and 'Dec' will be used for the month, unless the last study contact date also occurs in the same year; in this case, the last study contact date will be used. ○ Missing day, month and year: ▪ The last study contact date will be used.
Planned/Actual Visit Dates
• Planned/actual visit dates will be defined as follows: ○ Week 28 date: Non-missing Week 28 visit start date (from SV domain), otherwise randomization date + 28*7 ○ Week 36 date: Non-missing Week 36 visit end date (from SV domain), otherwise randomization date + 36*7 ○ Week 52 date: Non-missing Week 52 visit end date (from SV domain), otherwise randomization date + 52*7 ○ End of Study date: Non-missing End of Study visit end date (from SV domain), otherwise the middle of the End of Study window.
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.
Maintenance Period (MP)
• Defined as the period between and including Week 28 visit – End of Study 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 Date ≥ 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 Date ≥ 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, other, 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 to 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.
Last Known Alive Date

• The last know alive date for a subject in the study will be defined as the latest of the following dates:
  ○ The date of the last visit in the clinic
  ○ Last date recorded when the subject was last known alive
  ○ For the non-clinic visit, the last clinic information assessment date

10.6.2. Study Population

10.6.2.1. Subject Disposition

Subject Disposition
Screen Failures
• Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized.   ○ At the time of screening closure, there may have been subjects who had been consented but had not been entered into the eCRF. These subjects are not included in the clinical database but will be noted in a footnote on the Summary of Screening Status and Reasons for Screen Failures. • Any subject that consented, was entered into the eCRF, and was not randomized, but is

Subject Disposition

missing a screen failure record will have the following values imputed:

- Was this subject a screen failure? = Yes
- Reason for screen failure = Missing

Randomized Treatment Discontinuation

- Any randomized subject with a non-missing treatment start date that is missing an IP Discontinuation eCRF will have the following values imputed:
  - Date of last dose = See Last Non-Zero Dose Date in Section 10.6.1
  - Was the study treatment stopped permanently before the scheduled end of the treatment period? = Yes
  - Primary reason the treatment was stopped = Missing

Study Completers/Withdrawals

- Any randomized subject that is missing Study Conclusion eCRF will have the following values imputed:
  - Date of subject completion or withdrawal? = See Study Completion/Withdrawal Date in Section 10.6.1
  - Was the subject withdrawn from the study? = Yes
  - Primary reason for study withdrawal = Missing

Subjects Completion Status

Known Cardiovascular Endpoint Status at End of Study

The following scenarios will be considered as known CV endpoint status at End of Study:

- Subjects who die during the study
- Subjects who attend a clinic visit within the EOS window
- For the following non-clinic EOS visits, eCRF Visit Contact Details page indicates that a clinical events assessment was able to be performed and date clinical information was assessed is within the EOS window.
  - Telephone contact with subject
  - Other contact with subject (mail, email, text, social media, etc.)
  - Designated third party (e.g. family member, caretaker)
  - Health care provider or medical records

Unknown Cardiovascular Endpoint Status at End of Study

The following scenarios will be considered as incomplete CV endpoint status at End of Study:

- Subjects who withdraw from the study
- EOS visit type =
  - no contact able to be made for this visit
  - survival status search performed but could not confirm that the subject was alive or dead
  - Publicly available sources (e.g., public registry, newspaper)
  - Other, specify
- For the following non-clinic EOS visits, eCRF Visit Contact Details page indicates that a clinical events assessment was not able to be performed or date clinical information was assessed is before the EOS window:
  - Telephone contact with subject

Subjects Completion Status
○ Other contact with subject (mail, email, text, social media, etc.) ○ Designated third party (e.g. family member, caretaker) ○ Health care provider or medical records • eCRF Visit Contact Details page is missing information to determine if a clinical events assessment was performed or the date it was performed.
Known Vital Status at End of Study
The following scenarios will be considered as known vital status at End of Study: • Subjects who die during the study, or have a death date • Subjects who attend a clinic visit within the EOS window • For the following non-clinic EOS visits, latest date subject last known to be alive is within or after the EOS window. ○ Telephone visit ○ Other contact with subject (mail, email, text, social media, etc.) ○ Designated third party (e.g. family member, caretaker) ○ Health care provider or medical records ○ Publicly available sources (e.g., public registry, newspaper) ○ Other, specify • For subjects who withdraw from the study, the latest date subject last known to be alive is within or after the EOS window.
Unknown Vital Status at End of Study
The following scenarios will be considered as unknown vital status at End of Study: • For subjects who withdraw from the study, the latest date subject last known to be alive is missing or before the EOS window; • EOS visit type = no contact able to be made for this visit (LTFU subjects only); • EOS visit type = survival status search performed but could not confirm that the subject was alive or dead (LTFU subjects only); • For the following non-clinic EOS visits, latest date subject last known to be alive is missing or before the EOS window. ○ Telephone visit ○ Other contact with subject (mail, email, text, social media, etc.) ○ Designated third party (e.g. family member, caretaker) ○ Health care provider or medical records ○ Publicly available sources (e.g., public registry, newspaper) ○ Other, specify

10.6.2.2. Demographic & Baseline Characteristics

Demographic & Baseline Characteristics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Any subject with a missing day will have this imputed as day '15'. ○ Any subject with a missing date and month will have this imputed as '30th June'.

Demographic & Baseline Characteristics

- Birth date will be presented in listings as 'YYYY'.

High Level Race

- Geographic ancestry data will be combined into the following high level race categories:
    - American Indian or Alaskan Native
    - Asian (Asian-East Asian Heritage, Asian-Japanese Heritage, Asian-Central/South Asian Heritage, Asian-South East Asian Heritage, Mixed Asian Race)
    - Black or African American
    - Native Hawaiian or Other Pacific Islander
    - White (White-Arabic/North African Heritage, White-White/Caucasian/European Heritage, Mixed White Race)
    - 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:
    - American Indian or Alaskan Native
    - Asian-Central/South Asian Heritage
    - Asian-East Asian Heritage
    - Asian-Japanese Heritage
    - Asian-South East Asian Heritage
    - Mixed Asian Race (Only display if data exists)
    - Black or African American (African American/African Heritage)
    - Native Hawaiian or Other Pacific Islander
    - White-Arabic/North African Heritage
    - White-White/Caucasian/European Heritage
    - Mixed White Race (Only display if data exists)
    - Mixed Race (Multiple high level races are selected; only display if data exists)

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.

Dialysis Type at Randomization

- Dialysis type at randomization will use the subject's randomization date and the dialysis type information recorded on the Dialysis History and Dialysis Changes eCRF pages to determine the dialysis type on the randomization date and will be summarized as follows:
    - HD (which includes: HD – conventional and HDF/HF)
    - PD
    - Missing

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, darbepoetin 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:

Demographic & Baseline Characteristics

- 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 -8 visit to the day before the Randomization date.

- All prior ESA therapy concomitant medication records from screening/run-in 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

Demographic & Baseline Characteristics

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:
  - 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 -8 visit date, the duration of the record is 0.
  - If the concomitant medication record end date + gap factor ≥ Week -8 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 -8 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 -8 visit date ≤ concomitant medication record start date, then:
    - Frequency (for standardization formula) = 1
    - Duration = 7 days
  - If concomitant medication record start date < Week -8 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 -8 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 -8 visit date, the duration of the record is calculated as Stop Date – Start Date + 1, where:
      - Start date will be the Week -8 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$_{Record\ 1}$) + ... + (ESA total dose$_{Record\ n}$)]/[(Randomization Date – Week -8 Visit Date)/7days]

Demographic & Baseline Characteristics
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 • 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
Dosing Algorithm at Randomization
• Protocol Amendment 3 updated the dosing algorithm used to assign doses of randomized treatment to subjects in both treatment arms. The number of subjects randomized under the original algorithm and under the updated algorithm will be summarized. • A subject's randomization date will be compared to the site-specific ethics committee/regulatory protocol amendment approval date for their site. This date is stored in the IRT system as the Site Level Amendment Flag Date for each site. • Subjects randomized before their site's non-missing Site Level Amendment Flag Date or who have a missing Site Level Amendment Flag Date will be considered to have been randomized under the original algorithm, and subjects randomized on or after their site's non-missing Site Level Amendment Flag Date will be considered to have been randomized under the updated algorithm.
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*:

Demographic & Baseline Characteristics

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	

*For the intradialytic weight change (kg) parameter, a value of ≥-1.2kg will have a risk score of 0 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).

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, 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

Demographic & Baseline Characteristics
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 at least one record of the medical history terms that contains "Diabetic" or "Diabetes" except anything containing non-diabetic or variations relating to it (e.g. nondiabetic and other spellings) and also: o DIABETES INSIPIDUS, o NEPHROGENIC DIABETES INSIPIDUS • 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 either 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 either 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: neoplasms malignant or unknown/unspecified, allogenic bone marrow transplant. • Subjects who have indicated that they do not have a medical history of neoplasms malignant or unknown/unspecified or allogenic bone marrow transplant will be considered not to have a history of cancer. • If subjects have not been classified as either having or not having a history of cancer and are missing a response to either the neoplasms malignant or unknown/unspecified or allogenic bone marrow transplant medical condition, their cancer history status will be missing.

Demographic & Baseline Characteristics
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 any of the terms listed above will be considered not to have a history of heart failure. • If subjects have not been classified as either 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.
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 any of the terms listed above will be considered not to have a history of thromboembolic events. • If subjects have not been classified as either 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 any of the terms listed above will be considered not to have a history of cardiovascular disease. • If subjects have not been classified as either 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 10.6.3.
Dialysis Access Type Used at Randomization

• Dialysis access type at randomization will use the subject's randomization date and the dialysis access type information recorded on the Dialysis Access History and Dialysis Access Changes eCRF pages to determine the dialysis access type on the randomization date and will be summarized as follows:
  ○ Arteriovenous fistula
  ○ Arteriovenous graft
  ○ Central venous catheter – tunneled
  ○ Central venous catheter – non-tunneled
  ○ Peritoneal catheter
  ○ Other
  ○ Missing

Demographic & Baseline Characteristics
Phosphate Binder Use at Randomization
• Phosphate binder use at randomization will be summarized as follows: o Iron-based phosphate binders o Calcium-based phosphate binders o Non-calcium and non-iron based phosphate binders o 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: o ACEI/ARB o Vitamin D o Beta blockers o SGLT2i o Statin o Aspirin o Vitamin K o Insulin o Calcimimetics o Diabetic medication

10.6.2.3. Randomized Treatment Discontinuation, Study Withdrawal and Possible Follow-up Time

Randomized Treatment Discontinuation, Study Withdrawal, and Possible Follow-up Time
Randomized Treatment Discontinuation
• Randomized Treatment Discontinuation Censored Time (days) = Treatment stop date – Treatment start date +1 If the treatment stop date = death date 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 Randomized Treatment Discontinuation (days) = Treatment stop date – Treatment start date +1
• Randomized Treatment Person Years = (Cumulative total of time to randomized treatment discontinuation for subjects who discontinued randomized treatment + Cumulative total of randomized treatment discontinuation censoring time for subjects who did not discontinue randomized treatment) / 365.25
• Randomized Treatment Discontinuation Incidence Rate (per 100 person years) = 100* Number of subjects who discontinued randomized treatment / randomized 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

Randomized Treatment Discontinuation, Study Withdrawal, and Possible Follow-up Time
• 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) / Study Person Years
Possible Follow-up Time
• Possible follow-up time (days) = Study completion date or date of the middle of the end of study window for subjects who did not complete the study – randomization date + 1
• Total possible follow-up time (person years) = Cumulative total of possible follow-up time (days) for all subjects / 365.25

10.6.2.4. 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 ESA treatment in addition to randomized treatment o Non-randomized ESA treatment instead of randomized treatment
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.
Clopidogrel start date for new clopidogrel users
• New clopidogrel users are subjects who did not use clopidogrel on randomization day, but started their clopidogrel use after randomization during the on-treatment state for concomitant medications. To determine the start date of clopidogrel for the new users, only the first clopidogrel record during the on-treatment state for concomitant medications will be considered. The start date will be the first day subjects on both clopidogrel and randomized treatment.

10.6.2.5. 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 Details eCRF pages 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 randomized treatment exposure record 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 and any gaps between exposure records will be categorized in the under compliant category.
  - Daprodustat Doses

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 the exposure record is calculated as 100% * [# dispensed – (# returned + # lost)] / # tablets per day / (dose stop date – dose start date +1)		
# tablets per day: 1 tablet per day: 1mg, 2mg, 4mg, 6mg, 8mg, 10mg 2 tablets per day: 12mg, 16mg 3 tablets per day: 24mg		

  - rhEPO Every 4 Week Exposure Records: Based on Number of Doses Given

Duration of Exposure Record	Under Compliant	Compliant	Over Compliant
1 – 14 days	< 1 dose	1 dose	> 1 dose
15 – 42 days	< 1 dose	1 or 2 doses	> 2 doses
43 – 70 days	< 2 doses	2 or 3 doses	> 3 doses
71 – 98 days	< 3 doses	3 or 4 doses	> 4 doses
99 – 126 days	< 4 doses	4 or 5 doses	> 5 doses
Etc.			

  - rhEPO Every 2 Week Exposure Records: Based on Number of Doses Given

Duration of Exposure Record	Under Compliant	Compliant	Over Compliant
1 – 7 days	< 1 dose	1 dose	> 1 dose

Exposure and Compliance

8 – 21 days	< 1 dose	1 or 2 doses	> 2 doses
22 – 35 days	< 2 doses	2 or 3 doses	> 3 doses
36 – 49 days	< 3 doses	3 or 4 doses	> 4 doses
50 – 63 days	< 4 doses	4 or 5 doses	> 5 doses
64 – 77 days	< 5 doses	5 or 6 doses	> 6 doses
78 – 91 days	< 6 doses	6 or 7 doses	> 7 doses
92 – 105 days	< 7 doses	7 or 8 doses	> 8 doses
Etc.			

- rhEPO Every Week Exposure Records: Based on Number of Doses Given

Duration of Exposure Record	Under Compliant	Compliant	Over Compliant
1 – 3 days	< 1 dose	1 dose	> 1 dose
4 – 10 days	< 1 dose	1 or 2 doses	> 2 doses
11 days	< 1 dose	1 or 2 or 3 doses	> 3 doses
12 – 17 days	< 2 doses	2 or 3 doses	> 3 doses
18 days	< 2 doses	2 or 3 or 4 doses	> 4 doses
19 – 24 days	< 3 doses	3 or 4 doses	> 4 doses
25 days	< 3 doses	3 or 4 or 5 doses	> 5 doses
26 – 31 days	< 4 doses	4 or 5 doses	> 5 doses
32 days	< 4 doses	4 or 5 or 6 doses	> 6 doses
33 – 38 days	< 5 doses	5 or 6 doses	> 6 doses
39 days	< 5 doses	5 or 6 or 7 doses	> 7 doses
40 – 45 days	< 6 doses	6 or 7 doses	> 7 doses
46 days	< 6 doses	6 or 7 or 8 doses	> 8 doses
47 – 52 days	< 7 doses	7 or 8 doses	> 8 doses
53 days	< 7 doses	7 or 8 or 9 doses	> 9 doses
Etc.			

- rhEPO TIW Exposure Records: Based on Number of Doses Given

Duration of Exposure Record	Under Compliant	Compliant	Over Compliant
1 – 2 days	< 1 dose	1 dose	> 1 dose
3 – 4 days	< 1 dose	1 or 2 doses	> 2 doses
5 – 6 days	< 2 doses	2 or 3 doses	> 3 doses
7 days	< 2 doses	2 or 3 or 4 doses	> 4 doses
8 – 9 days	< 3 doses	3 or 4 doses	> 4 doses
10 – 11 days	< 4 doses	4 or 5 doses	> 5 doses
12 – 13 days	< 5 doses	5 or 6 doses	> 6 doses
14 days	< 5 doses	5 or 6 or 7 doses	> 7 doses

Exposure and Compliance

15 – 16 days	< 6 doses	6 or 7 doses	> 7 doses
17 – 18 days	< 7 doses	7 or 8 doses	> 8 doses
19 – 20 days	< 8 doses	8 or 9 doses	> 9 doses
21 days	< 8 doses	8 or 9 or 10 doses	> 10 doses
Etc.			

- Compliance will be summarized for the following time periods: Day 1 - < Week 28, Week 28 - < Week 52, Week 28 - < End of Treatment, and Day 1 - < End of Treatment (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 and will be based on the durations of each record within the period.
- A subject's compliance category will be the category that corresponds to the highest percentage of total time. In the unlikely event of a tie, the lower compliance category will be chosen (i.e., in a tie between under and compliant, under is chosen; in a tie between compliant and over, compliant is chosen; and in a tie between under and over, under is chosen; in a tie with missing, missing is chosen).

10.6.3. Efficacy

10.6.3.1. 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 co-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 10.4.1) 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 7.1.2). 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 co-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 Co-primary Hgb Analysis

- For each subject, the mean of all available (on and off treatment) Hgb values during the EP (See Section 10.6.1) 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 and the End of Study 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 10.6.1) 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 and the End of Study 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 10.6.1) 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 and the End of Study 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 co-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

Hemoglobin Values

			x	Unscheduled HemoCue Hgb value	Unscheduled
	multiple			Average of unscheduled central lab Hgb values	Unscheduled
			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 10.6.1), 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 (Rosendall, 1993).

Percent Time in Range During the EP

- Time in Range During the EP / [Earlier of (Date of the last evaluable Hgb value, Week 52 visit date) – Later of (Date of the first evaluable Hgb value that between Week 16 and Week 52 inclusive, 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 on or 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.

Time in Range During the MP

- Number of days that a subject's evaluable Hgb is within the analysis range of 10-11.5 g/dL inclusive between Weeks 28 and End of Study inclusive, including any unscheduled evaluable Hgb values that were taken during this time period.
- Linear interpolation is used to estimate Hgb between visits, accounting for any intermittent missing values (Rosendall, 1993).

Percent Time in Range During the MP

- Time in Range During the MP / [Earlier of (Date of the last evaluable Hgb value, End of study date)– Later of (Date of the first evaluable Hgb value that is on or after week 16, Week 28 visit

Time In Range
date)] • Note: Percent time in/below/above range during the MP is only defined for subjects with a Treatment Stop Date that is on or 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 MP and another evaluable Hgb value occurs within the range of the Week 16 visit through the Treatment Stop Date + 1 day.

10.6.3.2. Iron Endpoints

Iron Endpoints
Iron Medications
• During the study, subjects may be receiving iron in multiple routes, including: o IV iron o Oral iron o 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.
Baseline Iron Use
• The number and percentage of subjects in the following iron use categories at baseline will be summarized: o IV iron use only o Oral iron use only o Other iron use only o IV and oral iron use only o IV and other iron use only o Oral and other iron use only o IV, oral, and other iron use o 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 16 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. o 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.

Iron Endpoints

- 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
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 16 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 – 16 weeks) to 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

Iron Endpoints

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 – 16 weeks), the duration of the record is 0.
  - If the concomitant medication record end date + gap factor ≥ (Randomization date – 16 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 Randomization date – 16 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:
  - If concomitant medication record start date < Randomization date - 16 weeks, or if Randomization date ≤ concomitant medication record start date, then duration of the record is 0.
  - If Randomization date -16 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$_{\text{Record n}}$)]/[(16* 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 and before their first RBC or whole blood transfusion.
  - 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 – 16 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

Iron Endpoints

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 < 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, first transfusion date (RBC or whole blood), 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 (first transfusion date (RBC or whole blood), 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 (first transfusion date (RBC or whole blood), 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}.

Iron Endpoints

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 and before their first RBC or whole blood transfusion.
    - Note: Subjects who are randomized but never treated, who have a RBC or whole blood transfusion, or who permanently discontinue randomized 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
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

Iron Endpoints

the Week 28 visit date).
    - Stop date will be the earliest of (concomitant medication record stop date + gap factor, first transfusion date (RBC or whole blood), 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 (first transfusion date (RBC or whole blood), 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 (first transfusion date (RBC or whole blood), 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 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.
- Although baseline iron use is defined based on a period of 16 weeks, it 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)

Iron Endpoints
▪ 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: o For summaries of on & off treatment IV iron dose: death date, study completion/withdrawal date, and the planned quarter end date. o For summaries of on-treatment IV iron dose: death date, first transfusion (RBC or whole blood), 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. • Although the standardized baseline IV iron dose is defined based on a period of 16 weeks, it will also be included in summaries of average quarterly IV iron dose.
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%

10.6.3.3. Time to Rescue

Time to Stopping Randomized Treatment Due to Meeting Rescue Criteria
Meeting Rescue Evaluation Criteria and Rescue Criteria
• Subjects meeting evaluation criteria for rescue are identified from the Rescue Treatment 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 randomized treatment or withdrew from the study before the 4 week check). The outcome of initial intervention eCRF field on the Rescue Treatment eCRF will be blank for these subjects. • Subjects meeting rescue are identified by the response 'Met rescue criteria' to the outcome of initial intervention question on the Rescue Treatment eCRF.
Event Date
• Treatment stop date when the primary reason and subreason for randomized 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 randomized treatment for subjects who stopped randomized treatment due to meeting rescue criteria + cumulative total of censoring time for subjects who did not stop randomized treatment due to meeting rescue criteria) / 365.25 • Rescue incidence rate (per 100 person years) = (100 * number of subjects who stopped randomized 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 randomized treatment, use the date of randomization • For subjects whose treatment stop date is missing and who took randomized 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.

10.6.3.4. 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 10.6.3).
- 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", or where the frequency is unknown, 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 up to the 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 Transufsion 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 counted as one.
- 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 start date of 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 10.4.1).
- 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 be 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 up to the nearest integer). For example, a transfusion of 450ml represents a single unit:

  (450 x 0.0025) = 1.125 (rounded up to 2 Units)

Reported Units	Multiplier
Units	1
Milliliters (ml or CC)	0.0025
Milligram (mg)	0.0025
Milligrams/milliliters (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).
- Where a transfusion record has been entered with a missing number of units, the number of units associated with the record will be assumed to be 1 unit.

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 randomized treatment during the evaluation period + cumulative time from date of week 28 visit to the date of withdrawal from randomized treatment, for subjects who withdrew from randomized 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 randomized treatment prior to week 52 + cumulative time from date of randomization to the date of withdrawal from randomized treatment, for subjects who withdrew from randomized 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)
Randomization to End of Treatment
• Person Years (PY) = (cumulative total time from date of randomization to the study conclusion date, for subjects who did not withdraw from randomized treatment + cumulative time from date of randomization to the date of withdrawal from randomized treatment, for subjects who withdrew from randomized treatment) / 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 study conclusion or withdrawal from treatment) / Person 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 study conclusion or withdrawal from treatment) / Person 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 study conclusion or withdrawal from treatment) / Person 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 randomized treatment for subjects who stopped randomized treatment, or date of study completion for subjects who did not stop randomized 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 +1day. The end of this time period is defined as follows: o For subjects continuing on study past the (treatment stop date + 1day), use (treatment stop date + 1day) o For subjects whose study withdrawal/completion date is on or before (treatment stop date + 1day), use date of study withdrawal/completion
Model Specification
• Analysis of time to first RBC or whole blood transfusion will be performed using an analysis model identical to that described for the co-primary MACE analysis (Section 7.2.2) for the evaluation of superiority. • Analysis will include only transfusion occurring during the on-treatment period..

Model Results Presentation
• The model results presentation will be identical to the co-primary MACE model results, with the following exception: • A single one-sided p-value for the test of superiority of daprodustat vs. rhEPO will be presented (i.e. there will be no test for non-inferiority). • A Kaplan-Meier plot will be produced showing the survival function for time to first RBC or whole blood transfusion.

10.6.3.5. Delayed Graft Function Endpoints

DGF Endpoints
DGF Following Deceased Donor Kidney Transplantation
• DGF following deceased donor kidney transplantation will be identified using the following combination of responses to questions on the Kidney Transplant eCRF form: o Donor source of transplant = either ['Deceased donor – donation after cardiac death (DCD)' or 'Deceased donor – donation after brain death (DBD)'] and o Did the subject have delayed graft function requiring dialysis within the first 7 days = 'Yes'
Duration of DGF
• The duration of DGF following deceased donor kidney transplantation will be defined as date of last dialysis after transplant (from the Kidney Transplant eCRF form) – kidney transplant date + 1 day

10.6.3.6. Dose Adjustment Scheme Endpoints

Dose Adjustment Scheme Endpoints
General
• The IRT system assigns all randomized treatment doses in accordance with the dose adjustment scheme specified in the protocol. • During the study, it is possible for subjects to change randomized treatment doses at both scheduled and unscheduled visits. • Sites are instructed to complete an exposure record every time dosing instruction is received from the IRT, with the exception of re-dispensing situations where the subject is instructed to continue using the same randomized treatment. • Summary tables for some dose adjustment scheme endpoints may summarize subjects by the type of rhEPO treatment received (i.e., epoetin alfa, darbepoetin alfa). Since it is possible for subjects to switch from epoetin alfa to darbepoetin alfa during the study, these displays will include subjects who switch rhEPO treatments in both the epoetin alfa and darbepoetin alfa groups.
Daprodustat Doses
Sites will enter the dose of daprodustat into exposure records – the daily frequency will be auto-populated for this randomized treatment. The dose steps of daprodustat are shown below:

Total Daily Dose	**How Administered**

Dose Adjustment Scheme Endpoints

1 mg	single 1 mg tablet
2 mg	single 2 mg tablet
4 mg	single 4 mg tablet
6 mg	single 6 mg tablet
8 mg	single 8 mg tablet
10 mg	single 10 mg tablet
12 mg	two 6 mg tablets
16 mg	two 8 mg tablets
24 mg	three 8 mg tablets

Epoetin Alfa Doses

Sites will enter the dose and frequency of 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	Dose and Frequency
1500	1500 U once a week
2000	2000 U once a week
3000	3000 U once a week
4000	4000 U once a week
5000	5000 U once a week
6000	6000 U once a week
8000	8000 U once a week
10000	10000 U once a week
12000	4000 U 3 times a week
15000	5000 U 3 times a week
18000	6000 U 3 times a week
21000	7000 U 3 times a week
24000	8000 U 3 times a week
27000	9000 U 3 times a week
30000	10000 U 3 times a week
36000	12000 U 3 times a week
42000	14000 U 3 times a week
48000	16000 U 3 times a week
60000	20000 U 3 times a week

Darbepoetin Alfa Doses

Sites will enter the dose and frequency of each dose of darbepoetin alfa into exposure records. The dose steps of darbepoetin alfa (including the corresponding total 4-weekly doses) are shown below:

Total 4-Weekly Dose	Pre-filled Syringe Dose and Frequency
20 µg	20 µg every 4 weeks

Dose Adjustment Scheme Endpoints

30 µg	30 µg every 4 weeks
40 µg	40 µg every 4 weeks
60 µg	60 µg every 4 weeks
80 µg	80 µg every 4 weeks
100 µg	100 µg every 4 weeks
150 µg	150 µg every 4 weeks
200 µg	100 µg every 2 weeks
300 µg	150 µg every 2 weeks
400 µg	100 µg every 1 week

Assigned Dose at A Scheduled Visit

- The assigned dose at a particular visit refers to the dose the subject 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.
    - 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 the subject received in the period directly preceding the visit, as recorded in the eCRF. 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.
    - 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 randomized 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].

Dosing Algorithm Update

- The dosing algorithm update went into effect on different dates at different sites, due to variable approval times. The IRT records the date that each site changed algorithms. Subjects' randomization dates and Hgb assessment dates will be compared to their site's date of algorithm change. Any randomization/Hgb assessment dates before the day of the site's

Dose Adjustment Scheme Endpoints
algorithm change are considered to have occurred under the original algorithm. Any randomization/Hgb assessment dates on or after the day of the IRT algorithm change are considered to have occurred under the updated algorithm. • The 95% prediction interval for Hgb values at a visit provides an estimate of the range where future Hgb values would occur, with a probability of 95%. The 95% prediction interval for future Hgb values can be calculated using the approach described in (Francq, 2019), where the prediction interval at Visit x is calculated using adjusted mean Hgb value at Visit x $\pm$ 1.96 * sqrt (standard error^2 + total variance at Visit x). Due to the use of an unstructured covariance matrix (Section 8.1.3), the total variance at Visit x is found at (x, x) on the diagonal of the R matrix.

10.6.3.7. Phosphate Binder Use

Phosphate Binder Use
Baseline Phosphate Binder Use (Yes/No)
• Baseline Phosphate binder use will be categorized as either Yes, or No for the phosphate binder analyses. • Subjects will be counted in each applicable group, based on the concomitant medications they are receiving on the day of randomization.
Phosphate Binder Use at Week 28 (Yes/No)
• Phosphate binder use at Week 28 will be categorized as either Yes, or No for the phosphate binder analyses. • Subjects will be counted in each applicable group, based on the concomitant medications they are receiving between Week 24 and Week 28.
Phosphate Binder Use at Week 52 (Yes/No)
• Phosphate binder use at Week 52 will be categorized as either Yes, or No for the phosphate binder analyses. • Subjects will be counted in each applicable group, based on the concomitant medications they are receiving between Week 48 and Week 52.

10.6.4. Safety

10.6.4.1. 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 Death1 eCRF page • Myocardial infarction: date of onset of Myocardial Infarction/Unstable Angina symptoms from the MI/UA1 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

CV Safety Endpoints
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 will 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

Missing or Partial Event (Start) 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 10.6.4.
- 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., --

CV Safety Endpoints

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, 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 give 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..

Missing or Partial Hospitalization End Dates

- If hospitalization end dates are missing or partial, the following rules for missing or partial dates will be implemented as long as the imputed date is before the next hospitalization start date or study completion/withdrawal date (if there is no next hospitalization start date). If the imputed date is after the next hospitalization start date, then the date of the next hospitalization start date – 1day will be used as the hospitalization end date. If the imputed date is after the study completion/withdrawal date, then the date of the study

CV Safety Endpoints

completion/withdrawal date will be used as the hospitalization end date.

- If only the day of the month is missing, impute the last day of the month (e.g., --MAR2016 would impute as 31MAR2016)
- If the month and day of the month are missing, impute 31DEC (e.g., -----2016 would impute as 31DEC2016)
- If the year, month, and day of month are missing, impute the date of study completion/withdrawal.

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 adjudicated 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
  - 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.
- The concordance table for heart failure events will include the 4 adjudicated event types listed above.

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)

CV Safety Endpoints

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 and All-cause Hospital Re-admission within 30 days

- All-cause hospitalization events are defined to be hospital admissions recorded on the Hospitalization eCRF form with a hospitalization duration ≥ 24 hours.
- All-cause hospital re-admissions within 30 days are defined to be hospital admissions recorded on the Hospitalization eCRF form with a hospitalization duration of ≥ 24 hours and an admission date within 30 days following a previous discharge date of an all-cause hospitalization event, where the previous hospitalization should be ≥ 24 hours as stated above.

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

CV Safety Endpoints

General Definitions

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

- 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 10.6.1)
- 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 randomized 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 primary analysis during the time period for follow-up of CV safety endpoints,

CV Safety Endpoints
then use the censoring date for the primary analysis time period. 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.

10.6.4.2. Blood Pressure Endpoints

Blood Pressure Endpoints

Pre- and Post- Dialysis BP

- For subjects undergoing dialysis in-clinic, both pre- and post- dialysis BP values will be measured.
- Unless otherwise specified, for summaries and analyses of BP values, the post-dialysis BP values for subjects undergoing dialysis in-clinic will be used.

End of Treatment BP Value

- See Section 10.6.1

Mean Arterial Pressure (MAP)

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

Blood Pressure Exacerbations

- BP exacerbations will be defined as (≥ 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
            - ≥ 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
            - ≥ 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 10.4.1), 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.
- For subjects who have in-clinic dialysis, BP exacerbations identified using post-dialysis BP

Blood Pressure Endpoints
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 an 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 in the total BP exacerbation type.
Blood Pressure Exacerbation Event Date
• Date of BP exacerbation
On-Treatment BP Medication
• See Section 10.4.1 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 randomized treatment start date) and no change to anti-hypertensive records since baseline until date of visit while on randomized 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 randomized 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 randomized treatment • Switch = change with a reason of 'switched to another agent…' since baseline until date of visit while on randomized 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 randomized treatment to the Week 52 visit date while on randomized 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 randomized 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 randomized treatment to the Week 52 visit date while on randomized 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

Blood Pressure Endpoints
starting from the date of first randomized treatment to End of Treatment

10.6.4.3. Adverse Events

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

Adverse Events

values that occurred 4 weeks before the [AE start date – 30 days, AE start date +15 days] window of interest. HemoCue Hgb and 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 10.6.3 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
  - 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

Adverse Events

- Implant site ischaemia
- Infusion site ischaemia
- Injection site ischaemia
- Intestinal ischaemia
- Ischaemia
- Macular ischaemia
- Medical device site ischaemia
- Myocardial ischaemia
- Peripheral ischaemia
- Renal ischaemia
- Retinal ischaemia
- Spinal cord ischaemia
- Ischaemic limb pain
- Ischaemic mitral regurgitation
- Ischaemic nephropathy
- Ischaemic neuropathy
- Ischaemic pancreatitis
- Ischaemic skin ulcer
- Ischaemic stroke
- Necrosis ischaemic
- Ocular ischaemic syndrome
- Optic ischaemic neuropathy
- Reversible ischaemic neurological deficit
- Transient ischaemic attack

<u>Cardiomyopathy</u>

- Narrow SMQ: Cardiomyopathy

<u>Pulmonary artery hypertension</u>

- 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

<u>Cancer-related mortality and tumor progression and recurrence</u>

- 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
  - Pancytopenia

Adverse Events

- Cytopenia
- Myelosuppression
- 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

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

Adverse Events

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

False Discovery Rate (FDR) Method and Procedure

The FDR method adjusts p-values within a group (SOC or preferred terms (PTs) within a SOC) based on the following:

a) Order p-values from lowest to highest (1... m)

b) Compute adjusted p-values, p', as follows

p'(m) = p(m) i.e., the adjusted p-values for the highest p-value is the same as the highest p-value

$p'(j) = \min(\{p'(j+1), m/j*p(j)\}$ for $j \leq m - 1$

The FDR procedure is applied at the system organ class (SOC) level and for each AE preferred term (PT) reported as Tier 2 events. The following stops will be undertaken in this procedure:

1. Compute adjusted p-values for PTs within each SOC using the FDR method.
2. Order SOCs (small to large) according to the minimum FDR adjusted p-value observed for treatment differences across PTs within SOC.
3. Perform the FDR method on the minimum adjusted p-values from Step 2.
4. Select SOCs with FDR adjusted p-value from Step 3 <0.10.
5. Apply a single FDR adjustment to all unadjusted p-values belonging to all PTs from SOCs identified in Step 4. with a threshold of FDR adjusted p-values <0.10 will be used to flag PTs that warrant further investigation.

Note that 0.10 is recommended as a reasonable multiplicity adjustment for 0.05.

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 +

Adverse Events
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. ○ 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 2 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.

10.6.4.4. 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 10.6.3.
• 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.

Laboratory Parameters
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.
  ○ 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

10.6.4.5. Vital Signs

Vital Signs
Pre- and Post- Dialysis HR & Weight
• For subjects undergoing dialysis in-clinic, 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 for subjects undergoing dialysis in-clinic 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, 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.

10.6.4.6. COVID-19

COVID-19
Exposure Duration
• For subjects who DO NOT experience the event, the exposure duration is calculated as: (last non-zero dose 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 interest is prior to the country specific start date of COVID-19 pandemic measures. For example, for recruitment and demographic summaries, the subject will be counted in the pre COVID-19 period, if the randomization date of the subject is prior to the country specific start date of COVID-19 pandemic measures. • During COVID-19 period: the date of interest is after the country specific start date of COVID-19 pandemic measures. For example, for recruitment and demographic summaries, the subject will be counted in the during COVID-19 period, if 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.

10.6.5. Patient Reported Outcomes

SF-36
General Information & Scoring
• The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a subject's level of performance in the following eight health domains: Physical Functioning, Role-Physical (role limitations caused by physical problems), Social Functioning, Bodily Pain, Mental Health, Role-Emotional (role limitations caused by emotional problems), Vitality, and General Perception of Health. • Scoring of the questionnaire data will be performed using Optum PRO CoRE scoring software version 1.4 using a norms-based scoring approach using 2009 norms and the maximum data recovery mode to handle missing data. • The 8 domain scores and scores for the physical and mental component summary measures will be provided by the Optum PRO CoRE software.

EQ-5D-5L
General
• The EQ-5D-5L is a self-assessment questionnaire, consisting of five items covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a five-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems).

EQ-5D-5L
General
• The responses for the five dimensions together form a five-figure description of a health state (i.e., the score of 11112 describes the health state of no problems with mobility, self-care, usual activities or pain/discomfort, but slight problems with anxiety/depression). EQ-5D-5L health states are converted to a single summary index score by applying a country-specific value set formula that essentially attaches weights to each of the levels in each dimension. • The EuroQol Group's United Kingdom (UK) crosswalk value set for the health states will be used for all subjects, regardless of country. The converted single index using this value set will be on a scale from -0.594 to 1, where -0.594 is the CCI and 1 is the CCI .
• The EQ-5D-5L will only be assessed in the countries listed in Section 10.9.

EQ-VAS
General
• The EQ-VAS is a self-assessment visual analogue scale, ranging from 0=CCI – 100=CCI .
• The EQ-VAS will only be assessed in the countries listed in Section 10.9.

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 CCI as follows: ○ CCI ○ ○ ○ ○

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). • Scores range from CCI to CCI 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. ○ ○ ○ ○ ○

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

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completing all phases of the study including the End of Study visit, with the following exception: subjects who die while on study are also considered as having completed the study. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Per protocol, subjects may prematurely discontinue study drug but are encouraged to remain in the study.

10.7.2. Handling of Missing Data

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

10.7.2.1. 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: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o 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.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year or only year) to be recorded for AE start/worsening and end dates. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:

Element	Reporting Detail
	○ Imputing a Start/Worsening Date from a Partial Start/Worsening Date: ○ If an imputed worsening date is before the start date, then the start date will be used as the imputed worsening date. ○ <u>Completely missing stop date:</u> ➢ If only the day is missing, the first of the month will be used unless the Screen Week -8 visit date, Run-In visit date or treatment start date also occurs in the same month. • If the treatment start date occurs in the same month, then the treatment start date will be used as the start/worsening date. • Otherwise, if the Run-In visit date occurs in the same month (and the treatment start date is not in that month), then the Run-In visit date will be used as the start/worsening date. • Otherwise, if the Screen Week -8 visit date occurs in the same month (and the treatment start and Run-In visit dates are not in that month), then the Screen Week -8 visit date will be used as the start/worsening date. ➢ If the day and month are missing, then '01' will be used for the day and 'Jan' will be used for the month unless the Screen Week -8 visit date, Run-In visit date or treatment start date also occurs in the same year. • If the treatment start date occurs in the same year, then the treatment start date will be used as the start/worsening date. • Otherwise, if the Run-In visit date occurs in the same year (and the treatment start date is not in that year), then the Run-In visit date will be used as the start/worsening date. • Otherwise, if the Screen Week -8 visit date occurs in the same year (and the treatment start and Run-In visit dates are not in that year), then the Screen Week -8 visit date will be used as the start/worsening date. ○ <u>Partial or non-missing stop date is before the Run-in visit date:</u> ➢ If only the day is missing, the first of the month will be used unless the Screen Week -8 visit date also occurs in the same month; in this case the Screen Week -8 visit date will be used as the start/worsening date. ➢ If the day and month are missing, then '01' will be used for the day and 'Jan' will be used for the month unless the Screen Week -8 visit date also occurs in the same year; in this case the Screen Week -8 visit date will be used as the start/worsening date.

Element	Reporting Detail
	○ Partial or non-missing stop date is before treatment start date, and either on or after Run-In date or has the same year (or year and month) as the Run-In date: ➢ If only the day is missing, then the first of the month will be used unless the Run-In Visit date also occurs in the same month; in this case the Run-In Visit date will be used as the start/worsening date. ➢ If the day and month are missing, then '01' will be used for the day and 'Jan' will be used for the month unless the Run-In Visit date also occurs in the same year; in this case the Run-In Visit date will be used as the start/worsening date. ○ Stop date is partial with the same year (or year and month) as the treatment start date or is on or after the treatment start date: ➢ If only the day is missing, then the first of the month will be used unless the start date of study treatment also occurs in the same month; in this case the study treatment start date will be used as the start/worsening date. ➢ If the day and month are missing, then '01' will be used for the day and 'Jan' will be used for the month unless the start date of study treatment occurs in the same year; in this case the study treatment start date will be used as the start/worsening date. ○ Imputing a Stop Date from a Partial Stop Date: ○ Latest of (start date and latest worsening date) is on or before the treatment stop date or is partial with the same year (or year and month) as the treatment stop date: ➢ If only the day is missing, the last day of the month will be used unless the treatment stop date also occurs in the same month; in this case the treatment stop date will be used at the stop date. ➢ If the day and month are missing, then '31' will be used for the day and 'Dec' will be used for the month, unless the stop date of study treatment also occurs in the same year; in this case the study treatment stop date will be used as the stop date. ○ Latest of (start date and latest worsening date) is partial or non-missing and is after treatment stop date: ➢ If only the day is missing, the last day of the month will be used unless the study conclusion date also occurs in the same month; in this case, the study conclusion date will be used as the stop date. ➢ If the day and month are missing, then '31' will be used for the day and 'Dec' will be used for the month, unless the study conclusion date also occurs in the same year; in this case, the study conclusion date will be used as the stop

Element	Reporting Detail
	date. • Completely missing start, worsening or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
CV Safety Endpoint Events	Discussed in Section 10.6.4

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. 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

10.8.2. Vital Signs

Vital Sign Parameter (Absolute)	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	≤ 85 mmHg	≥ 180 mmHg
Diastolic Blood Pressure	mmHg	≤ 45 mmHg	≥ 110 mmHg

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
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.
- For subjects who undergo in-clinic dialysis, the post-dialysis BP and HR values will be used to assess PCI criteria, unless otherwise specified.

10.9. Appendix 9: Multicenter Studies

10.9.1. Methods for Handling Centres

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

Region	Countries[2]
Region 1: Asia Pacific	India, Malaysia[1], Republic of Korea[1], Singapore[1], Taiwan[1]
Region 2: Eastern Europe/South Africa	Bulgaria, Turkey, Czech Republic, Estonia, Hungary, Poland, Romania, Russian Federation, Ukraine, South Africa[1]
Region 3: Western Europe/Canada/ANZ	Australia[1], Austria, Belgium, Canada[1], Denmark[1], France, Germany, Greece, Italy, Netherlands[1], New Zealand[1], Norway[1], Portugal, Spain[1], Sweden[1], United Kingdom[1]
Region 4: Latin America	Argentina, Brazil[1], Mexico
Region 5: USA	USA[1]

NOTES:

[1]: Countries which will collect the EQ-5D-5L and EQ VAS.

[2] Countries that do not participate or do not randomize any subjects will be removed from the regional grouping.

For any summaries which 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.

10.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

10.10.1. Handling of Covariates, Subgroups & Other Strata

- 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, any subgroup statistical comparison should be interpreted with caution.
- 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 co-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 (Cox Proportional Hazards or ANCOVA) will be adjusted for the covariates used in the original analysis, subgroup, treatment and treatment by subgroup interaction. For the prognostic randomization stratification factors (region and dialysis type), the actual status of the factor derived from the eCRF will be used (see Section 10.10.2). Note that for the cardiovascular risk score covariate, the above model will not include a term for dialysis type as this analysis is restricted to HD patients only. 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 and selected PRO endpoints using MMRM model in the original analysis, the statistical model for the corresponding subgroup analyses will have the following factors: dialysis type, 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. For the selected Hgb, BP, and PRO endpoints using MMRM in the original model that contain only main effects and two-way interaction terms, both the main effects and the two-way interaction terms will be included in the model statement. If any of the above MMRM models encounter 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 any of the models still fail to converge after Step 3, model-adjusted analyses 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 one of the prognostic stratification variables, 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 two-sided 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 co-primary Hgb endpoint.

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
Key Covariates/Subgroups of Regulatory/Clinical Interest or Potential Biological Plausibility for Different Subgroup Effects				
Age (years)	Summary statistics of continuous values	Yes	No	No
Age at randomization (Grouping 1)	< 65 years, 65-<75 years, ≥75 years	Yes	Yes	Yes
Age at randomization (Grouping 2)	≤18 years, 19 - 64 years, ≥ 65 years	Yes	No	No
Age at randomization (Grouping 3)	18-64 years, 65 - 84 years, ≥ 85 years	No (included in stand-alone age ranges table)	No	No
Gender	Female, Male	Yes	Yes	Yes
Ethnicity	Hispanic or Latino, Not Hispanic or Latino	Yes	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	Yes
Race detail	American Indian or Alaskan Native	Yes	No	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
	Asian – Central/South Asian Heritage Asian – East Asian Heritage Asian – Japanese Heritage Asian – South East Asian Heritage Black or African American Native Hawaiian or Other Pacific Islander White – Arabic/North African Heritage White – White/Caucasian/European Heritage Mixed Asian Race Mixed White Race Mixed Race			
Region	See Region categories defined in Section 10.9.1	Yes	Yes	Yes
Regions combined	USA, Non-USA	Yes	Yes	Yes
Country	See Countries listed in Section 10.9.1	Yes	No	No
Dialysis type at randomization[1]	HD, PD, Missing (repeat using HD - conventional, HDF/HF, PD, Missing)	Yes	Yes (HD/PD only)	Yes (HD/PD only)
Prior ESA type at randomization	Darbepoetin alfa only, Epoetin only, Methoxy PEG-epoetin beta only,	Yes	No	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
	Multiple, Missing			
Standardized prior ESA dose (U/week)[2]	Summary statistics of continuous values	Yes	No	No
Standardized prior ESA dose group[2]	< 7,000 U/week, ≥7,000 U/week, Missing	Yes	Yes	Yes
Baseline erythropoietin resistance index (ERI) (U/kg/wk/g/L)	Summary statistics of continuous values	Yes	No	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	No
rhEPO hyporesponder[2]	No, Yes, Missing	Yes	Yes	Yes
Standardized Prior ESA Dose (U/week) for rhEPO Hyporesponders	Summary statistics of continuous values	Yes	No	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
Standardized Prior ESA Dose (U/week) for rhEPO Non-hyporesponders	Summary statistics of continuous values	Yes	No	No
Alternate definition of rhEPO hyporesponder Definition 2[2]	No, Yes, Missing	Yes	No	No
Alternate definition of rhEPO hyporesponder Definition 3[2]	No, Yes, Missing	Yes	No	No
Baseline Hgb (g/dL)	Continuous covariate for Hgb co-primary analysis; summary statistics of continuous values	Yes	No	No
Baseline Hgb group	< 9 g/dL, 9- <10 g/dL, 10-11 g/dL, > 11 g/dL, Missing	Yes	Yes	Yes
Baseline post-dialysis body mass index (kg/m^2)	Summary statistics of continuous values	Yes	No	No
Baseline post-dialysis body mass index group	<30 kg/m^2, ≥30 kg/m^2, Missing	Yes	Yes	Yes
Baseline post-dialysis weight (kg)	Summary statistics of continuous values	Yes	No	No
Baseline post-dialysis weight group	<75 kg, ≥75 kg, Missing	Yes	No	No
Baseline post-dialysis weight	Overall ITT Population Quartile 1: < xx	Yes	Yes	Yes

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
quartiles	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			
Baseline hsCRP (mg/L)	Summary statistics of continuous values	Yes	No	No
Baseline hsCRP group	≤3 mg/L, >3 mg/L, Missing	Yes	No	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	Yes
Standardized prior ESA dose (U/week) for baseline hsCRP	Summary statistics of continuous values	Yes	No	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
Overall ITT Population Quartile 1: < xx mg/L				
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	No
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	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	No
Dosing algorithm at randomization	Original algorithm, Updated algorithm	Yes	No	Yes (Hgb only)
Other Exploratory Covariates/Subgroups where Biological Plausibility for Heterogeneous Effects Are Not Known or Anticipated				
CV risk score for HD subjects	Low risk (Overall ITT Population Tertile 1: < xx), Medium risk (Overall ITT Population Tertile 2: xx - < xx), High risk (Overall ITT Population	Yes	Yes	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
	Tertile 3: ≥ xx) (Note: only defined for HD subjects See Section 10.6.2 for details.)			
Dialysis vintage at screening	0 - <2 years, 2-<5 years, ≥5 years, Missing	Yes	Yes	Yes
History of diabetes	No, Yes, Missing	Yes	Yes	Yes
History of stroke	No, Yes, Missing	Yes	Yes	Yes
History of MI	No, Yes, Missing	Yes	Yes	Yes
History of cancer	No, Yes, Missing	Yes	Yes	Yes
History of heart failure	No, Yes, Missing	Yes	Yes	Yes
History of thromboembolic events	No, Yes, Missing	Yes	Yes	Yes
Hospitalization within 6 months prior to screening	No, Yes, Missing	Yes	Yes	Yes
Transfusion within 6 months prior to screening	No, Yes, Missing	Yes	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	Yes	No	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
	IV and other iron use only Oral and other iron use only IV, oral and other iron use			
Standardized baseline IV iron dose (mg/month)	Continuous covariate for monthly IV iron dose analysis, summary statistics of continuous values	Yes	No	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	No
Baseline post-dialysis SBP (mmHg)	Continuous covariate for change from baseline in SBP analysis, summary statistics of continuous values	Yes	No	No
Baseline post-dialysis DBP (mmHg)	Continuous covariate for change from baseline in DBP analysis, summary statistics of continuous values	Yes	No	No
Baseline post-dialysis MAP (mmHg)	Continuous covariate for change from baseline in MAP analysis, summary statistics of continuous values	Yes	No	No
Dialysis access type used at randomization	Arteriovenous fistula Arteriovenous graft Central venous catheter – tunneled Central venous catheter – non-	Yes	No	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
	tunneled Peritoneal catheter Other Missing			
ACEI/ARB use at randomization	No, Yes	Yes	Yes	Yes
Phosphate binder use at randomization	Iron-based phosphate binders Calcium-based phosphate binders Non-calcium and non-iron based phosphate binders No phosphate binder use	Yes	No	No
Vitamin D use at randomization	No, Yes	Yes	No	No
Baseline Kt/V urea for HD subjects	Summary statistics of continuous values	Yes	No	No
Baseline Kt/V urea for PD subjects	Summary statistics of continuous values	Yes	No	No
Baseline URR for HD subjects (%)	Summary statistics of continuous values	Yes	No	No
History of cardiovascular disease	No, Yes	Yes	Yes	No
Beta blockers use at	No, Yes	Yes	No	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Co-primary MACE & Principal Secondary Safety Endpoints Note: Do not include 'Missing' categories.	Subgroup Analysis for Co-primary Hgb & Principal Secondary Efficacy Endpoints Note: Do not include 'Missing' categories.
randomization				
SGLT2i use at randomization	No, Yes	Yes	No	No
Statin use at randomization	No, Yes	Yes	No	No
Aspirin use at randomization	No, Yes	Yes	No	No
Vitamin K antagonist use at randomization	No, Yes	Yes	No	No
Insulin use at randomization	No, Yes	Yes	No	No
Calcimimetics use at randomization	No, Yes	Yes	No	No
Diabetic medication use at randomization	No, Yes	Yes	No	No
Baseline estimated dry weight (kg)	Summary statistics of continuous values	Yes	No	No

NOTES:

1: Subjects who change dialysis modalities during the study will be counted in the subgroup corresponding to their dialysis modality at randomization.

2: Prior ESA dose standardization and ESA hyporesponsiveness are defined in Section 10.6.2. Supportive definitions of hyporesponders will be included in the summary of demographics and baseline characteristics, but will not be used in subgroup analyses.

10.10.2. Randomization Stratification

Randomization is stratified by dialysis type (HD or PD), region and by participation in an ABPM sub-study to ensure balance across treatment groups for both the overall parent study and within the ABPM sub-study. The prognostic stratification factors (i.e., dialysis type and region) will be taken into account within the analysis models. Stratification by ABPM sub-study participation was implemented for logistical reasons, and will not be taken into account within analysis models.

Baseline dialysis type strata will be identified by two data sources:

- PPD's IRT dataset
- eCRF

The proposed approach is to use the IRT strata in the adjusted analysis models in order to provide a randomization-based test statistic in accordance with the principle of 'analyze as randomized'. In summaries of subgroups however, the actual status of the factor for stratification derived from the eCRF form will be used. Additionally, subjects who change dialysis modality during the study will remain in the dialysis modality strata that was assigned at randomization.

10.11. Appendix 11: Multiple Comparisons & Multiplicity

10.11.1. Handling of Multiple Comparisons & Multiplicity

10.11.1.1. Interim Analyses

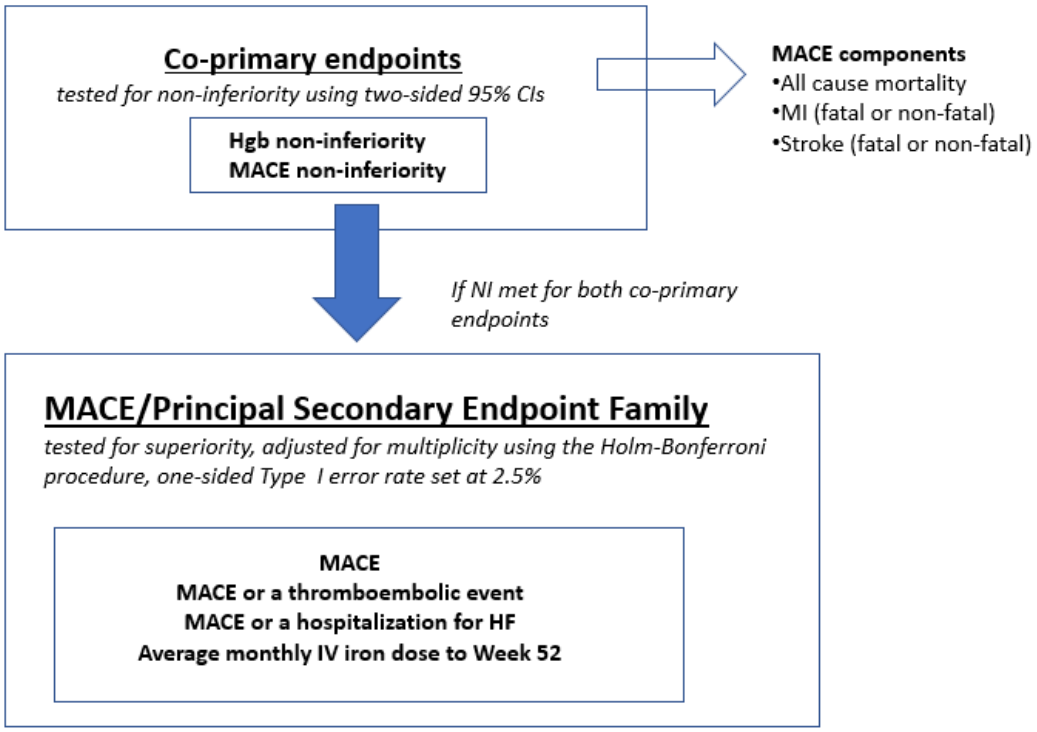
The interim analysis will only result in stopping the study for harm or futility. There are no prospectively defined plans to stop any of the ASCEND trials early for benefit. As such, no multiplicity adjustments are required since the type I error rate will not be increased. Further details including stopping guidelines for harm and futility are included in the IDMC charter.

10.11.1.2. Final Analyses

The multiplicity strategy for this trial will use a combination of a gatekeeper approach on the co-primary endpoints, followed by a closed-test multiplicity procedure wrapped around the family of principal secondary analyses.

Figure 1 illustrates the structure of the statistical testing plan. First, the co-primary endpoints will be evaluated for at least non-inferiority by comparing each two-sided 95% CI to the appropriate non-inferiority margin. Then, the principal secondary analyses will be performed and superiority will be tested for the individual analyses. Conditional on both co-primary endpoints achieving non-inferiority (i.e., passing the gatekeeper), the family of principal secondary analyses will be formally tested for superiority using the widely known Holm-Bonferroni procedure [Holm, 1979]. The procedure will be conducted based on a family-wise Type I error rate set at the one-sided 2.5% level.

Figure 1 Multiplicity controlled statistical testing plan



Details of the Holm-Bonferroni procedure for testing secondary endpoints:
The procedure starts with conducting the statistical analyses for each of the principal secondary analyses and ranking the resulting one-sided p-values from most significant (i.e. the lowest p-value) to the least significant. The Holm-Bonferroni formula is calculated for each rank using a target alpha. The formula for the Holm-Bonferroni method is:

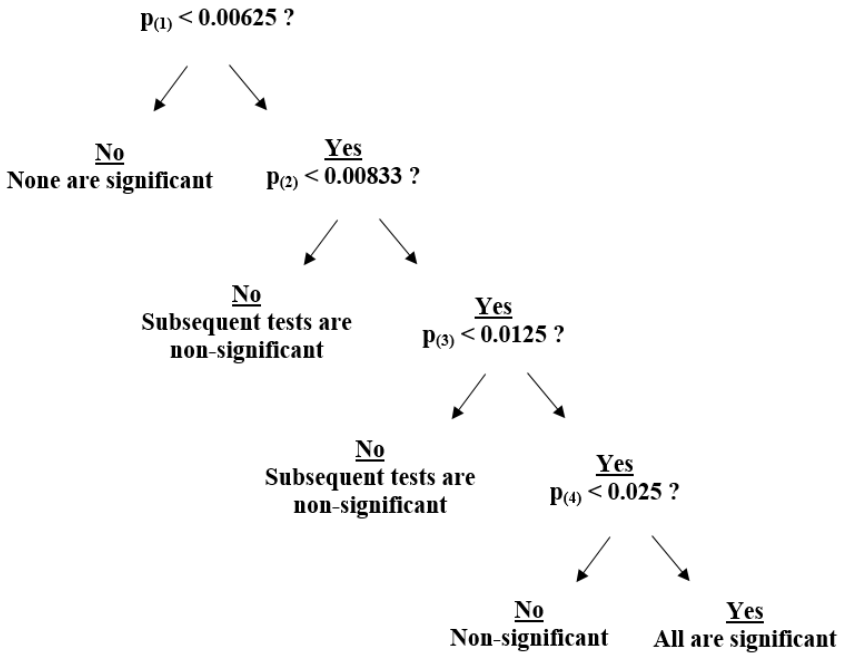
$$Holm - Bonferroni_i = \frac{Target\ \alpha}{n - rank_i + 1}$$

Where:

- the $target\ \alpha$ is the overall alpha level (one-sided 2.5% significance)
- n is the total number of tests

The most significant p-value is compared to the rank-associated alpha derived from the Holm-Bonferroni method. If a positive statistically significant treatment effect is observed, then the testing continues to the next ranked test. If the endpoint fails to achieve statistical significance when compared to the Holm-Bonferroni rank-associated alpha, the testing stops and all subsequent endpoints are declared to have failed to achieve statistical significance. This algorithm is described in detail in Figure 2 for the four principal secondary analyses defined for the trial.

Figure 2 The Holm-Bonferroni Procedure for Multiplicity Control



10.11.1.3. Subgroup Analyses

Subgroup analyses will not be adjusted for multiplicity.

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

10.12.1. Statistical Analysis Assumptions

Endpoint(s)	• Hgb Change from Baseline to the EP
Analysis	• ANCOVA
• 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. • Models will be examined for treatment interactions with baseline Hgb and stratification factors	
Analysis	• Multiple Imputation/Tipping Point Analysis
	• Intermittent missing data imputation: o If there are error and or warning messages related to the by statement (e.g. not enough observations to fit regression models), try to impute by randomized treatment and baseline dialysis type, then by randomized treatment only until no error/warning messages. o If convergence issue still occurs, the convergence precision may be set to 1E-3. • Monotone missing data imputation: o When imputing for each of the monotone missing dataset (out of the 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) impute by randomized treatment and baseline dialysis type, with baseline Hgb and region as covariates, 2) impute by randomized treatment, with baseline Hgb, baseline dialysis type, and region as covariates, 3) impute by randomized treatment, with baseline Hgb, and baseline dialysis type as covariates, 4) impute by randomized treatment with baseline Hgb as a covariate, until no error/warning messages.
Endpoint(s)	• Time to first event endpoints: MACE and MACE or thromboembolic events or hospitalization for HF
Analysis	• Cox proportional hazards
• To inform on the validity of the adjusted Cox proportional hazards model, the proportional hazards assumption will be assessed by plotting the logarithm of the negative logarithm of the estimated survivor function against the logarithm of time, for each treatment group, region and dialysis type. If the hazards are proportional, the lines should be approximately parallel. • Should there be evidence of a violation of the proportional hazards assumption, the following methods may be considered: o Use of a stratified Cox proportional hazards model (including prognostic factors in a	

STRATA statement in PROC PHREG, rather than in the MODEL statement)	
Endpoint(s)	• Time to first event endpoints with death as a competing risk
Analysis	• Cox proportional hazards
• If there is a notable difference between one or both of all-cause mortality and non-CV mortality, and one or more of the secondary CV endpoints that do not include death as a component, then additional analysis methods to address competing risks may be pursued such as: o Fine & Gray's Subdistribution Hazards (Fine, 1999) o Use of cumulative incidence functions instead of KM curves	

10.13. Appendix 13: Pharmacokinetic Sub-study Analysis Plan

10.13.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the "Pharmacokinetic" population, unless otherwise specified. The Pharmacokinetic population is defined as subjects for whom additional PK eligibility was confirmed and have at least one non-missing PK sample measurement.

Table 16 provides an overview of the planned analyses.

Table 16 Overview of Planned Pharmacokinetic Analyses for GSK1278863, and/or GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13)

Parameter	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
GSK1278863, GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13)														
GSK1278863 and Metabolites Plasma Pharmacokinetic Concentration Time Data (ng/ml) by Treatment				Y	Y[1]	Y	Y					Y[1]	Y	
GSK1278863 and Metabolites Plasma Pharmacokinetic Parameter[2] Data				Y			Y				Y			
GSK1278863														
GSK1278863 Dose Parameter Data				Y			Y							
GSK1278863 Special Parameter[3] Data				Y			Y				Y			

NOTES:

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

1. Mean and median plots will be generated
2. Cmax, Tmax, Ctau
3. Ctau/1mg Dose, Ctau/avg Dose EP TIR, Ctau/ avg Dose EP, Ctau/ Dose at MACE, Ctau/Final Dose for subjects without MACE, Ctau/ Dose at MACE++, Ctau/ Final Dose for subjects without MACE++, Cmax/1mg Dose, Cmax/avg Dose EP TIR, Cmax/avg Dose EP, Cmax/ Dose at MACE, Cmax/ Final Dose for subjects without MACE, Cmax/ Dose at MACE++, Cmax/ Final Dose for subjects without MACE++

10.13.2. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).

10.13.3. Pharmacokinetic Parameters

10.13.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).
- The pharmacokinetic parameters of parent GSK1278863, and metabolites (GSK2391220 (M2), GSK2506104 (M3), and GSK2531401 (M13)) will be calculated by programming methods.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 17 will be determined from the plasma concentration-time data, as data permits.

Table 17 Derived Pharmacokinetic Parameters for GSK1278863, and/or GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13)

Parameter	Parameter Description
GSK1278863, GSK2391220 (M2), GSK2506104 (M3) and GSK2531401 (M13)	
tmax	Time to reach Cmax, determined directly from the concentration-time data.
Ctau	Observed concentration at dosing interval (tau=24 h, predose sample)
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
GSK1278863	
Avg Dose EP TIR	The average daily GSK1278863 dose when the subject is on-treatment and in target Hgb range during the evaluation period (EP) Weeks 28-52 (See Section 10.6.3.1). Evaluable Hgb values are used to determine time in range. Subjects who permanently stop randomized 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 daily GSK1278863 dose when the subject is on-treatment during the EP.
Dose at first MACE	The daily GSK1278863 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 GSK1278863 dose during the study.
Dose at first MACE++	The daily GSK1278863 dose at the time of the subject's first on-treatment adjudicated MACE++ (defined as the first adjudicated MACE, hospitalization for heart failure, or thromboembolic event) 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 GSK1278863 dose during the study.
Ctau/1mg Dose	Ctau extrapolated to 1mg dose: Observed Ctau divided by dose administered on the PK day

Parameter	Parameter Description
Ctau/Avg Dose EP TIR	Ctau extrapolated to average dose during EP TIR: Ctau/1mg multiplied by the average daily GSK1278863 dose when the subject is on-treatment and in target Hgb range during Weeks 28-52 (see Section 10.6.3.1). Evaluable Hgb values are used to determine time in range.
Ctau/Avg Dose EP	Ctau extrapolated to average dose during EP: Ctau/1mg multiplied by the average daily GSK1278863 dose during the EP.
Ctau/Dose at first MACE	Ctau extrapolated to dose at first on-treatment adjudicated MACE: Ctau/1mg multiplied by the daily GSK1278863 dose at the time of the subject's first on-treatment adjudicated MACE.
Ctau/Final Dose for subjects without MACE	For subjects without an on-treatment adjudicated MACE, this is the subject's Ctau/1mg multiplied by the subject's final daily GSK1278863 dose during the study.
Ctau/Dose at first MACE++	Ctau extrapolated to dose at first on-treatment adjudicated MACE++: Ctau/1mg multiplied by the daily GSK1278863 dose at the time of the subject's first on-treatment adjudicated MACE++.
Ctau/Final Dose for subjects without MACE++	For subjects without an on-treatment adjudicated MACE++, this is the subject's Ctau/1mg multiplied by the subject's final daily GSK1278863 dose during the study.
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 daily GSK1278863 dose when the subject is on-treatment and in target Hgb range during Weeks 28-52 (see Section 10.6.3.1). Evaluable Hgb values are used to determine time in range.
Cmax/Avg Dose EP	Cmax extrapolated to average dose during EP: Cmax/1mg multiplied by the average daily GSK1278863 dose during the EP.
Cmax/Dose at first MACE	Cmax extrapolated to dose at MACE: Cmax/1mg multiplied by the daily GSK1278863 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 daily GSK1278863 dose during the study.
Cmax/Dose at first MACE++	Cmax extrapolated to dose at MACE++: Cmax/1mg multiplied by the daily GSK1278863 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 daily GSK1278863 dose during the study.

10.13.4. Pharmacokinetic / Pharmacodynamic Analyses

- The primary goal of this analysis is to characterize the pharmacokinetic/pharmacodynamic relationship of parent GSK1278863 and efficacy and safety endpoints in the "Pharmacokinetic" population from this study.
  - The influence of subject demographics and baseline characteristics, including disease activity in this population may be investigated.
- A summary of the planned population pharmacokinetic/pharmacodynamic analyses are outlined below:
  - Relationships between drug exposure and selected efficacy, MACE and MACE ++ events will be explored and characterized as data permit. The exposure will be estimated on the sparse PK collected in a sub-set of the study population. The data may be dose- extrapolated to the dose administered during the PK collection period. Any changes to the proposed analyses would be described in the CSR.

Table 18 Overview of Planned Pharmacokinetic / Pharmacodynamic Analyses for GSK1278863

Parameter	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
GSK1278863														
Scatter plot of % Time Evaluable Hgb in Range during EP vs. Avg Dose EP TIR						Y								
Scatter plot of Evaluable Hgb Change from Baseline during EP vs. Avg Dose EP						Y								
Scatter plot of % Time Evaluable Hgb in Range during EP vs. Ctau/Avg Dose EP TIR						Y								
Scatter plot of Evaluable Hgb Change from Baseline during EP vs. Ctau/Avg Dose EP						Y								
Boxplot of Ctau/Dose at on-treatment MACE or MACE++ by subjects with or without on-treatment MACE or MACE++						Y								
Scatter plot of % Time Evaluable Hgb in Range during EP vs. Cmax/Avg						Y								

Parameter	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Dose EP TIR														
Scatter plot of Evaluable Hgb Change from Baseline during EP vs. Cmax/Avg Dose EP						Y								
Boxplot of Cmax/Dose at on-treatment MACE or MACE++ by subjects with or without on-treatment MACE or MACE++						Y								

NOTES :

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

10.14. Appendix 14: ABPM Sub-study Analysis Plan

Hypertension is one of the major risk factors associated with cardiovascular morbidity and mortality and is common in patients with advanced CKD Stages 3b through 5.

Treatment of anemia associated with CKD using ESAs has the associated risk of increased blood pressure. ESA-induced elevation of BP often necessitates initiation of, or increases in, anti-hypertensive medications in patients with CKD. While both SBP and DBP are of prognostic importance, SBP is the overall best predictor of future cardiovascular risk in a hypertensive population [Peters, 2013]. Therefore, SBP was chosen as the primary endpoint in this ambulatory blood pressure monitoring (ABPM) sub-study. In addition, ABPM is being used to measure BP in this sub-study because previous studies have used this BP measurement modality in dialysis subjects to establish an association with mortality [Agarwal, 2010].

This sub-study is intended to compare daprodustat to rhEPO on BP as assessed by ABPM in dialysis-dependent subjects with anemia associated with CKD who switch from ESAs.

10.14.1. Summary of Key Protocol Information

10.14.1.1. Changes to the Protocol Defined Statistical Analysis Plan

No statistical analysis will be conducted for this sub-study due to the small number of subjects recruited. Instead all data will either be summarized or listed.

10.14.1.2. ABPM Sub-Study Objectives and Endpoints

Objectives	Endpoints	Summary plans
Primary Objective	**Primary Endpoint**	
• To compare daprodustat to rhEPO for effect on SBP (superiority) by ABPM in subjects receiving maintenance hemodialysis in the ABPM ITT population	• Change in 24-hour average SBP from baseline to end of sub-study [1] between treatment groups	• Summary only

Objectives	Endpoints	Summary plans
Secondary Objectives	**Secondary Endpoints**	
• To assess the effect of daprodustat and rhEPO independently within treatment groups on SBP, DBP and mean arterial blood pressure (MAP) by ABPM in the ABPM ITT population	• Change in 24-hour average SBP from baseline to end of sub-study [1] within each treatment group • Change in 24-hour average DBP from baseline to end of sub-study [1] within each treatment group • Change in 24-hour average MAP from baseline to end of sub-study [1] within each treatment group	• Summary only
• To compare the effect of daprodustat to rhEPO on DBP and MAP by ABPM in the ABPM ITT population	• Change in 24-hour average DBP from baseline to end of sub-study [1] between treatment groups • Change in 24-hour average MAP from baseline to end of sub-study [1] between treatment groups	• Summary only
• To compare the effect of daprodustat to rhEPO on BP parameters in the ABPM Per-Protocol population	• Change in o 24-hour average SBP o 24-hour average DBP o 24-hour average mean arterial pressure from baseline to end of sub-study [1] between treatment groups	• Not done (i.e., no ABPM PP summaries)
• To assess the effect of daprodustat and rhEPO on BP parameters in the ABPM Per-Protocol population	• Change in: o 24-hour average SBP o 24-hour average DBP o 24-hour average mean arterial pressure from Baseline to end of sub-study [1] within each treatment group	• Not done (i.e., no ABPM PP summaries)
• To compare the percentage of subjects in each treatment group requiring a change in anti-hypertensive in the ABPM ITT population	• Difference between treatment groups in percentage of subjects requiring no change in number or dosage of anti-hypertensive medications • Difference between treatment groups in percentage of subjects requiring an increase in number or dosage of anti-hypertensive medications • Difference between treatment groups in percentage of subjects requiring a decrease in number or dosage of anti-hypertensive medications	• Not done

Objectives	Endpoints	Summary plans

• To characterize the dipping pattern of sleeping blood pressure in each treatment group in the ABPM ITT and ABPM Per-Protocol populations	• 24-hour blood pressure profile as measured by ABPM, with subjects categorized according to their sleeping BP behaviors as:
	  • dippers (normal) when the reduction in the average SBP during the sleeping period is >10% to 20% of mean SBP during waking hours the day,
	  • extreme dippers when this reduction is >20%,
	  • non-dippers when the reduction is 0% to 10%, and reverse dippers when the mean sleep SBP is higher than the awake SBP [Bakris, 2014]
		• Not done

• To compare the percentage of subjects that convert from non-dipper status to dipper status between treatment groups in the ABPM ITT and ABPM Per-Protocol populations	• Difference between treatment groups in percentage of subjects that convert from non-dipper status at baseline to dipper status at end of sub-study [1]	• Not done
• To compare the percentage of subjects that convert from dipper status to non-dipper status between treatment groups in the ABPM ITT and ABPM Per-Protocol populations	• Difference between treatment groups in percentage of subjects that convert from dipper status at baseline to non-dipper status at end of sub-study [1]	• Not done
• To compare daprodustat to rhEPO on heart rate by ABPM in the ABPM ITT population	• Change in 24-hour average heart rate from baseline to end of sub-study [1] as measured by ABPM relative to time since administration of medication	• Summary only
[1] The end of sub-study is defined as the date recorded in the ABPM sub-study conclusion form. It is expected that the majority of the participants will complete this form after the completion of week 16 ABPM assessment, however, a small number of the participants will complete this form after the completion of their week 28 ABPM assessment, since before this protocol amendment, the scheduled second ABPM assessment was at week 28 instead of week 16.		

10.14.1.3. Study Design

Overview of Study Design and Key Features	
Design Features	• This is a multi-center sub-study of the main protocol focusing on subjects that meet the additional inclusion and exclusion criteria outlined in the sub-study protocol. The main study is stratified by participation in this sub-study.
Dosing and Treatment Assignment	• A central randomization approach will be used in the main study to protect against potential selection bias due to the open-label design. The randomization schedule will be generated by PPD and PPD's Interactive Response Technology (IRT) will be used for treatment allocation. • Subjects will be stratified by dialysis type [hemodialysis (HD*) or peritoneal dialysis (PD)], by region (see Section 10.9.1) and by participation in this ABPM sub-study. Following stratification, subjects will be randomized 1:1 to receive open-label oral daprodustat or rhEPO (IV epoetin alfa for HD subjects and SC darbepoetin alfa for PD subjects). ** In addition to HD this group also includes combination methods such as hemodiafiltration (HDF) or hemofiltration (HF).* • This sub-study includes a subset of subjects that are in the HD and ABPM participant strata from the main study. • Please refer to the protocol for starting doses, dose steps and elements of the dose adjustment scheme.
Interim Analysis	• An IDMC will review safety data periodically from all ongoing clinical trials in the daprodustat clinical development program for the treatment of subjects with anemia of chronic kidney disease. • In addition, a formal interim analysis is planned for the main study. See Section 3.1 for further details. Information from this sub-study will be included in the IDMC evaluation at the interim.

10.14.1.4. Statistical Hypothesis

The primary sub-study estimand is to compare the treatment effect on change from baseline in 24-hour average SBP at end of sub-study, in all randomized sub-study subjects with evaluable ABPM assessments at both baseline and end of sub-study (effectiveness estimand). The statistical model for analysis will be an ANCOVA with terms for treatment and baseline 24-hour average SBP. This model will provide a point estimate and two-sided 95% CI for the treatment effect and a one-sided p-value for the superiority assessment. The primary analysis population will be the ABPM ITT population defined in Section 10.14.3, and subjects' randomized medication will be used for this analysis.

The statistical hypotheses are as follows:

Null: The difference between treatment groups (Dapro – rhEPO) in change from baseline in 24-hour average SBP at end of sub-study is ≥ 0.

Alternative: The difference between treatment groups (Dapro - rhEPO) in change from baseline in 24-hour average SBP at end of sub-study is less than 0.

ABPM measurements are only collected once post randomization, and it is expected that approximately 20% of subjects will have missing end of sub-study ABPM data. To assess the impact of missing data on the interpretation of the primary analysis, the reason for missing data will be assessed. If the majority (> 70%) of missing data is due to either patient unwillingness to repeat the ABPM procedure or due to an un-evaluable reading, then the data will be considered to be missing at random and no adjustment will be made to the primary analysis.

If more than 30% of the data is missing for other reasons, then multiple imputation will be used for subjects with data missing due to these reasons. Regardless of randomized treatment group, this data will be imputed using the distribution of non-missing rhEPO subject data. There will be no imputation for subjects with data missing due to either patient unwillingness to repeat the ABPM procedure or due to an un-evaluable reading. This is in keeping with the primary interest in the effectiveness estimand.

The efficacy estimand is also of interest, so the primary analysis will be repeated with the ABPM Per-Protocol population using actual treatment received. Missing data will not be imputed for this analysis.

The originally-planned statistical hypotheses described above will no longer be tested.

10.14.2. Planned Analyses

10.14.2.1. Interim Analysis

ABPM sub-study information will be used by the IDMC in the overall assessment of risk throughout the trial. In particular, there is a planned interim analysis for futility for which this data will be included. As these interim looks will not be used to stop the trial for benefit, there will be no adjustment to the significance level, alpha.

10.14.2.2. Final Analysis

The final analysis will be performed after the completion of the trial as outlined in the main study RAP.

10.14.3. Analysis Populations

10.14.3.1. Populations

Population	Definition / Criteria	Analyses Evaluated
ABPM Screened	• All screened subjects for ABPM sub-study	• ABPM sub-study • Study Pop
ABPM ITT	• Subjects in the 'ITT' population who signed the informed consent for the sub-study and were also entered into the ABPM sub-study. • Subjects will be analyzed according to the treatment to which they were randomized.	• ABPM sub-study • Study Pop • Efficacy

Population	Definition / Criteria	Analyses Evaluated
ABPM Safety	• ABPM ITT subjects who receive at least one dose of randomized treatment. • Subjects will be analyzed according to the treatment received.[1]	• ABPM sub-study • Safety
[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.		

10.14.4. Considerations for Data Analyses and Data Handling Conventions

The definition of assessment windows, treatment states and phases, data display standards and handling conventions, reporting processes and standards, data derivations, and handling of partial dates will be the same as the main study RAP except where specifically highlighted in this sub-study RAP.

10.14.4.1. ABPM Evaluation Criteria

In order to be considered an evaluable assessment, the following criteria need to be met for the 24-hour ABPM assessment:

1) There must be at least 20 awake ABPM readings and 10 sleep ABPM readings captured during the 24 hours that the subject wears the ABPM device.

2) Any ABPM readings collected after the 24 hour period will not be analyzed.

The subject's reported times of waking up and going to sleep during this 24-hour period will be recorded in the eCRF.

10.14.4.2. Dipping Status

For each ABPM measurement, dipping status will be defined based on asleep and awake SBP measurements as follows:

- dippers (normal): the reduction in the average SBP during the sleeping period is >10% to 20% of mean SBP during awake hours
- extreme dippers: the reduction in the average SBP during sleeping is >20% of the mean SBP during awake hours
- non-dippers: the reduction in the average SBP during sleeping is 0% to 10% of the mean SBP during awake hours
- reverse dippers: when the average SBP during sleeping is greater than the mean SBP during awake hours [Bakris, 2014]

10.14.4.3. End of Sub-study Values

- The majority of the participants reach the end of sub-study after the completion of Week 16 ABPM assessment. If the ABPM fails the QC criteria at week 16, up to two additional attempts may be made and can be considered as week 16 ABPM.

- It is also expected that a small percentage of the participants would have Week 28 ABPM assessment instead of Week 16 ABPM assessment due to enrollment before the third study protocol amendment (dated 05OCT2017). Their Week 28 ABPM and other parameters of interests will be used as the end of sub-study value in the analyses unless specified otherwise. If the ABPM fails the QC criteria at week 28, up to two additional attempts may be made and can be considered as week 28 ABPM.

10.14.4.4. Data Handling Conversions

- Timepoint averages: The 24-hour ABPM readings will be sorted by the time of the day (not the order in which the ABPM readings were measured). The timepoint 0h is associated with data collected in 00:00-00:29, timepoint 0.5h is associated with date collected in 00:30-00:59, timepoint 1h is associated with data collected in 01:00-01:29, etc. For a specific timepoint, the average of all measurements that associate with the specified timepoint will be calculated, per subject per visit.

- 24-hour average: Average of all measurements collected on a subject at a visit using all 24-hour ABPM data.

10.14.5. Study Population Analyses

Study population displays described in this section will be created for the ABPM ITT or Safety population where applicable.

10.14.5.1. Overview of Planned Analyses

Parameter	Data Displays Generated		
	Table	Figure	Listing
Disposition			
Reasons for Screen Failure for the Sub-study	Y		
Summary of Subject Disposition for the Sub-study	Y		
Demographic & Baseline Characteristics			
Demographic and Baseline Characteristics	Y		
Treatment Compliance			
Extent of Exposure to Randomized Treatment During the Sub-study	Y		

NOTES : Y = Yes display generated.

10.14.5.2. Display Details

Disposition

The number and percentage of subjects completing the sub-study, withdrawing early from the sub-study, or discontinuing study treatment during the sub-study, overall and by reason, will be summarized by treatment group.

The number and percentage of subjects who failed screening for the sub-study (e.g. lack of eligibility, withdrawal of consent or other reasons such as needing to wear a device) and were therefore not entered into the sub-study, overall and by reason, will be summarized by treatment group.

Demographic & Baseline Characteristics

The number and percentage of subjects or summary statistics will be provided by treatment group for the demographic and baseline characteristics described in the main RAP.

Treatment Compliance

Months on randomized medication during the sub-study will be summarized using mean, P25, median, P75, standard deviation, minimum and maximum by treatment group.

10.14.6. Efficacy Analyses

ABPM summaries will be performed using the ABPM ITT population. All analyses performed on ABPM ITT population will use on and off treatment values.

10.14.6.1. Overview of Efficacy Analyses

Parameter	Absolute					Change from BL					
	Analysis		Summary		Individual	Analysis		Summary		Individual	
	T	F	T	F	L	T	F	F	T	F	L
ABPM											
SBP, DBP, MAP, Heart Rate ABPM Values – ABPM ITT			Y	Y							
24-hour average SBP, DBP, MAP, Heart Rate - ABPM ITT			Y						Y		
In-Clinic Visit											
SBP, DBP, Heart Rate, Weight and Dry Weight from in-			Y								

Parameter	Absolute					Change from BL					
	Analysis		Summary		Individual	Analysis		Summary		Individual	
	T	F	T	F	L	T	F	F	T	F	L
clinic visits											
Anti-hypertensive Medications											
Listing of anti-hypertensive medication use					Y						

Efficacy Summary Details

ABPM

ABPM parameter values (SBP, DBP, MAP, and Heart Rate) will be summarized at each collected time point using mean, median, standard deviation, minimum, P25, P75, and maximum at baseline and end of sub-study by treatment group. These parameters will also be displayed graphically via a line plot of the means and 95% confidence intervals.

24-hour average ABPM parameter values (SBP, DBP, MAP, and Heart Rate) will be summarized using mean, median, standard deviation, minimum, P25, P75, and maximum at baseline and end of sub-study by treatment group.

ABPM parameter change from baseline values (SBP, DBP, MAP, and Heart Rate) will be summarized using mean, median, standard deviation, minimum, P25, P75, and maximum at end of sub-study by treatment group.

A data listing of ABPM data will be produced.

In Clinic Visit

The BP measurements (SBP, DBP, Heart Rate) and weight before and after dialysis, and estimated dry weight before dialysis from in-clinic visits will be summarized using mean, median, standard deviation, minimum, P25, P75, and maximum at each visit by treatment group.

Anti-hypertensive Medications

The types of anti-hypertensive medications are:

1) Angiotensin-II Receptor Blockers/ Angiotensin Converting Enzyme Inhibitors (ARB/ACE-I)

2) Calcium Channel Blockers (CCB)

3) Beta-Adrenergic Receptor Blockers

4) Alpha-Adrenergic Receptor Blockers

5) Centrally Acting Agents (e.g. clonidine, methyldopa)

6) Direct Vasodilators (e.g. hydralazine)

A data listing of anti-hypertensive medication use during the ABPM sub-study will be produced.

10.14.7. Safety Analyses

Safety displays described in this section will be created for the ABPM Safety population.

10.14.7.1. Overview of Planned Adverse Event Analyses

Parameter	Data Display To Be Generated		
	Summary		Individual
	T	F	L
Adverse Events (AEs) and Blood Pressure related Events			
All on-treatment Blood Pressure Related Events During the ABPM Sub-study [1]	Y		Y
Subject Numbers for Individual Blood Pressure Related AEs During the Sub-study [2]			Y
Serious and Other Significant Adverse Events and other safety related events			
Treatment Emergent Blood Pressure Related SAEs During the Sub-study [2] by Primary System Organ Class and Preferred Term	Y		
Treatment Emergent AEs Leading to Permanent Discontinuation of Study Treatment During the Sub-study [2] by Primary System Organ Class and Preferred Term	Y		Y

[1] As identified by the CRF described in Section 10.14.7.

[2] Include AEs that have a start or worsening date up to and including the earliest of the last non-zero dose date +1 day or the final ABPM Visit date + 1 day

10.14.7.2. AE Summary Details

Blood Pressure Related AEs/ Events Identification

Blood pressure AEs will be identified during the study via periodic programmatic sweeps of preferred terms entered into the eCRF. AEs identified this way will require an additional eCRF page to be filled out that characterizes the event as clinically significant

and/or symptomatic. In addition, subjects that experience BP (in clinic) that meet the following criteria at any visit will be required to fill out this eCRF:

- SBP: an increase from baseline of ≥ 25 mmHg or SBP ≥ 180 mmHg
- DBP: an increase from baseline of ≥ 15 mmHg or DBP ≥ 110 mmHg

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

The number and percentage of subjects reporting at least one treatment emergent blood pressure related SAE during the sub-study will be provided for each treatment group by primary system organ class and preferred term. Treatment emergent blood pressure related SAEs are those that have been identified via the eCRF page described above.

The number and percentage of subjects reporting each treatment emergent AE leading to permanent discontinuation of study treatment during the sub-study will be summarized by treatment group using primary system organ class and preferred term.

Data listings of on-treatment blood pressure related events during the ABPM sub-study, subject numbers for individual blood pressure related AEs during the ABPM sub-study, and treatment emergent AEs leading to permanent discontinuation of randomized treatment during the ABPM sub-study will be produced.

10.15. Appendix 15 – Abbreviations & Trade Marks

10.15.1. Abbreviations

Abbreviation	Description
ABPM	Ambulatory Blood Pressure Monitoring
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
CDISC	Clinical Data Interchange Standards Consortium
CEC	Clinical Endpoint Committee
CFB	Change from Baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DGF	Delayed Graft Function
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EOS	End of Study
EP	Evaluation Period
ERI	Erythropoietin Resistance Index
ESA	Erythropoiesis Stimulating Agent
FDA	Food and Drug Administration
FDR	False Discovery Rate
FSH	Follicle-stimulating Hormone
GSK	GlaxoSmithKline
HbA1c	Hemoglobin A1c
HBPM	Home Blood Pressure Monitoring
HD	Hemodialysis
HDF	Hemodiafiltration
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure
HF	Hemofiltration
Hgb	Hemoglobin
HR	Heart Rate

Abbreviation	Description
HRQoL	Health Related Quality of Life
hsCRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IG	Implementation Guide
IMMS	International Modules Management System
iPTH	Intact Parathyroid Hormone
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IV	Intravenous
KM	Kaplan-Meier
LDL-C	Low Density Lipoprotein Cholesterol
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
MCS	Mental Component Score
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed Model Repeated Measures
MP	Maintenance Period
NI	Non-inferiority
PCI	Potential Clinical Importance
PCS	Physical Component Score
PD	Pharmacodynamic
PGx	Pharmacogenetics
PhRMA	Pharmaceutical Research and Manufacturers of America
PK	Pharmacokinetic
PP	Per-Protocol
PPD	Pharmaceutical Product Development
PRO	Patient Reported Outcome
PT	Preferred Term
QC	Quality Control
RAP	Reporting & Analysis Plan
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
RTF	Rich Text Format
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Subcutaneous
SDTM	Study Data Tabulation Model

Abbreviation	Description
SE	Standard Error
SI	System Independent
SMQ	Standard MedDRA Query
SOC	System Organ Class
SPERT	Safety Planning Evaluation Reporting Team
TC	Total Cholesterol
TFL	Tables, Figures & Listings
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
UK	United Kingdom
US	United States
VAS	Visual Assessment Scale
WBC	White Blood Cell

10.15.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS