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The GlaxoSmithKline group of companies 201410

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

Title	:	Reporting and Analysis Plan for A 52-week open-label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with anemia associated with chronic kidney disease who are initiating dialysis.
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 Protocol GSK Document Number 2015N234534_01.

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TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS 7

2. SUMMARY OF KEY PROTOCOL INFORMATION 9
2.1. Changes to the Protocol Defined Statistical Analysis Plan 9
2.2. Study Objective(s) and Endpoint(s) 10
2.3. Study Design 14
2.4. Statistical Hypotheses 14
2.4.1. Hgb Efficacy Primary Hypothesis 14

3. PLANNED ANALYSES 15
3.1. Interim Analyses 15
3.2. Final Analyses 15

4. ANALYSIS POPULATIONS 16
4.1. Protocol Deviations and Study Population Exclusions 17

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS 17

6. STUDY POPULATION ANALYSES 18
6.1. Overview of Planned Analyses 18
6.2. Display Details 19
6.2.1. Populations Analyzed 19
6.2.2. Subject Disposition 19
6.2.3. Protocol Deviations 21
6.2.4. Demographic & Baseline Characteristics 21
6.2.5. Prior and Concomitant Medications 22
6.2.6. Exposure and Randomized Treatment Compliance 22
6.2.7. COVID-19 Impacted Visits 23

7. PRIMARY STATISTICAL ANALYSES 24
7.1. Primary Hgb Efficacy Analysis 24
7.1.1. Overview of Planned Primary Hgb Efficacy and Supportive Analyses 24
7.1.2. Planned Primary Hgb Efficacy Statistical Analyses 24
7.1.2.1. Endpoint / Variables 25
7.1.2.2. Summary Measure 25
7.1.2.3. Population of Interest 25
7.1.2.4. Strategy for Intercurrent (Post-Randomization) Events 25
7.1.2.5. Statistical Analyses/Methods 26

8. OTHER STATISTICAL ANALYSES 30
8.1. Efficacy Analyses 30
8.1.1. Principal Secondary Efficacy Analyses 30
8.1.1.1. Overview of Planned Principal Secondary Efficacy Analyses 30
8.1.1.2. Planned Principal Secondary Efficacy Statistical Analyses 31

8.1.2. Additional Secondary Efficacy Analyses 32
8.1.2.1. Overview of Planned Additional Secondary Efficacy Analyses 32
8.1.2.2. Planned Additional Secondary Efficacy Statistical Analyses 34
8.1.3. Exploratory Efficacy Analyses 36
8.1.3.1. Overview of Planned Exploratory Efficacy Analyses 36
8.1.3.2. Planned Exploratory Efficacy Display Details 38
8.2. Safety Analyses 42
8.2.1. Secondary Safety Analyses 42
8.2.1.1. Overview of Planned Secondary Safety Analyses 42
8.2.1.2. Planned Secondary Safety Statistical Analyses 42
8.2.2. Exploratory Safety Analyses 44
8.2.2.1. Overview of Planned Exploratory Safety Analyses 44
8.2.2.2. Planned Exploratory Safety Display Details 46
8.2.2.3. Overview of Exploratory Cardiovascular Safety Analysis 47
8.2.2.4. Planned Exploratory Cardiovascular Safety Analysis Details 48
8.2.3. Adverse Event Safety Analyses 50
8.2.3.1. Overview of Planned Adverse Event Analyses 50
8.2.3.2. Planned Adverse Event Safety Statistical Analyses 51
8.2.4. Clinical Laboratory Safety Analyses 55
8.2.4.1. Overview of Planned Clinical Laboratory Safety Analyses 56
8.2.4.2. Planned Clinical Laboratory Safety Display Details 57
8.2.5. Vital Signs Analyses 58
8.2.5.1. Overview of Planned Vital Signs Analyses 59
8.2.5.2. Planned Vital Signs Display Details 59
8.2.6. Electrocardiograms 60
8.2.7. Pregnancies 60
8.2.8. Other Safety Analyses 60
8.3. Pharmacokinetic Analyses 60
8.3.1. Overview of Planned Pharmacokinetic Analyses 60
8.3.2. Drug Concentration Measures 61
8.3.3. Pharmacokinetic Parameters 61
8.3.3.1. Deriving Pharmacokinetic Parameters 61
8.4. Pharmacokinetic / Pharmacodynamic Analyses 63
8.5. Patient Reported Outcomes Analyses 65
8.5.1. Overview of Planned Patient Reported Outcomes Analyses 66
8.5.2. Planned Patient Reported Outcomes Statistical Analyses 67
8.5.2.1. HRQoL and Utility Score 67
8.5.2.2. Symptom Severity & Change 68
8.6. Biomarker Analyses 69
8.7. Pharmacogenetics Analyses 69

9. REFERENCES 70

10. APPENDICES 71
10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population 72
10.1.1. Exclusions from Per Protocol Population 72
10.2. Appendix 2: Time & Events 73
10.2.1. Protocol Defined Time & Events 73
10.2.1.1. Time and Events Table for Subjects on Randomized Treatment 73
10.2.1.2. Time and Events Table for Subjects that Permanently Discontinue Randomized Treatment 76
10.3. Appendix 3: Assessment Windows 77
10.3.1. Assessment Windows 77
10.4. Appendix 4: Treatment States and Phases 78
10.4.1. Treatment Phases 78
10.4.1.1. Treatment States for Hgb, Iron Parameters, IV Iron Dose Endpoints, Iron Use Summaries, Transfusion and PRO Data 78
10.4.1.2. Treatment States for CV Endpoint Data 78
10.4.1.3. Treatment States for BP, Lipid Parameters, Clinical Chemistry, Hematology, Other Laboratory Tests, Hepatobiliary (Liver) and Vital Signs Data 78
10.4.1.4. Treatment States for AE Data 78
10.4.1.5. Treatment States for Concomitant Medications (Other Than IV Iron Dose Endpoints and Iron Use Summaries) 80
10.5. Appendix 5: Data Display Standards & Handling Conventions 82
10.5.1. Study Treatment & Sub-group Display Descriptors 82
10.5.2. Baseline Definition & Derivations 82
10.5.2.1. Baseline Definitions 82
10.5.2.2. Derivations and Handling of Missing Baseline Data 83
10.5.3. Reporting Process & Standards 85
10.6. Appendix 6: Derived and Transformed Data 88
10.6.1. General 88
10.6.2. Study Population 91
10.6.2.1. Subject Disposition 91
10.6.2.2. Demographic & Baseline Characteristics 91
10.6.2.3. Randomized Treatment Discontinuation and Study Withdrawal 96
10.6.2.4. Prior and Concomitant Medications 96
10.6.2.4 Exposure and Compliance 97
10.6.3. Efficacy 99
10.6.3.1. Hemoglobin Endpoints 99
10.6.3.2. Iron Endpoints 101
10.6.3.3. Time to Rescue 108
10.6.3.4. RBC and Whole Blood Transfusion Endpoints 109
10.6.3.5. Dose Adjustment Scheme Endpoints 113
10.6.4. Safety 115
10.6.4.1. CV Safety Endpoints 115
10.6.4.2. Blood Pressure Endpoints 120
10.6.4.3. Adverse Events 122

10.6.4.4. Laboratory Parameters 127
10.6.4.5. Vital Signs 129
10.6.4.6. COVID-19 129
10.6.5. Patient Reported Outcomes 130
10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data 133
10.7.1. Premature Withdrawals 133
10.7.2. Handling of Missing Data 133
10.7.2.1. Handling of Missing and Partial Dates 133
10.8. Appendix 8: Values of Potential Clinical Importance 136
10.8.1. Laboratory Values 136
10.8.2. Vital Signs 137
10.9. Appendix 9: Multicenter Studies 138
10.9.1. Methods for Handling Centres 138
10.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata 139
10.10.1. Handling of Covariates, Subgroups & Other Strata 139
10.10.2. Randomization Stratification 146
10.11. Appendix 11: Multiple Comparisons & Multiplicity 147
10.11.1. Handling of Multiple of Comparisons & Multiplicity 147
10.11.1.1. Interim Analyses 147
10.11.1.2. Final Analyses 147
10.11.1.3. Subgroup Analyses 147
10.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses 148
10.12.1. Statistical Analysis Assumptions 148
10.13. Appendix 13: Abbreviations & Trade Marks 149
10.13.1. Abbreviations 149
10.13.2. Trademarks 151

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 201410
Protocol	• This RAP is based on the first protocol amendment [(Dated: 06OCT2017) of study 201410 (GSK Document Number. 2015N234534_01)].
Primary Objective	• To compare daprodustat to darbepoetin alfa for hemoglobin (Hgb) efficacy (non-inferiority)
Primary Endpoint	• The mean change in Hgb between baseline and the evaluation period (EP, mean over Weeks 28-52)
Study Design	• This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center study in subjects with anemia associated with CKD who are not regularly using erythropoiesis-stimulating agents (ESAs) and who are initiating dialysis. • This study will comprise three study periods: a screening period (2 weeks), a 52-week active treatment period, and a follow-up period (4-6 weeks). Weeks 28-52 are defined as the efficacy evaluation period (EP) for the primary efficacy comparison. Screening period can be extended by an additional 4 weeks for ultrasound examination, IV iron supplementation and/or vitamin B12 treatment as needed. • The treatment period consists of (1) the stabilization period, defined as the period from Day 1 to Week 28 during which randomized treatment will be dose titrated to achieve the appropriate Hgb target and (2) the evaluation period (EP), defined as the period from the end of the stabilization period (Week 28) to Week 52 (titrations may also occur during this treatment period), to assess safety and efficacy. • A central randomization approach will be used to protect the trial from potential for selection bias due to the open-label design. All subjects will be treated to achieve and maintain an Hgb within a range of 10-11 g/dL. • Subjects will be stratified by dialysis type (hemodialysis [HD], or peritoneal dialysis [PD]) and by whether their dialysis start is planned or unplanned (urgent). • Following stratification, subjects will be randomized 1:1 to receive daprodustat or darbepoetin alfa (darbepoetin alfa); all randomized treatments will be supplied by GSK. • Although prior regular ESA use is prohibited, limited ESA use is allowed around the time of dialysis initiation only. • To ensure consistency of treatment across the study there are protocol-mandated algorithms for dose adjustments of daprodustat and darbepoetin alfa, iron management, and anemia rescue therapy.

Overview	Key Elements of the RAP
Planned Analyses	• All planned analyses will be performed after study unblinding. • No formal interim analyses are planned in this study. • The IDMC will periodically receive unblinded safety reports containing clinical endpoints (whether adjudicated or pending adjudication) and SAEs, from an independent Statistical Data Analysis Center (SDAC) while Phase 3 studies with daprodustat are ongoing. The IDMC may recommend stopping this study for safety at any time.
Key Analysis Populations	• The primary population for Hgb efficacy analyses will be the All Randomized Intent-To-Treat (ITT) Population. Subjects will be analysed according to the treatment to which they were randomized.

Hypothesis	• The primary Hgb efficacy objective will assess the estimand defined as the effect of daprodustat treatment relative to darbepoetin alfa 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 with anemia secondary to CKD who are initiating dialysis and assuming subjects do not die before the end of the EP. The analysis will test whether daprodustat is non-inferior to darbepetin alfa according to the following statistical hypotheses:
	  • Null: The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-darbepoetin alfa), is less than or equal to -0.75 g/dL.
	  • Alternative: The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-darbepoetin alfa), is greater than -0.75 g/dL.

Primary Analyses	• For the Hgb efficacy analyses, an analysis of covariance (ANCOVA) model including prognostic randomization stratification factors (dialysis type and dialysis start), baseline Hgb, and treatment will be performed to obtain a point estimate and the two-sided 95% confidence interval (CI) for the treatment difference (daprodustat-darbepoetin alfa) 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.
Key Secondary Analyses	Principal Secondary Endpoint (adjusted for multiplicity, tested for superiority) • Average monthly IV iron dose (mg)/subject from baseline to Week 52
Safety Endpoints	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including those 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

In the original RAP, an additional time period of 'Day 1 -<End of Treatment' was added to the exploratory endpoint of evaluating the dose adjustment schemes, which was not part of the first protocol amendment (dated:06OCT2017). Since Week 52 is the end of treatment period, 'Day 1 -<End of Treatment' has been replaced by 'Day 1 -<Week 52.' See details in Section 2.2.

Further changes from the originally planned statistical analysis are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• None	• New displays related to COVID-19 pandemic have been added	• Assessing the impact of the COVID-19 pandemic
• Only include randomized subjects who have both baseline and at least one Hgb assessment during the EP in the primary Hgb analysis	• All randomized subjects will be included in the primary Hgb analysis by imputing missing post-baseline Hgb data using pre-specified multiple imputation approach	• Addressing the feedback from FDA
• None	• Worsening of Hypertension has been added to the list of AESI is included in the summary and analysis of AESI	• Worsening of Hypertension has been added to the list of AESI based on Safety Review Team update on AESI
• 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
• PK exploratory endpoints described as dose normalized	• PK exploratory endpoints described as dose extrapolated	• Terminology clarification following discussion with regulatory agencies.
PK exploratory endpoints include: • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs.	PK exploratory endpoints modified as follows: • *Endpoints removed:* Scatter plots of daprodustat PK	• Removed as these endpoints do not provide additional information for efficacy explorations than

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
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. • 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	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. • 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	what will be available from remaining endpoints.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare daprodustat to rhEPO for Hgb efficacy (non-inferiority)	• Mean change in Hgb between baseline and evaluation period (EP, mean over Weeks 28-52)
Principal Secondary Objectives	**Principal Secondary Endpoints (tested for superiority, adjusted for multiplicity)**
• To compare daprodustat to rhEPO on the use of intravenous (IV) iron	• Average monthly IV iron dose (mg)/subject from baseline to Week 52
Secondary Objectives	**Secondary Endpoints (tested for superiority[1], no multiplicity adjustment)**
• To compare daprodustat to rhEPO on BP	• Change from baseline in SBP, DBP, and MAP at Week 52 and at end of treatment

Objectives	Endpoints
	• 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 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 the EP (Weeks 28 to 52) • % time Hgb in analysis range 10-11.5 g/d during the EP (non-inferiority analysis that will use a margin of 15% less time in range)[1]
• 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 (PCS, 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 Weeks 28 and 52 • Change from baseline in Health Utility (EQ-5D-5L) score at Week 52 • Change from baseline in EQVAS at Week 52
• To compare daprodustat to rhEPO on the symptom severity and change	• Change from Baseline at Wk 52 by domain and overall symptom score on the CKD-AQ • Change from Baseline at Wk 8,12, 28, 52 in PGI-S
• To summarize the PK parameters of daprodustat and three major metabolites in dialysis subjects	• Plasma daprodustat, M2, M3, and M13 PK parameters pre-dose trough (Ctau) and Cmax
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 analysis range (10-11.5 g/dL) during EP • 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 • Number of times Hgb <7.5 g/dL during the EP • Number (%) 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 • Number (%) 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 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 • Number of times Hgb ≥ 12 g/dL during the EP • % of time Hgb ≥12 g/dL during the EP

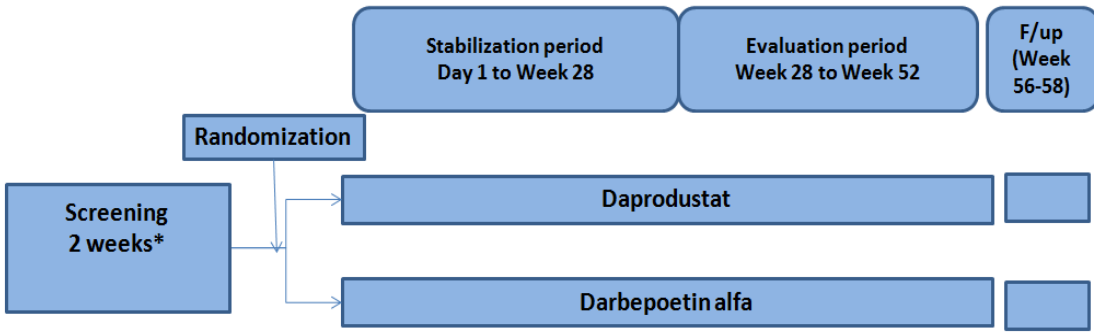
Objectives	Endpoints
• To compare daprodustat to rhEPO on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, transferrin saturation, total iron, total iron binding capacity (TIBC) across all visits to end of treatment • Average quarterly TSAT • Average quarterly ferritin • Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria
• 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 transfusion by Week 52 • Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years •
• To evaluate the dose adjustment schemes	• Assigned dose by visit and at Day 1, Week 28, Week 52 • Most recent dose prior to Week 28, Week 52 • Number (%) of subjects 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 - < Week 52 • Number of dose adjustments during the following periods: o Day 1 - < Week 28 o Week 28 - < Week 52 o Day 1 - < Week 52 • Time dose held for Hgb ≥12 g/dL
• 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 lipid parameters	• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)]
• To further compare daprodustat to rhEPO on the symptom severity and change	• Change from Baseline at Wk 8,12, 28, & 52, by item on the CKD-AQ • Shift tables (Baseline to Wk 8, 12, 28, & 52) in PGI-S • N (%) of subjects within each PGI-C symptom change level at Wk 8, 12, 28, 52.
• To further compare daprodustat to darbepoetin alfa on HRQoL and Utility score	• Change from baseline in Health Utility (EQ-5D-5L) score at Weeks 8,12, & 28 • Change from baseline in EQ VAS at Weeks 8, 12, & 28
• To evaluate graphical relationships between exposure parameters and selected efficacy endpoints	• Scatter plots of daprodustat PK parameters (Ctau and Cmax) dose normalized to 1 mg vs. percent time in range during EP.

Objectives	Endpoints
	• Scatter plots of average daprodustat dose during EP vs. percent time in range during EP. • Scatter plots of daprodustat PK parameters (Ctau and Cmax) dose normalized to average dose during EP vs. percent time in range during EP. • Scatter plots of daprodustat PK parameters (Ctau and Cmax) dose normalized to 1 mg vs. change from baseline of Hgb during EP. • Scatter plots of average daprodustat dose during EP vs. change from baseline of Hgb during EP. • Scatter plots of daprodustat PK parameters (Ctau and Cmax) dose normalized to average dose during EP vs. change from baseline of Hgb during EP.
• To evaluate graphical relationships between daprodustat exposure and MACE and the composite endpoint of MACE + thromboembolic event + hospitalization for heart failure	• Boxplots of daprodustat PK parameters (Ctau and Cmax) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint. • Boxplots of daprodustat PK parameters (Ctau and Cmax) dose normalized to dose at time of MACE or combined safety endpoint (or end of treatment if no endpoint) by subjects with or without MACE or combined safety endpoint.
Safety Objective	**Safety Endpoints**
• To compare the safety and tolerability of daprodustat to rhEPO	• Incidence and severity of AEs and SAEs including those special interest • Reasons for discontinuation of randomized treatment • Absolute values and changes from baseline in laboratory parameters, BP and heart rate (HR)

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

2.3. Study Design

Overview of Study Design and Key Features



* Screening period may be extended by an additional 4 weeks for ultrasound examination, IV iron supplementation and/or vitamin B12 treatment as needed.

Design Features	• This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center study in subjects with anemia associated with CKD who are not regularly using erythropoiesis-stimulating agents (ESAs) and who are initiating dialysis.
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]) and by whether their dialysis start is planned or unplanned (urgent). • Following stratification, subjects will be randomized 1:1 to receive daprodustat or rhEPO (darbepoetin alfa). • Please refer to the protocol for starting doses, dose steps, and elements of the dose adjustment scheme.
Interim Analysis	• An IDMC will periodically receive unblinded safety reports containing clinical endpoints (whether adjudicated or pending adjudication) and SAEs, from an independent Statistical Data Analysis Center (SDAC) while Phase 3 studies with daprodustat are ongoing. The IDMC may recommend stopping this study for safety at any time. No formal interim analyses are planned in this study

2.4. Statistical Hypotheses

2.4.1. Hgb Efficacy Primary Hypothesis

The primary Hgb efficacy objective will assess the estimand defined as the effect of daprodustat treatment relative to darbepoetin alfa 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 with anemia secondary to CKD who are initiating dialysis and assuming subjects do not die before the end of the EP. The analysis will test whether daprodustat is non-inferior to darbepoetin alfa according to the following statistical hypotheses:

- **Null:** The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat -darbepoetin alfa), is less than or equal to -0.75 g/dL.
- **Alternative:** The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat -darbepoetin alfa), 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 randomization stratification factors (dialysis type and whether dialysis start is planned or unplanned), baseline Hgb and treatment will be used to obtain a point estimate and two-sided 95% CI for the treatment difference (daprodustat -darbepoetin alfa) and generate the p-value for the non-inferiority test. The non-inferiority p-value will show strength of evidence against the null hypothesis. Non-inferiority will be established if the lower limit of the two-sided 95% CI for the treatment difference is greater than -0.75 g/dL.

3. PLANNED ANALYSES

3.1. Interim Analyses

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

There are no prospectively defined interim analyses planned to stop the study early for Hgb efficacy or futility.

3.2. Final Analyses

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

1. All subjects have completed the study 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 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]	• Efficacy
Safety	• All randomized subjects who receive at least one dose of randomized treatment. • Subjects will be analyzed according to the treatment received.[1]	• Safety
Pharmacokinetic (PK)	• Subjects for whom a PK sample was obtained and analyzed	• PK

[1]: only subjects receiving incorrect randomized treatment for the duration of their study participation will be analysed 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 study populations 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 deviationsare captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the 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
10.13	Appendix 13: Abbreviations & Trade Marks

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be mostly based on ITT population. Summaries 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 Population	ITT	Y		Y
Subject Disposition				
Subject Status and Reasons for Study Withdrawal	ITT	Y	Y	Y
Subjects Who Were Rescreened	Screened			Y
Treatment Status and Reasons for Discontinuation of Randomized Treatment	ITT	Y	Y	Y
Number of Subjects by Region, Country and Site ID	Enrolled	Y		
Type of Subject Contact at Wk52	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 by Baseline Dialysis Type	ITT	Y		
Demographic & Baseline Characteristics by Baseline Dialysis Start Manner	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		

Parameter	Analysis Population	Data Displays Generated		
		Table	Figure	Listing
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
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 PK 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 who completed the study, the 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.

This summary 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, and subreason for withdrawal.

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 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.

This summary 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, and site ID will be summarized by treatment group and overall for the enrolled population.

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

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

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, and 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 produced. 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 by baseline dialysis type (HD/PD) and baseline dialysis start manner.

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 and Week 52 will be provided by treatment group and overall. This summary will include the number and percentage of subjects who have temporarily or permanently stopped dialysis at these time points, as well as summary statistics for total residual urine volume 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 10.4.1.5 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, and Day 1 - < Week 52 (Overall Compliance).

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

The number and percentage of subjects with no dose discrepancy, and at least one dose 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, and Day 1 - < Week 52 (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 would include the impact and the reason for impact overall (any visit) and at each impacted visit.

A summary of the number and percentage of subjects with any treatment interruption while on treatment due to COVID-19 pandemic overall and by visit may be produced. The summary would include the summary on the total duration of interruption per subject at a certain visit, since the last visit (e.g. 1-7 days, 8-14 days, etc.). Only the visits that had subjects who had treatment interruption, or whose randomized treatment was not able to be dispensed at the visit, would be presented in this table.

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 would be a stacked bar chart for each impacted visit. The stack bar would be color coded by impact.

7. PRIMARY STATISTICAL ANALYSES

7.1. Primary Hgb Efficacy Analysis

7.1.1. Overview of Planned Primary Hgb Efficacy and Supportive Analyses

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

Table 4 Overview of Planned Primary Hgb Efficacy 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												
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			

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). Subgroup is defined in Section 10.10.

7.1.2. Planned Primary Hgb Efficacy Statistical Analyses

The primary efficacy estimand is the effect of daprodustat relative to darbepoetin alfa 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 with anemia secondary to CKD who are initiating dialysis 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 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 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 deaths prior to the end of the EP, a treatment policy strategy will be used in which all Hgb data recorded during the EP (Weeks 28-52) will be included in the primary efficacy analysis, regardless of discontinuation or interruption of study medication due to any reasons, and regardless of receipt of non-randomized ESA medications for any reason including rescue, or blood transfusions. For deaths, a hypothetical strategy will be used as described in Section 7.1.2.5

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

- Study withdrawal prior to the end of the EP
- Permanent switching from clinic visits to remote visits prior to the end of 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

Primary Hgb Efficacy 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 0)
  ○ Dialysis start manner (whether dialysis start is planned or unplanned; as randomized)

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 201410. The imputations will be done by randomized treatment, dialysis type, and dialysis starting manner.
  ○ 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 dialysis start manner. The monotone regression will have baseline Hgb, prior scheduled (possibly imputed) Hgb values, and may include dialysis type and dialysis start manner, as covariates (see Model Checking & Diagnostics, below). The seed for reproducibility is set to 201410.
  ○ 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 EP and mean Alt EP values will be included (see Section 10.6.3).

Primary Hgb Efficacy Statistical Analyses

  - 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)).
- 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 mean EP and mean Alt EP values (see Section 10.6.3).
  - 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)).
- The number and percentage of subjects with imputed data in the primary Hgb analysis will be provided by treatment group. The number and percentage of subjects by reason for data imputation will be provided. Reasons include: intermittent missing Hgb values, death before Week 28, death during Week 28 – 52, investigator site closed before Week 28, investigator site closed during Weeks 28-52, lost to follow-up before Week 28, lost to follow-up during Week 28 – 52, consent withdrawn before Week 28, consent withdrawn during Week 28 – 52, and other monotone missing Hgb values. Subjects will be further classified as either having observed all 7 scheduled EP Hgb values, having observed a partial schedule of EP Hgb values, having observed no scheduled EP Hgb values with at least one unscheduled EP Hgb value, or having observed no EP Hgb values, scheduled or unscheduled. For subjects with partial scheduled EP Hgb values, both the pattern of imputed data (intermittent, monotone) and the amount of imputed data (1 – 6 scheduled Hgb values missing) will be summarized. For subjects with partial scheduled EP Hgb values and a monotone imputed data pattern, the reason for the monotone imputed scheduled EP Hgb values will be provided. Reasons include: death during Week 28-52, investigator site closed during Weeks 28-52, lost to follow-up during Week 28 – 52, consent withdrawn during Week 28 – 52, and other monotone imputed Hgb values. And for summaries of the amount of missing scheduled EP Hgb values, the presence or absence of additional unscheduled EP Hgb values will be summarized.
- The least square (LS) mean estimates and standard errors by treatment group, LS mean difference, two-sided 95% CI and one-sided non-inferiority p-value for the difference in the primary Hgb endpoint between the daprodustat and darbepoetin alfa 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 Hgb values (on and off-treatment, observed and imputed (see Section 10.6.3)) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values ± 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.
- All available Hgb change from baseline values (on and off-treatment, observed and imputed (see Section 10.6.3)) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values ± 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.

Primary Hgb Efficacy Statistical Analyses
• 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 primary estimand.
• Tipping point sensitivity analyses will be conducted under a range of missing data assumptions to determine how extreme assumptions need to be for non-inferiority conclusions to change. Assumptions about missing Hgb values on the daprodustat and darbepoetin alfa arms will vary independently, and will include scenarios where subjects with missing data on daprodustat have worse outcomes than subjects with missing data on darbepoetin alfa.
  • 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 201410. The imputations will be done by randomized treatment, dialysis start manner, and dialysis type.
  • 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, dialysis start manner, and dialysis type. The monotone regression will include baseline Hgb, prior scheduled (possibly imputed) Hgb values, and may have dialysis start manner, and dialysis type as covariates (see Model Checking & Diagnostics, below). The seed for reproducibility is set to 201410.
  ○ 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 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

Sensitivity Statistical Analyses
(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 darbepoetin alfa, while on-treatment and without the use of non-randomized ESA medication or blood transfusions. • For this analysis, the primary Hgb analyses and summaries described above will be performed using evaluable Hgb values (see Section 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 95% CI from this analysis will be included on a forest plot with the primary Hgb analysis results. • The number and percentage of subjects meeting each evaluable Hgb (see Section 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 primary Hgb analysis results.
Alternative EP (Week 28-36) Analysis
• The following analyses will be repeated using an alternative EP from Week 28-36:   ○ The primary analysis and summaries (using on- and off-treatment, observed and imputed Hgb values (see Section 10.6.3))

Supportive Statistical Analyses
○ 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 primary Hgb analysis results.
COVID Supportive Analyses
• The adjusted treatment difference in mean change in Hgb from baseline to the EP and the corresponding 95% CI will be estimated using the same ANCOVA model specified in the co-primary Hgb analysis. Then they will be presented quarterly in a scatter plot, starting at around a year after the first subject was randomized, and ending after the last subject last visit. At each time point, all available observed post-randomization Hgb values (on and off treatment) up to that time will be used to fit the ANCOVA model as in the Hgb efficacy co-primary analysis(See Section 7.1.2). A vertical reference line will be used to represent the date the pandemic measures begin in the majority of the countries.
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.

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 5 provides an overview of the planned principal secondary efficacy analyses.

Table 5 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 from baseline 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[1]	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] Subgroup is defined in Section 10.1.1

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 from baseline 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 Day 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 Day 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 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 0)
  ○ Dialysis start manner (whether dialysis start is planned or unplanned; as randomized, see Section 0).

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 darbepoetin alfa 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 to 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 6 provides an overview of the planned additional secondary efficacy analyses

Table 6 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										

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.
[2] Analysis will be performed using evaluable Hgb values only (see Section 10.6.3).
[3] Subgroup analysis will be only using stratification factors (dialysis type and dialysis start manner).

8.1.2.2. Planned Additional Secondary Efficacy Statistical Analyses

Hgb Variability

Additional 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) *(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 0), 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 0), 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 [Rosendaal, 1993] will be used to calculate the percentage of time (days) a subject's Hgb is below, within and above the Hgb analysis range of 10 to 11.5 g/dL during the EP (Weeks 28-52) (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 0). 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 - darbepoetin alfa) at Week 52. The one-sided non-inferiority p-value for this test will be calculated.

Additional Secondary Efficacy Statistical Analyses: Hgb Variability
• For the responder analysis, the number and percentage of subjects with mean EP Hgb above, within and below the Hgb analysis range will be summarized by treatment group. • For the responder analysis, the number and % of responders by treatment group, difference in response rate (daprodustat – darbepoetin alfa) 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 CMH 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 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-Whitney estimate of the treatment difference (daprodustat - darbepoetin alfa) 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-darbepoetin alfa) and associated two-sided 95% CI will be presented.
Model Results Interpretation
• For the MMRM analysis of change from baseline in Hgb, the NI margin used in the primary analysis of Hgb (-0.75 g/dL) will be used for reference in this comparison, thus generating support for non-inferiority if the lower bound of the two-sided 95% CI is above -0.75 g/dL. • For the responder analysis, the one-sided CMH p-value will be compared to 0.025 to assess nominal significance. • For the percent time in range analysis, a NI margin of -15% will be used as a reference in this comparison, thus generating support for non-inferiority if the lower limit of the two-sided 95% CI of Hodges-Lehmann estimate is above -0.15. If non-inferiority is established, nominal superiority will be achieved if the one-sided p-value from the van Elteren test is < 0.025.

Supportive Statistical Analyses
Subgroup Analysis
• Subgroup analyses will be performed for all Hgb variability endpoints, using the stratification factor subgroups only (described in Section 0).

Time to Rescue

Additional Secondary Efficacy Statistical Analyses: Time to Rescue
Endpoint(s)
• Time to stopping randomized treatment due to meeting rescue criteria
Model Specification

• The Cox Proportional Hazards model will adjust for the following baseline categorical values:
  ○ Treatment
  ○ Dialysis type (as randomized, see Section 0)
  ○ Dialysis start manner (whether dialysis start is planned or unplanned; as randomized, see Section 0)

Additional Secondary Efficacy Statistical Analyses: Time to Rescue
• Confidence intervals for the rate per 100 person-years will also be reported. For within-group rates, the 95% CI will be obtained using an exact Poisson method. For difference in rates between treatments, the two-sided 95% CI will be constructed with a Normal approximation using Wald's method [Liu, 2006]. • Analysis will include only those efficacy endpoints occurring within the time period for treatment discontinuation. Calculation of time-to-event or censoring is described in further detail in Section 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 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 hazard ratio, two-sided 95% CI, and one-sided p-value for the statistical superiority test will be presented for the comparison of daprodustat vs. darbepoetin alfa using the Cox Proportional Hazards model. The number and percentage of subjects with the event of stopping treatment due to meeting rescue criteria and the number censored at the end of the study, the incidence rate per 100 person-years, and associated two-sided 95% CI will be displayed with the results of the Cox proportional hazards regression model.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance.

8.1.3. Exploratory Efficacy Analyses

8.1.3.1. Overview of Planned Exploratory Efficacy Analyses

Table 7 provides an overview of the planned exploratory efficacy analyses.

Table 7 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) cross all visits to end of treatment	ITT	Included with Hgb primary and supportive analyses (Section 7.1)							
% of time Hgb is above, within and below Hgb analysis range (10-11.5 g/dL) during EP	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[1]	ITT	Y							
Number of times Hgb < 7.5 g/dL during EP[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, Week4, Week6, and Week 8) 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[1]	ITT	Y							
Number of times Hgb ≥ 12 g/dL during the EP[1]	ITT	Y							
% of time Hgb ≥ 12 g/dL during the EP[1]	ITT	Y							
Iron Parameters									
Hepcidin, ferritin, TSAT, total iron, TIBC observed and CFB cross all visits to end of treatment	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							
RBC and Whole Blood Transfusions									
Number (%) of subjects receiving at least one RBC or whole blood transfusion by Week 52	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						
Dose Adjustment Scheme Evaluation									
Assigned dose by visit	ITT	Y	Y						

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	L	T	F	F	L
Most recent dose by visit	ITT		Y						Y
Number (%) of subjects with 0,1,2, or >2 dose adjustments during the following periods Day 1 - <Week 28, Week 28 -< Week 52, Day 1 - < the end of treatment	ITT	Y							
Number of dose adjustments during the following periods: Day 1 - <Week 28, Week 28 -< Week 52, Day 1 -< the end of treatment	ITT	Y							
Time dose held for Hgb ≥ 12 g/dL	ITT	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] Summaries will be presented using evaluable Hgb values only (see Section 10.6.3).

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 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 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 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 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 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 will while on IV iron be grouped by the action taken with 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 see Section 10.6.3) according to concomitant medication records for IV iron.

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 10.6.3.4.

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 summarised.

The above summaries will be produced for the Evaluation Period and Week 52.

An analysis of time to first RBC or whole blood transfusion will be performed as described in Section 10.6.3.4., including a Kaplan-Meier plot.

Dose Adjustment Scheme

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

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 subjects with 0, 1, 2, …, 10, or >10 dose adjustments will be summarized by treatment group. Summaries will be presented for the following categories of time: Day 1 – < Week 28, Week 28 – <Week 52, and Day 1 – < Week 52.

The number of dose adjustments per subject will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. Summaries will be presented for the following categories of time: Day 1 – < Week 28, Week 28 – <Week 52, and Day 1 – < Week 52.

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, and Day 1 – < Week 52.

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

- Dialysis type at randomization
- Dialysis start manner
- 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 overlaid on a graph of corresponding mean Hgb values by visit

8.2. Safety Analyses

8.2.1. Secondary Safety Analyses

8.2.1.1. Overview of Planned Secondary Safety Analyses

Table 8 provides an overview of the planned secondary safety analyses.

Table 8 Overview of Planned Secondary Safety 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
Blood Pressure															
SBP, DBP and MAP changes from Baseline[1,2]	ITT				Y	Y			Y			Y	Y		
Number of BP exacerbation events per 100 patient years[2]	ITT	Y			Y										
Subjects experiencing at least one BP exacerbation event during study[2]	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] Analysis will be performed using all available (on and off treatment) BP values.
[2] Analysis will be performed using on-treatment BP values only.

8.2.1.2. Planned Secondary Safety Statistical Analyses

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

Secondary Safety Statistical Analyses: Blood Pressure
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: o On-treatment BP values only, excluding values collected during the stabilization period (Randomization date + 1 day to <Week 28). o 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 0), 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 0) and the corresponding baseline BP parameter. This analysis will be performed using on-treatment BP values only. • The number of on-treatment BP exacerbation events per 100 patient years will be calculated (see Section 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 derivedend 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.

Secondary Safety Statistical Analyses: Blood Pressure

• 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 - darbepoetin alfa) 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 darbepoetin alfa 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. darbepoetin alfa.
• 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
  ▪ 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.

8.2.2. Exploratory Safety Analyses

8.2.2.1. Overview of Planned Exploratory Safety Analyses

Table 9 provides an overview of the planned exploratory safety analyses.

Table 9 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 8.2.1)							
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.

8.2.2.2. 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 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 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 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 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 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 on-treatment total cholesterol, LDL-C (direct), and HDL-C values will be summarized using percent change geometric mean, 95% confidence interval, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group.

8.2.2.3. Overview of Exploratory Cardiovascular Safety Analysis

Table 10 provides an overview of exploratory cardiovascular safety analyses.

Table 10 Overview of Exploratory Cardiovascular Safety Analyses

Endpoint[1]	Analysis Population	Absolute						
		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L
MACE	ITT	Y			Y	Y		Y
MACE or a thromboembolic event	ITT	Y			Y			
MACE or hospitalization for HF	ITT	Y			Y			
All-cause mortality	ITT	Y			Y			Y
CV mortality	ITT	Y			Y			
MI (fatal and non-fatal)	ITT	Y			Y			
Stroke (fatal and non-fatal)	ITT	Y			Y			

Endpoint[1]	Analysis Population	Absolute						
		Stats Analysis			Summary		Individual	
		T	F	L	T	F	F	L
CV mortality or non-fatal MI	ITT	Y			Y			
All-cause hospitalization	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.

8.2.2.4. Planned Exploratory Cardiovascular Safety Analysis Details

Exploratory CV Safety Analyses

Endpoint(s)[1]:

- MACE (all-cause mortality, non-fatal MI, or non-fatal stroke)
- MACE or a thromboembolic event
- MACE or hospitalization for HF
- All-cause mortality
- CV mortality
- MI (fatal and non-fatal)
- Stoke (fatal and non-fatal)
- CV mortality or non-fatal MI
- All-cause hospitalization

Model Specification

- For all exploratory CV endpoints, confidence intervals for the rate per 100 person-years will be reported. For within-group rates, the 95% CI will be obtained using an exact Poisson method. For difference in rates between treatments, the two-sided 95% CI will be constructed with a normal approximation using Walds' method [Liu, 2006].
-
- For MACE endpoint, the calculation of time-to-event or censoring is described in further detail in Section 10.6.4.1.
- First occurrence of adjudicated MACE for a subject is defined as the first adjudicated event, determined by the event date, which is indicated as all-cause mortality, non-fatal MI or non-fatal stroke with further details in Section 10.6.4.1.
- For those endpoints or components of endpoints intended to go through the adjudication process, only the adjudicated results will be used.

Model Results Presentation

- A summary of the number and percentage of subjects having first-occurrence MACE will be provided by treatment group. The number and percentage of the types of events that make up the first occurrence of MACE will also be provided by treatment group. This summary table will be repeated for MACE plus thromboembolic events, for MACE plus hospitalization for heart failure and for MACE plus thromboembolic events or hospitalization for CHF.

Exploratory CV Safety Analyses

- A summary of all MACE including the number and percentage of subjects and number of events (including first and subsequent MACE) by type of event will be provided by treatment group.
- A summary of the number and percentage of subjects having first-occurrence adjudicated COVID-19 MACE will be provided by treatment group. The number and percentage of the types of events that make up the first occurrence of adjudicated COVID-19 MACE will also be provided by treatment group.
- Summaries of adjudication details of all-cause mortality will include the number and percentage of subjects by cause of death.
- Summaries of adjudication details of MI will include the number and percentage of events by outcome of MI (fatal or non-fatal), type of MI, increased cardiac markers (y/n), ST segment classification [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial 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).
- A summary of adjudicated exploratory CV endpoints above (except all-cause hospitalization) will be provided to include the number and percentage of subjects and the number of events for each endpoint.
- The model results presentation for the endpoints above (except all –cause hospitalization) will be provided to include within-group incidence rates per 100 person-years (along with two-sided 95% CI), and difference in rates between treatments (along with two-sided 95% CI), For composite endpoints, the number and percentage of the type of first occurrence will be provided by treatment group.
- A summary of all-cause hospitalization will be provided by treatment group including summaries of the number of hospitalizations per subject, average length of stay per hospitalization and primary diagnosis at discharge by system organ class and lower level term.
- Time from Randomization to first occurrence of adjudicated MACE event or end of trial will be evaluated using Kaplan-Meier (KM) methodology and displayed graphically for the comparison of daprodustat vs. darbepoetin alfa.
- • Summary of concordance between events referred for adjudication and adjudicated endpoint events (Positively Adjudicated or Negatively Adjudicated) will be presented.

Exploratory CV Safety Analyses
• 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. • A listing of all all-cause mortality events that occur during the study will be provided. This listing will include treatment, site ID, unique subject ID, select demographic information, event date, study day, and cause of death.

[1] Adjudicated events used where available.

8.2.3. Adverse Event Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. For the purpose of AE summaries and analysis, the investigator-reported AE details will be used, regardless of the adjudication outcome of the event.

See Section 10.4.1 for AE treatment state definitions. The adverse event safety analyses will be based on the Safety population, unless otherwise specified.

8.2.3.1. Overview of Planned Adverse Event Analyses

Table 11 provides an overview of the planned adverse event safety analyses.

Table 11 Overview of Planned Adverse Event Safety Analyses

Parameter	Absolute			
	Summary		Individual	
	T	F	F	L
AESIs				
Summary of AESIs	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 Subgroups	Y			
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
Pregnancy Data				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

Parameter	Absolute			
	Summary		Individual	
	T	F	F	L
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

NOTES :

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- 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.

8.2.3.2. Planned Adverse Event Safety Statistical Analyses

AESIs 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, with the exception of the composite endpoint AESI (death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access). This endpoint will use a Kaplan-Meier plot. If there are less than 20 subjects total for both the daprodustat and darbepoetin alfa arm, then these plots will not be created. Competing risks for the AESI cumulative incidence plots include:

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

Dot plots displaying the incidence of the event will be provided for AESIs by AESI term and treatment group. The incidence rate in each treatment group and corresponding two-sided 95% confidence interval for the relative risk of the daprodustat group compared to the darbepoetin alfa 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, baseline dialysis start manner, and weight quartile subgroups. Summaries of treatment emergent AEs by subgroup will be produced twice: by system organ class and preferred term and separately by overall frequency.

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

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

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

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

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

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

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

A listing of subjects who became pregnant while participating in the study will be provided.

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 on-treatment 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.

8.2.4. 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	Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)	Bilirubin (total and direct/indirect)
	Potassium (serum)	Blood urea nitrogen (BUN)	Albumin
	Calcium (albumin corrected)	Phosphate	Creatinine (and eGFR CKD-EPI)

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)	High-sensitivity C-reactive protein (hsCRP)	Vitamin B12
	Vitamin B9		

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, creatinine, eGFR, phosphate, albumin, BUN, total cholesterol, LDL-C, HDL-C, and Vitamin B9. 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.

8.2.4.1. Overview of Planned Clinical Laboratory Safety Analyses

Table 12 provides an overview of the planned clinical laboratory safety analyses.

Table 12 Overview of Planned Clinical Laboratory Safety Analyses

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

Parameter	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
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.

8.2.4.2. 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 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. S*ee 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 8.2.4.

Other Laboratory Tests

The displays presented for clinical chemistry laboratory values will also be presented for the other laboratory tests listed in Section 8.2.4..

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. S*ee Section 10.6.4 for additional information on worst case values and PCI categories.*

8.2.5. 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.

8.2.5.1. Overview of Planned Vital Signs Analyses

Table 13 provides an overview of the planned vital signs analyses.

Table 13 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.

8.2.5.2. 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. Pre-dialysis BP values outside of the PCI range will be summarized separately.

The difference between on-treatment post-dialysis weight and estimated dry weight will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit during the evaluation period 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.

8.2.6. Electrocardiograms

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

8.2.7. Pregnancies

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

8.2.8. Other Safety Analyses

Medical Conditions

A listing of all medical conditions for all subjects will be provided by treatment group. Each subject's corresponding medical condition(s) will be provided using the medical history free text.

COVID-19 Analyses

The following COVID-19 related displays will be provided.

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

A summary of exposure adjusted incidence rates over time (see Section 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. Pharmacokinetic Analyses

8.3.1. Overview of Planned Pharmacokinetic Analyses

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

Table 14 provides an overview of the planned analyses.

Table 14 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++

8.3.2. Drug Concentration Measures

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

8.3.3. Pharmacokinetic Parameters

8.3.3.1. 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 15 will be determined from the plasma concentration-time data, as data permits.

Table 15 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 during 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
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.

Parameter	Parameter Description
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.

8.4. 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 16 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 Dose EP TIR						Y								
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.
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- 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.

8.5. 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
- CKD-AQ

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

8.5.1. Overview of Planned Patient Reported Outcomes Analyses

Table 17 provides an overview of the planned patient reported outcomes analyses.

Table 17 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			
Symptom Severity															
PGI-S score	ITT				Y				Y	Y		Y			
PGI-S categories	ITT											Y			
PGI-C categories	ITT				Y										
CKD-AQ domain and single item scores	ITT				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.

8.5.2. Planned Patient Reported Outcomes Statistical Analyses

8.5.2.1. 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 and 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 and 28. • Change from baseline in EQ VAS at Weeks 8, 12 and 28.
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 HRQoL data collected after baseline up to Week 52. The model will include factors for treatment, time, prognostic randomization stratification factors, baseline HRQoL parameter value and the baseline HRQoL 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 - darbepoetin alfa) and a one-sided superiority p-value for this test at Weeks 8,

Patient Reported Outcomes Statistical Analyses: HRQoL and Utility Score
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 supplemental RAP.
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 and gender 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.

8.5.2.2. Symptom Severity & Change

Patient Reported Outcomes Statistical Analyses: Symptom Severity & Change
Secondary Endpoint(s)
• Change from Baseline at Wk 52 by domain and single item on the CKD-AQ • 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 subjects within each PGI-C symptom change level at Weeks 8, 12, 28, 52
Model Specification
• Scoring for the PGI-S, PGI-C, and CDK-AQ parameters is outlined in Section 10.6.5. • The mean change from baseline in PGI-S scores, CKD-AQ domain and single item scores 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, the corresponding baseline score value (e.g. using baseline PGI-S score for PGI-S MMRM analysis) and the baseline 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, CKD-AQ domain and single item 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, CKD-AQ domain and single item scores will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Bar graphs displaying mean baseline and at visit values for the Week 8, 12, 28, and 52 visits for the CKD-AQ domain and single item scores will be provided by treatment group. • For the MMRM analyses of change from baseline in PGI-S, CKD-AQ domain and single item scores, 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 - darbepoetin alfa) and a one-sided superiority p-value for this test at Weeks 8, 12, 28, and 52.

Patient Reported Outcomes Statistical Analyses: Symptom Severity & Change
• 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.

8.6. 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.

8.7. 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.

9. REFERENCES

GlaxoSmithKline Document Number 2015N234534_01, 201410, A 52-week open label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with anemia associated with chronic kidney disease who are initiating dialysis, 06-OCT-2017

GlaxoSmithKline Document Number 2015N230102_03, 200808, A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multicenter, event driven study in non-dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa (ASCEND-ND). 12-OCT-2016

GlaxoSmithKline Document Number Atlas IS 16443, GSK1278864, Evaluating the measurement properties of the chronic kidney disease and anemia questionnaire (CKD-AQ) in two Phase 3 randomized open-label studies in patients with anemia associated with chronic kidney disease. 3-OCT-2018

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.

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.

Rosendaal 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 & Events
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Treatment States and 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 Outcome
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: Multicenter Studies • Methods for Handling Centres
Section 10.10	Appendix 10: Examination of Covariates, Subgroups & Other Strata • Handling of Covariates, Subgroups & Other Strata • Randomization Stratification
Section 10.11	Appendix 11: Multiple Comparisons & Multiplicity
Section 10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.13	Appendix 13: 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 will 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. Time and Events Table for Subjects on Randomized Treatment

Protocol Activity (visits ± 1 week, except Weeks 2 and 4 which are ±3 days)	Screening Week -2[1]	Randomization (Day 1)	Weeks 2, 6	Full study visit Weeks 4, 16, 28, 40	Abbreviated study visit Weeks 8, 12, 20, 24, 32, 36, 44, 48	Week 52	Unscheduled	Follow-up Weeks 56-58
Written informed consent[19]	X							
IRT system	X	X	X	X	X		X	X
Entry criteria	X	X						
History: medical, hospitalization, transfusion; demography, height	X							
Weight and estimated dry (target) weight	X	X	X	X	X	X	X	X
SBP/DBP[2], HR[2]	X	X[2] (triplicate)	X	X	X	X[2] (triplicate)	X	X
ECG[3]	X	X						
Ultrasound of kidneys and adrenal glands	X[4]							
Randomized treatment dispensing[16]		X		X	X		X[5,6]	
Randomized treatment compliance[16]			X	X	X	X	X[7]	
Iron therapy, transfusions (record in eCRF, if applicable)		X	X	X	X	X		X
Rescue medication (record in eCRF, if applicable)			X	X	X	X		X
Females only: estradiol & FSH (if required)	X							
Serum pregnancy test[8] (FRP only)	X	X		X	X[17]	X	X	X
HemoCue Hgb	X	X	X	X	X	X	X	
Hematology[9]	X	X		X	Hgb only	X	X	X
Clinical chemistry[9]	X	X		X		X	X	X
Ferritin, serum iron, UIBC	X[1]	X		X		X		X

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Protocol Activity (visits ± 1 week, except Weeks 2 and 4 which are ±3 days)	Screening Week -2[1]	Randomization (Day 1)	Weeks 2, 6	Full study visit Weeks 4, 16, 28, 40	Abbreviated study visit Weeks 8, 12, 20, 24, 32, 36, 44, 48	Week 52	Unscheduled	Follow-up Weeks 56-58
Vitamin B12[1], folate	X							
Hepcidin		X		X		X		X
iPTH		X		X		X		X
Storage biomarkers[18]		X		Wk 28		X		
Kt/V_{urea} for dialysis adequacy[10]				X		X		
Lipids (non-fasting), direct LDL		X				X		
PK Sampling[11]				Weeks 4, 8, 12[11]				
Genetics sample[12]		X						
hsCRP		X		Week 28 only		X		
EQ-5D-5L & VAS[13], SF-36[13]		X		Weeks 8,12, 28 only		X		
CKD Anemia Symptoms Questionnaire (CKD-AQ)[13,14], PGI-S[13]	X	X		Weeks 8,12, 28 only		X		
PGI-C[13]				Weeks 8,12, 28 only		X		
Healthcare resource utilization (subject reported)	X	X	X	Weeks 4, 8, 12, 16, 20, 24, 28 only		X		X
Hospitalization / kidney transplant (record in eCRF, if applicable)			X	X		X		X
Non-serious AEs, SAEs, AEs of Special Interest, clinical events	X[15]	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X

Abbreviations: FRP, females of reproductive potential; FSH, follicle stimulating hormone; UIBC, unsaturated iron binding capacity; iPTH, intact parathyroid hormone; hsCRP, high-sensitivity C-reactive Protein; PGI-S, Patient Global Impression of Severity; PGI-C, Patient Global Impression of Change.

1. The screening period may be extended by an additional 4 weeks for subjects who require IV iron supplementation and/or vitamin B12 as outlined in Protocol Section 5.2. Ferritin, TSAT, and/or vitamin B12 must be re-assessed, where appropriate, following iron and/or B12 supplementation prior to randomization to meet entry criteria.
2. A single measurement each of SBP, DBP and HR will be taken, except at Day 1 and Week 52 where the measurements will be take in triplicate. Measurements will be taken post-dialysis for subjects receiving in-center dialysis. See Protocol Section 7.4.8.
3. ECG assessment must be recorded pre-dialysis for dialysis subjects. ECG may be performed as early as at screening Week -2 and prior to randomization (Day 1).
4. Ultrasound of the kidneys and adrenal glands must be performed prior to randomization. The screening period may be extended up to 4 weeks if needed. 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.
5. Additional visits to check Hgb and dispense randomized treatment are required under the circumstances described in Protocol Appendix 3. Hematology and chemistry samples are not required. For any unscheduled visit, compliance checking will be required when a dose of randomized treatment is changed.
6. Required only if dose is changed or randomized treatment is dispensed.
7. If dose does not change, then randomized treatment is returned to subject.
8. If a subject becomes post-menopausal (as defined in Protocol Appendix 5) during the study pregnancy tests are no longer required.
9. Testing panel in Protocol Table 9. Please note, creatinine and eGFR will only be tested and calculated at screening and randomization.
10. 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.
11. PK sampling will be collected from all subjects randomized to the daprodustat arm, at 1 of these 3 visits, Details in Protocol Section 7.5.
12. 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.
13. Subjects who are unable to or require assistance to read must not complete the questionnaires.
14. To be completed if available (e.g., translations may be not available in time in all countries).
15. Only SAEs assessed as related to study participation or a GSK product are collected during screening period.
16. 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.
17. For Argentina, ONLY: pregnancy testing will be performed every 4 weeks for FRP as required by local law.
18. Biomarker samples will be stored for future analyses for all subjects, except if not permitted by IRB/EC or refused by subject.
19. Informed consent will be obtained prior to any study procedures.

10.2.1.2. Time and Events Table for Subjects that Permanently Discontinue Randomized Treatment

Protocol Activity Dialysis: In-clinic assessments done pre-dialysis.	**Early Treatment Discontinuation Visit (within 2 weeks of the last dose of randomized treatment)**	**Day 1 – Week 52 (every 12 weeks ± 2 weeks)**	**Unscheduled**	**Follow-up (4 weeks post-study termination ± 1 week)**
IRT SYSTEM	X			
SBP/DBP[1], HR[1]	X (triplicate)	X	X	X
Iron therapy, transfusions[2]	X			
Serum pregnancy test (FRP only)	X			
HemoCue Hgb	X	X	X	
Hematology	Hgb only	X		X
Clinical chemistry	X			
Ferritin, serum iron, UIBC, hepcidin, lipids	X			
Hospitalization[2] / kidney transplant[2]	X	X	X	X
Non-serious AEs, AEs of Special Interest, SAEs, clinical events	X	X	X	X
Review concomitant medications	X	X	X	X
Healthcare resource utilization (subject reporting)	X			
CKD Anemia Symptoms Questionnaire (CKD-AQ) questionnaire, PGI-S, PGI-C[3]	X			
SF-36[3], EQ-5D-5L[3]	X			

1. See Protocol Section 7.4.8 for details.
2. Record in eCRF, if applicable
3. Subjects who are unable to or require assistance to read must not complete the questionnaires.

10.3. Appendix 3: Assessment Windows

10.3.1. 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 Phases

Assessments and events will be classified according to the time of occurrence relative to 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 Phase	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

AEs are to be recorded on the eCRF from the start of randomization treatment until the Follow-up visit, at the timepoints specified in the Time and Events table from Section 10.2.1. Serious AEs assessed as related to study participation or related to a GSK product are to be reported on the eCRF from the time a subject consents to participate in the study

up to and including any follow-up contact. AE of worsening of an on-going event will be counted once in a particular 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
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 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

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

NOTES:

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

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]
1	daprodustat	Dapro	1
2	darbepoetin alfa	Darbe	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
	Screening Week -2	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: pre-dialysis BP parameters, HR and weight		X	Randomization Date
Subjects who have in-clinic HD: post-dialysis BP parameters, HR, weight, and dry weight[2]	X		Week -2/Randomization Date

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening Week -2	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
CKD-AQ		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 10 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 -2 visit.

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 =

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

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

To calculate 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 assuming a normal distribution: Mean -/+ z(1- α/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 =

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

Where i = subject.

Unless otherwise specified, the baseline definitions specified in Section 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

Reporting Process

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)
  - Some BP endpoints will include unscheduled BP values (see Section 10.6.4)
- All unscheduled visits will be included in listings.

Reporting Process	
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 (except patient-reported outcome data) 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)
  ○ If there are multiple responses recorded by a subject for a PRO questionnaire at the same visit, the first complete response will be used
• 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 start date
Last Non-Zero Dose Date

• Date of last actual dose of randomized study treatment from 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 actually be 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 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.
    - 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
Stabilization Period
• Defined as the period between and including the Randomization date + 1 day - <Week 28 visit, using planned/actual dates.
Alternative Evaluation Period (Alt. EP)
• Defined as the period between and including Week 28 visit – Week 36 visit, using planned/actual dates.
Evaluation Period (EP)
• Defined as the period between and including Week 28 visit – Week 52 visit, using planned/actual dates.
Study Day
• Calculated as the number of days from randomization date : • Ref Date = Missing → Study Day = Missing • Ref Date < Randomization Date → Study Day = Ref Date – Randomization Date • Ref 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, 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.

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 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

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 Initiation 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
- Subjects may start dialysis up to 4 weeks after randomization. For subjects who have not yet started dialysis on the randomization date, the earliest dialysis type entered on the Dialysis Initiation eCRF page will be summarized.

Demographic & Baseline Characteristics
Dialysis Start Manner
• Dialysis start manner will use information recorded in the stratification level field of the Randomization eCRF page and the following two groups will be summarized: o Planned start o Unplanned (urgent) start
Dialysis Status at Randomization
• Dialysis status at randomization will use the subject's randomization date and the dialysis type information recorded on the Dialysis Initiation and Dialysis Changes eCRF pages to determine the dialysis status on the randomization date and will be summarized as follows: o Dialysis not initiated o On dialysis
Baseline Body Mass Index (BMI)
• Calculated as baseline weight (kg) / [height (m)]^2 Note: For subjects with in-clinic dialysis, baseline post-dialysis weight is used.
B12 Supplementation Required to Be Eligible for Randomization
• If a randomized subject's B12 value at screening is below the lower limit of the reference range, and there is a Vitamin B12 concomitant medication (any route) start date after the screening date, but before the randomization date, then the subject is considered to have required B12 supplementation to be eligible for randomization.
IV Iron Supplementation Required to Be Eligible for Randomization
• If a randomized subject has an IV iron concomitant medication record with a reason of 'study eligibility', then the subject is considered to have required IV iron supplementation to be eligible for randomization.
Dosing Algorithm at Randomization
• Protocol Amendment 1 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.
History of Diabetes
• Subjects are considered to have a history of diabetes if they have a yes response to any of the following medical history conditions: diabetes, diabetic autonomic neuropathy, diabetic neuropathy peripheral, diabetic dermopathy, diabetic renal disease, diabetic retinopathy. • If subjects have indicated that they do not have any of the listed diabetic medical history conditions above, they are considered not to have a history of diabetes. • If subjects have not been classified as 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.

Demographic & Baseline Characteristics
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.
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.

Demographic & Baseline Characteristics
• 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
• Subjects may start dialysis up to 4 weeks after randomization. For subjects who have not yet started dialysis on the randomization date, the earliest dialysis access type entered on the Dialysis Access History eCRF page will be summarized.

Phosphate Binder Use at Randomization

• Phosphate binder use at randomization will be summarized as follows:
  ○ Iron-based phosphate binders
  ○ Calcium-based phosphate binders
  ○ Non-calcium and non-iron based phosphate binders
  ○ No phosphate binder use
• Subjects will be counted in each applicable group, based on the concomitant medications they are receiving on the day of randomization.

Concomitant Medication Use at Randomization

• Concomitant medication records on the day of randomization will be used to determine the following classifications of concomitant medication use at randomization:
  ○ ACEI/ARB
  ○ Vitamin D
  ○ Beta blockers

Demographic & Baseline Characteristics
○ SGLT2i ○ Statin ○ Aspirin ○ Vitamin K ○ Insulin ○ Calcimimetics ○ Diabetic medication

10.6.2.3. Randomized Treatment Discontinuation and Study Withdrawal

Randomized Treatment Discontinuation and Study Withdrawal
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
• 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

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: ○ Non-randomized ESA treatment in addition to randomized treatment ○ Non-randomized ESA treatment instead of randomized treatment

Prior and Concomitant Medications
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.

10.6.2.4 Exposure and Compliance

Exposure and Compliance
Exposure
• Exposure (days) = Treatment stop date – treatment start date + 1 day
Compliance
• Compliance will be calculated based on data recorded in the Study Treatment 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.

o 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		

o darbepoetin alfa 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

Exposure and Compliance

71 – 98 days	< 3 doses	3 or 4 doses	> 4 doses
99 – 126 days	< 4 doses	4 or 5 doses	> 5 doses
Etc.			

- darbepoetin alfa 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
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.			

- darbepoetin alfa 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.			

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

Exposure and Compliance
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 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 10.4.1.1) 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. • For the primary efficacy Hgb analysis and the corresponding subgroup analyses using all available observed and imputed Hgb values (on and off-treatment), Rubin's rules [Rubin, 1987] will be used to combine results of the imputed datasets using SAS PROC MIANALYZE procedure.
EP Hemoglobin Value for Primary Hgb Analysis
• For each subject, the mean of all available (on and off treatment) Hgb values during the EP (See Section 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 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.

Hemoglobin Values

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 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 fall within the Alt. EP, then these values will be included as unscheduled Hgb values. Hgb values from the Follow-up visit will not be included in the Alt. EP mean.

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

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

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

Hemoglobin Values

	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 (Rosendaal, 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.

10.6.3.2. Iron Endpoints

Iron Endpoints

Iron Medications

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

Baseline Iron Use

- The number and percentage of subjects in the following iron use categories at baseline will be summarized:
  - IV iron use only
  - Oral iron use only
  - Other iron use only
  - IV and oral iron use only
  - IV and other iron use only
  - Oral and other iron use only

Iron Endpoints

- IV, oral, and other iron use
- No iron use

- When determining baseline iron use, the gap factors mentioned below in the IV iron standardization algorithm will be applied to the end date for each iron record, and the baseline period of 10 weeks before the Randomization date until the day before the Randomization date will also be used.

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

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

Note: Frequency defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)
2 times per week	2
3 times per week	3
4 times per week	4
5 times per week	5
BID	14
Once daily	7
One time dose	1
Every 12 Hours	14
Every 2 weeks	0.5
Every 4 weeks	0.25
Once a month	0.23
Once a week	1
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 10 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 (the Randomization date – 10 weeks) to the Randomization date will be selected and ordered by start and end date.

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 and Gap Factors defined as follows:

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

- If the frequency of the record is not 'one time dose', then duration is calculated as follows:
  - If the concomitant medication record start date ≥ Randomization date, the duration of the record is 0.
  - If the concomitant medication record end date + gap factor < (Randomization date – 10 weeks), the duration of the record is 0.
  - If the concomitant medication record end date + gap factor ≥ (Randomization date – 10 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 – 10 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 – 10 weeks, or if Randomization date ≤ concomitant medication record start date, then duration of the record is 0.
  - If Randomization date – 10 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:

Iron Endpoints

- Mean baseline monthly IV iron dose = [(IV iron total dose$_{\text{Record 1}}$) + ... + (IV iron total dose$_{\text{Record n}}$)]/[(Randomization Date – Screening Week -2 Visit Date)/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 – 10 weeks to the Week 52 visit date will be selected and ordered by start date and end date.
- The standardization will be carried out with the following formula:
  - Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency

Note: Frequency and Gap Factors defined as follows:

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

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

Iron Endpoints

- 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}.

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

Iron Endpoints

Every 12 Hours	14	0 days
Every 2 weeks	0.5	13 days
Every 4 weeks	0.25	27 days
Once a month	0.23	29 days
Once a week	1	6 days
TID	21	0 days

- If the frequency of the record is not 'one time dose', then duration is calculated as follows:
  - If the concomitant medication record start date > earliest of (treatment stop date + 1 and Week 52 visit date), the duration of the record is 0.
  - If the concomitant medication record end date + gap factor < Week 28 visit date, the duration of the record is 0.
  - If the concomitant medication record end date + gap factor ≥ Week 28 visit date or the record is ongoing, the duration of the record will be calculated as Stop Date – Start Date +1 day where:
    - Start date will be the latest of (concomitant medication record start date, and the Week 28 visit date).
    - Stop date will be the earliest of (concomitant medication record stop date + gap factor, 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

Iron Endpoints

- 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 10 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)
    - Quarter 3 = [Week 24 – Week 36)
    - Quarter 4 = [Week 36 – Week 48)
- To determine the planned start date and end date of quarters, the visit end date (from the SV domain) will be used. If there is not a corresponding visit, or if the subject is missing that visit, the planned visit date (Randomization date + 7*x) will be used, where x is the scheduled week (e.g., Week 24, x = 24).
- A subject's quarterly average IV iron dose will end at the earliest of the following:
  - For summaries of on & off treatment IV iron dose: death date, study completion/withdrawal date, and the planned quarter end date.
  - For summaries of on-treatment IV iron dose: death date, 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 10 weeks, it will also be included in summaries of average quarterly IV iron dose.

TIBC

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

TSAT

- TSAT will be calculated automatically by the central laboratory using:
  - 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:
  - Baseline average quarterly ferritin and TSAT will take the average of all available records before or on randomization ferritin and TSAT values.

Iron Endpoints
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) – darbepoetin alfa rescue incidence rate (per 100 person years)

Time to Stopping Randomized Treatment Due to Meeting Rescue Criteria
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 10.4.1).
- For records with a frequency of “Once only” or “Continuous infusion”, each record is considered to be a single transfusion (regardless of start and end dates or number of units).
- For records with a frequency of “Once daily”, the number of transfusions will equal the duration (end date – start date +1).
- For records with a frequency of “PRN”, 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 Transfusion Event
1 unit	Once only	19FEB2019	19FEB2019	15FEB2019	26FEB2019	

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

- 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).

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 to up 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/millilitres (mg/ml)	0.0025

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

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) – darbepoetin alfa 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:
    - For subjects continuing on study past the (treatment stop date + 1day), use (treatment stop date + 1day)
    - 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 time to stopping randomized treatment due to meeting rescue criteria (Section 8.1.2). • 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. darbepoetin alfa 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. 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.
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
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

Dose Adjustment Scheme Endpoints

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
30 µg	30 µg every 4 weeks
40 µg	40 µg every 4 weeks
60 µg	60 µg every 4 weeks
80 µg	40 µg every 2 weeks
120 µg	60 µg every 2 weeks
160 µg	80 µg every 2 weeks
200 µg	100 µg every 2 weeks
300 µg	150 µg every 2 weeks
400 µg	100 µg once a 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.

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 • 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 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

CV Safety Endpoints
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. 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.

CV Safety Endpoints

Missing or Partial Endpoint Dates

Missing of 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., --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.

CV Safety Endpoints

- 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 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 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:

CV Safety Endpoints

- 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)
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

All-cause Hospitalization

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

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

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) – darbepoetin alfa 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.

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.

Blood Pressure Endpoints

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 values will be used in summaries and analyses of BP exacerbations, unless otherwise specified.
- Subjects with multiple exacerbation events on the same calendar date for each type defined above are considered to have one exacerbation event for event counts by type. For example, a subject with a SBP and a DBP exacerbation on the same date would count in each of the SBP and DBP types, but would only count as one BP exacerbation event in 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

Blood Pressure Endpoints
• 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 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. • 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.

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 • Death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access • Cardiomyopathy • Pulmonary artery hypertension • Cancer-related mortality and tumor progression and recurrence • Esophageal and gastric erosions • Proliferative retinopathy, macular edema, choroidal neovascularization • Exacerbation of rheumatoid arthritis • Worsening of hypertension

Adverse Events
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 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 <u>Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis</u> • Narrow SMQ: Embolic and thrombotic events, arterial

Adverse Events

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

<u>Death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access</u>

- Death: all fatal SAEs
- Myocardial infarction:
  - Broad SMQ: Myocardial infarction
  - Additional Preferred Terms:
    - Angina pectoris
    - Anginal equivalent
    - Cardiac arrest
    - Chest discomfort
    - Chest pain
    - Myocardial ischaemia

Adverse Events

- Prinzmetal angina
- Non-cardiac chest pain

- Stroke:
  - Broad SMQ: Conditions associated with central nervous system haemorrhages and cerebrovascular accidents
  - Narrow SMQ: Ischaemic central nervous system vascular conditions
  - Narrow SMQ: Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic
- Heart failure: Narrow SMQ: Cardiac failure
- Thromboembolic events & thrombosis of vascular access:
  - 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

<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
  - 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

Adverse Events

- Haematological tumours of unspecified malignancy
- Non-haematological tumours of unspecified malignancy
- Malignant lymphomas
- Uterine and fallopian tube malignant tumours
- Uterine and fallopian tube tumours of unspecified malignancy

- Additional Preferred Terms:
  - Aplastic anaemia
  - Cytopenia
  - Pancytopenia
  - Aplasia pure red cell

Esophageal and gastric erosions

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

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

Adverse Events
Exacerbation eCRF page: • SBP: an increase from baseline of ≥ 25 mmHg or SBP ≥ 180 mmHg • DBP: an increase from baseline of ≥ 15 mmHg or DBP ≥ 110 mmHg
BP-related SAEs are those SAEs that have been identified via the BP Exacerbation eCRF page.
General Definitions
• Post-Randomization last contact date for censoring (subjects not having AE) will be defined as the study completion date.
• Treatment emergent last contact date for censoring (subjects not having AE) will be defined as follows: o 1 day after 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) o Last non-zero dose date for all other subjects
• AE Patient Years: (Cumulative total of time to AE for subjects who have the AE + Cumulative total of censoring time for subjects without the AE) / 365.25 o For treatment emergent AEs, the start date of the patient year value for each subject should be the treatment start date. o For post-randomization AEs, the start date of the patient year value for each subject should be the randomization date. o For follow-up AEs, the start date of the patient year 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. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01

Laboratory Parameters

- 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.
  - Creatinine: Divide the umol/L value by 88.4 to get the mg/dL value.
  - eGFR: Multiply the mL/sec/1.73m^2 value by 60 to get the mL/min/1.73m^2 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.
  - Vitamin B9: Divide the nmol/L by 2.266 to get the ng/mL value

Normal Range Categories, PCI Criteria Categories and Worst Case Values

- Normal range categories are: To Low, To Normal or No Change, To High
- PCI criteria categories are: To Low, To w/in Range or No Change, To High
- Subjects with a missing baseline value are to be assumed to have a normal/within range baseline value.
- The determination of the worst case post baseline value takes into account both planned and unscheduled assessments.
- Worst case can be either High or Low.
  - If a subject has both a decrease 'To Low' and an increase 'To High', then the subject is counted in both the 'To Low' and 'To High' categories.
  - 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: o 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). • 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). Each of these five-figure health states has an attached valuation (index value), expressed as a single index on a scale from 0-1, where 1 is CCI and 0 is CCI . • 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) value set for the health states will be used for all subjects, regardless of country.

EQ-VAS
General
• The EQ-VAS is a self-assessment visual analogue scale, ranging from 0=CCI – 100=CCI .

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-S
General
○ CCI [redacted] ○

PGI-C
General
• The PGI-C is a 1-item questionnaire designed to assess a subject's impression of change in their anemia of CKD on a 7-point Likert-type response scale (very much improved, moderately improved, minimally improved, no change, minimally worse, moderately worse, or very much worse). • Scores range from CCI [redacted] to CCI [redacted] as follows: ○ CCI [redacted] ○ ○ ○ ○ ○ ○

CKD-AQ
General
• The CKD-AQ is a newly-developed 21-item PRO measure assessing symptoms and symptom impact in patients with anemia associated with CKD. An interim cut of blinded observations from approximately 400 participants, approximately 350 from study 200808 (GSK Document Number 2015N230102_03) and approximately 50 from study 201410 (GSK Document Number. 2015N234534_01), who had completed the baseline (Day 1) CKD-AQ was taken to establish the scoring algorithm and any potential domains of the instrument. Further details of the scoring can be found in the psychometric report (GSK Document Number). • CKD-AQ originally had 23 questions/items, the psychometric analysis identified three domains (multi-item scales) and four single items, which consist of 21 items. The three domains are: (1) a Tired/Low Energy/Weak scale consisting of ten items – Items CCI [redacted] 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. [redacted] CCI [redacted]; (2) a Chest Pain/Shortness of Breath scale consisting of four items – Items CCI [redacted] CCI [redacted] CCI [redacted] This factor was labeled Chest Pain/Shortness of Breath.); and (3) a Cognitive scale consisting of three item – Items CCI [redacted] CCI [redacted] The four CKD-AQ single items are: Items CCI [redacted]

CKD-AQ
General
CCI CCI, were retained based upon their CKD-relevant content. The CKD-AQ domains and single-item measures were recoded based on a 0-100 scoring with 0 representing CCI and 100 CCI. • Scoring instruction: o Step 1: For items 1-8, 17-23, recode from 5-pt scale (CCI CCI) to 0-100 (CCI scale by using (5-raw score)*25; for items 9-16, recode from 11-pt scale (CCI) to 0-100 scale (CCI) by using (10-raw score)*10. o Step 2: calculate the domain and single item scores as follows: (items 16 and 23 were NOT used currently based on the psychometric report.) ▪ Tired/Low Energy/Weak domain: average items CCI (0-100 scale) ▪ Chest Pain/Shortness of Breath domain: average items CCI (0-100 scale) ▪ Cognitive domain: average items CCI (0-100 scale) ▪ CCI (0-100 scale) ▪ CCI (0-100 scale) ▪ CCI (0-100 scale) ▪ CCI (0-100 scale)

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 through the End of Treatment visit (i.e. Week 52), 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 : ○ These data will be indicated by the use of a “blank” in subject listing displays, unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any 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: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
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: • Imputing a Start/Worsening Date from a Partial Start/Worsening Date:

Element	Reporting Detail
	○ If an imputed worsening date is before the start date, then the start date will be used as the imputed worsening date. ○ Completely missing stop date: ➢ If only the day is missing, the first of the month will be used unless the Screen Week -2 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 Screen Week -2 visit date occurs in the same month, then the Screen Week -2 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 -2 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 Screen Week -2 visit date occurs in the same year, then the Screen Week -2 visit date will be used as the start/worsening date. ○ Partial or non-missing stop date is before treatment start date: ➢ If only the day is missing, then the first of the month will be used unless the Screen Week -2 Visit date also occurs in the same month; in this case the Screen Week -2 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 -2 Visit date also occurs in the same year; in this case the Screen Week -2 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:

Element	Reporting Detail
	➢ 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 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 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 date. • Completely missing start or end dates (i.e. no year specified) 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 (AST)	IU/L		≥ 3x ULRR
Alanine Aminotransferase (ALT)	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
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
Region 1: USA	USA[1]
Region 2: Europe	France, Germany, Italy, Spain[1], United Kingdom[1], Poland, Russia, South Africa[1]
Region 3: Rest of World	Australia[1], Argentina, Brazil[1], Canada[1], India, Malaysia[1], Mexico, South Korea[1]

Note: countries that do not participate or do not randomize any subjects will be removed from the regional grouping.

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

- 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. Due to small sample sizes in American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, and Mixed race categories, statistical comparison for race group will include Asian, Black, and White categories only. For baseline Hgb subgroup, if there are fewer than 25 subjects in the category >11 g/dL, the categories 10-11 g/dL and >11 g/dL will be combined to ≥ 10 g/dL. For any other subgroups, 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 primary and principal secondary endpoints will be evaluated for the subgroups below. Although subgroup analyses are aimed to assess for consistency with the overall results, they may have low power, especially if the subgroup is small or has a low number of events. Statistical models (ANCOVA) will be adjusted for the covariates used in the original analysis, subgroup, treatment and treatment by subgroup interaction. For the prognostic randomization stratification factors (dialysis type and dialysis start manner), the actual status of the factor derived from the eCRF will be used (see Section 0).
- 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, dialysis start manner, 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 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.

Category	**Covariates and / or Subgroups**	**Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.**	**Subgroup Analysis for Primary Hgb & Principal Secondary Efficacy Endpoint 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
Age at randomization (Grouping 1)	<65 years, 65-<75 years, ≥75 years	Yes	Yes

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Primary Hgb & Principal Secondary Efficacy Endpoint Note: Do not include 'Missing' categories.
Age at randomization (Grouping 2)	≤18 years, 19 - 64 years, ≥ 65 years	Yes	No
Age at randomization (Grouping 3)	18-64 years, 65-84 years, ≥85 years	No (included in stand-alone age ranges table)	No
Gender	Female, Male	Yes	Yes
Ethnicity	Hispanic or Latino, Not Hispanic or Latino	Yes	Yes
High level race	American Indian or Alaskan Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Mixed Race	Yes	Yes (Asian, Black or African American, and White will be used in subgroup analyses due to small sample size in other groups)
Race detail	American Indian or Alaskan Native 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	Yes	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Primary Hgb & Principal Secondary Efficacy Endpoint Note: Do not include 'Missing' categories.
Region	Region 1: USA Region 2: Europe Region 3: Rest of World	Yes	Yes
Regions combined	USA, Non-USA	Yes	Yes
Dialysis type at randomization[1]	HD, PD (repeat using HD, HDF/HF, PD)	Yes	Yes (HD/PD only)
Dialysis start manner	Planned Start, Unplanned (Urgent) Start	Yes	Yes
Dialysis status at randomization	Dialysis not initiated, On dialysis ≤90 days	Yes	No
Baseline Hgb (g/dL)	Continuous covariate for Hgb co-primary analysis; summary statistics of continuous values	Yes	No
Baseline Hgb group	<9 g/dL, 9- <10g/dL, 10-11g/dL, >11 g/dL, Missing	Yes	Yes (the last two subgroups will be combined into a single >=10 g/dL group if there are < 25 subjects in either group)
Baseline body mass index (kg/m^2) [2]	Summary statistics of continuous values	Yes	No
Baseline body mass index group[2]	<30 kg/m^2, ≥30 kg/m^2, Missing	Yes	Yes
Baseline weight (kg)[2]	Summary statistics of continuous values	Yes	No
Baseline weight group[2]	<75 kg, ≥75 kg, Missing	Yes	No
Baseline weight quartiles[2]	Overall ITT Population Quartile 1: < xx kg Overall ITT Population Quartile 2: xx kg - < xx kg Overall ITT Population Quartile 3: xx kg - < xx kg	Yes	Yes

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Primary Hgb & Principal Secondary Efficacy Endpoint Note: Do not include 'Missing' categories.
	Overall ITT Population Quartile 4: ≥ xx kg Missing		
Baseline hsCRP (mg/L)	Summary statistics of continuous values	Yes	No
Baseline hsCRP group	≤3 mg/L, >3 mg/L, Missing	Yes	No
Baseline hsCRP quartiles	Overall ITT Population Quartile 1: < xx mg/L Overall ITT Population Quartile 2: xx mg/L - < xx mg/L Overall ITT Population Quartile 3: xx mg/L - < xx mg/L Overall ITT Population Quartile 4: ≥xx mg/L Missing	Yes	Yes
Required B12 supplementation to be eligible for randomization	No, Yes	Yes	No
Required IV iron supplementation to be eligible for randomization	No, Yes	Yes	No
Dosing algorithm at randomization	Original algorithm, Updated algorithm	Yes	No
Other Exploratory Covariates/Subgroups where Biological Plausibility for Heterogeneous Effects Are Not Known or Anticipated			
History of diabetes	No, Yes, Missing	Yes	Yes
History of stroke	No, Yes, Missing	Yes	Yes
History of MI	No, Yes, Missing	Yes	Yes
History of cancer	No, Yes, Missing	Yes	Yes
History of HF	No, Yes, Missing	Yes	Yes

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Primary Hgb & Principal Secondary Efficacy Endpoint Note: Do not include 'Missing' categories.
History of thromboembolic events	No, Yes, Missing	Yes	Yes
Hospitalization within 6 months prior to screening	No, Yes, Missing	Yes	Yes
Transfusion within 6 months prior to screening	No, Yes, Missing	Yes	Yes
Baseline iron use	No iron use IV iron use only Oral iron use only Other iron use only IV and oral iron use only IV and other iron use only Oral and other iron use only IV, oral and other iron use	Yes	No
Standardized baseline IV iron dose (mg/month)	Continuous covariate for monthly IV iron dose analysis; summary statistics of continuous values	Yes	No
Standardized baseline IV iron dose (mg/month) for subjects using IV iron at baseline	Continuous covariate for monthly IV iron dose analysis; summary statistics of continuous values	Yes	No
Baseline SBP (mmHg) [2]	Continuous covariate for change from baseline in SBP analysis, summary statistics of continuous values	Yes	No
Baseline DBP (mmHg) [2]	Continuous covariate for change from baseline in SBP analysis, summary statistics of continuous values	Yes	No
Baseline MAP (mmHg) [2]	Continuous covariate for change from baseline in SBP	Yes	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Primary Hgb & Principal Secondary Efficacy Endpoint Note: Do not include 'Missing' categories.
	analysis, summary statistics of continuous values		
Dialysis access type used at randomization	Arteriovenous fistula Arteriovenous graft Central venous catheter – tunneled Central venous catheter – non-tunneled Peritoneal catheter Other Missing	Yes	No
ACEI/ARB use at randomization	No, Yes	Yes	No
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
Vitamin D use at randomization	No, Yes	Yes	No
History of cardiovascular disease	No, Yes	Yes	No
Beta blockers use at randomization	No, Yes	Yes	No
SGLT2i use at randomization	No, Yes	Yes	No
Statin use at randomization	No, Yes	Yes	No
Aspirin use at randomization	No, Yes	Yes	No
Vitamin K antagonist use at randomization	No, Yes	Yes	No

Category	Covariates and / or Subgroups	Summary of Demographics & Baseline Characteristics Note: Include 'Missing' categories, if applicable.	Subgroup Analysis for Primary Hgb & Principal Secondary Efficacy Endpoint Note: Do not include 'Missing' categories.
Insulin use at randomization	No, Yes	Yes	No
Calcimimetics use at randomization	No, Yes	Yes	No
Diabetic medication use at randomization	No, Yes	Yes	No
Baseline estimated dry weight (kg)	Summary statistics of continuous values	Yes	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]: Note: For subjects with in-clinic dialysis, post-dialysis value are used.

10.10.2. Randomization Stratification

Randomization is stratified by dialysis type (HD or PD) and dialysis start manner (whether their dialysis start is planned or unplanned (urgent)) to ensure balance across treatment groups for the overall study. The prognostic stratification factors (i.e., dialysis type and dialysis start manner) will be taken into account within the analysis models.

Baseline dialysis type strata and baseline dialysis start manner 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 of Comparisons & Multiplicity

10.11.1.1. Interim Analyses

There is no formal intent to evaluate the interim data from this study for the purpose of stopping early for Hgb efficacy or futility.

10.11.1.2. Final Analyses

The multiplicity strategy for this trial will use the gatekeeper approach on the primary endpoint. First, the primary endpoint will be evaluated for non-inferiority by two-sided 95% CI to the appropriate non-inferiority margin. Conditional on primary endpoint achieving non-inferiority (i.e., passing the gatekeeper), the principal secondary analysis will be formally tested for superiority using a one-sided 2.5% significance level.

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 dialysis start manner, 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 dialysis start manner, with baseline Hgb and dialysis type as covariates, 2) impute by randomized treatment, with baseline Hgb, dialysis start manner, and dialysis type as covariates, 3) impute by randomized treatment, with baseline Hgb, and dialysis start manner use as covariates, 4) impute by randomized treatment with baseline Hgb as a covariate, until no error/warning messages.	

10.13. Appendix 13: Abbreviations & Trade Marks

10.13.1. Abbreviations

Abbreviation	Description
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
CKD-AQ	Chronic kidney disease anemia symptoms questionnaire
CKD-EPI	Chronic kidney disease epidemiology collaboration
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EP	Evaluation Period
EQ-5D-5L	EuroQoL 5 Dimension 5 Level Health Utility Index
EQ-VAS	EuroQol Visual Analogue Scale
ERI	Erythropoietin Resistance Index
ESA	Erythropoiesis Stimulating Agent
FDA	Food and Drug Administration
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
HRQoL	Health Related Quality of Life

Abbreviation	Description
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 Summary
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed Model Repeated Measures
NI	Non-inferiority
PCI	Potential Clinical Importance
PCS	Physical Component Summary
PD	Pharmacodynamic
PGI-S	Patient Global Impression of Change
PGI-C	Patient Global Impression of Severity
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
TIR	Time in Range
TSAT	Transferrin Saturation
UK	United Kingdom
US	United States
VAS	Visual Assessment Scale
WBC	White Blood Cell

10.13.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
CKD-AQ

Trademarks not owned by the GlaxoSmithKline Group of Companies
EQ-5D-5L
SAS
SF-36