

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	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
Short title:	<u>A</u> nemia <u>S</u> tudies in <u>C</u> KD: <u>E</u> rythropoiesis via a <u>N</u> ovel PHI <u>D</u> aprodustat- in <u>I</u> ncident <u>D</u> ialysis (<u>ASCEND-ID</u>)

Compound Number: GSK1278863

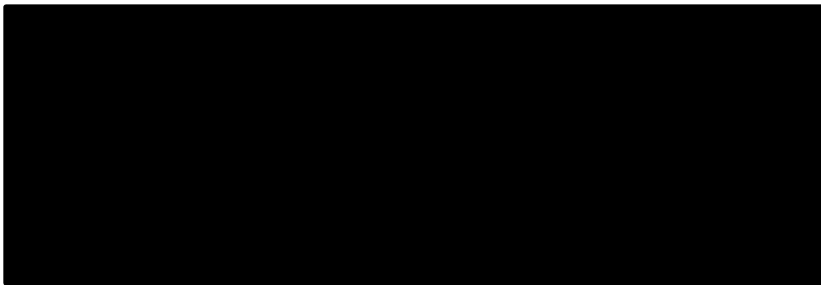
Development Phase III

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Author(s):

[REDACTED]

SPONSOR SIGNATORY:



10/18/2016
Date

Executive Director Clinical Development
Metabolic Pathways & Cardiovascular Unit
GlaxoSmithKline

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

As this is a multinational study medical monitor/SAE contact information will be provided as a separate document.

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

PPD is the contract research organization for this study.

In some countries, the clinical trial Sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

I confirm agreement to conduct the study in compliance with the protocol.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature

Date

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1. PROTOCOL SYNOPSIS

This Phase 3 study will evaluate the efficacy and safety of daprodustat (GSK1278863) compared to recombinant human erythropoietin (rhEPO) in the treatment of anemia associated with chronic kidney disease (CKD) in subjects who are planning to start or who have recently started dialysis. This study will also provide information on daprodustat dosing initiation and titration in subjects initiating dialysis.

Primary Objective/Primary Efficacy Endpoint

The primary objective of the study is to compare daprodustat to rhEPO for hemoglobin (Hgb) efficacy (non-inferiority).

The primary efficacy endpoint will be the mean change in Hgb between baseline and the evaluation period (EP, mean over Weeks 28-52).

Overall 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).

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

- 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); all randomized treatments (Section 6.1) 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 rhEPO, iron management, and rescue.

Type and Number of Subjects

- The study will enroll the following types of subjects with anemia associated with CKD: Planned initiation of dialysis: Subjects who are planning to start chronic dialysis (HD or PD) within the next 2-4 weeks (from the day of screening).

- Unplanned (urgent) initiation of dialysis: For Subjects who have started chronic dialysis in an urgent manner, meaning they started HD with a temporary vascular access with no previous planning for chronic dialysis or have started PD with recent (< 2 weeks) PD catheter insertion and/or who have not been seen by a kidney specialist (nephrologist) or other specialist with expertise in dialysis care within previous 4 months prior to screening.

Approximately 475 subjects are expected to be screened in order to randomize approximately 300 subjects, or 150 subjects per treatment group.

Primary Efficacy Analysis

The primary Hgb efficacy analysis will assess whether daprodustat is non-inferior to rhEPO for change from baseline. The analysis will be based on the mean change in Hgb between baseline and the efficacy EP (defined as Weeks 28 to 52) using a non-inferiority margin of -0.75 g/dL (two-sided 95% CI). An analysis of the ITT Population, comprising all subjects with at least one Hgb measurement (on or off-treatment) during the EP and an analysis of covariance (ANCOVA) model will be used. The model will include randomization stratification factors, and factors for baseline Hgb and treatment.

2. INTRODUCTION

2.1. Brief Background

Daprodustat (GSK1278863) is an oral hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI) currently being investigated as a treatment for anemia associated with CKD in both subjects on dialysis and not on dialysis. Safety and efficacy have been investigated in clinical trials up to 24 weeks' duration. Both pre-clinical and clinical data show that daprodustat stimulates endogenous erythropoietin (EPO) production and increased erythropoiesis, resulting in elevation of Hgb concentrations. These increases in Hgb are achieved with peak plasma EPO levels substantially lower than those observed with IV rhEPO. Data from completed clinical and preclinical studies are provided in the current daprodustat Investigator Brochure (IB) and IB supplement(s) (if applicable).

2.2. Study Rationale

Based on its mechanism of action to stimulate erythropoiesis via inhibition of HIF-prolyl hydroxylase enzymes, daprodustat is postulated to be associated with fewer major adverse cardiovascular events (MACE) by raising Hgb without the supraphysiologic EPO concentrations associated with IV rhEPO therapy, potentially avoiding blood pressure (BP) elevations and other adverse effects of high EPO levels.

A Phase 2B clinical trial (PHI133633) in dialysis subjects with anemia associated with CKD demonstrated that daprodustat can maintain Hgb up to 24 weeks with minimal effects on plasma EPO concentration. Daprodustat treatment for up to 24 weeks demonstrated an adverse event (AE) profile consistent with the patient population.

This Phase 3 study will evaluate the safety and efficacy of daprodustat compared to rhEPO for treatment of anemia associated with CKD in subjects who are starting dialysis

or who have recently started dialysis. Data from this trial are intended to support the use of daprodustat for the treatment of anemia in subjects initiating chronic dialysis.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
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 (tested for superiority, adjusted for multiplicity)	
To compare daprodustat to rhEPO on the use of intravenous (IV) iron	1. Average monthly IV iron dose (mg)/subject from baseline to Week 52
Safety	
To compare the safety and tolerability of daprodustat to rhEPO	<ul style="list-style-type: none"> Incidence and severity of AEs and SAEs including those AEs of special interest Reasons for discontinuation of randomized treatment Absolute values and changes from baseline in laboratory parameters, blood pressure, and heart rate

Secondary and exploratory objectives/endpoints are listed in [Appendix 2](#).

4. STUDY DESIGN

4.1. Overall Design

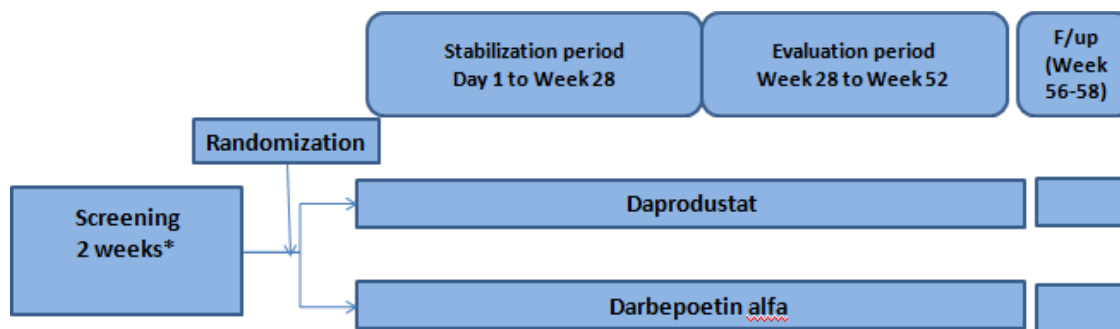
- This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center study in subjects with anemia associated with CKD who are not regularly using routine erythropoiesis-stimulating agent (ESA) users and who are initiating dialysis.
- The study will comprise three study periods: a screening period (2 weeks*), a 52-week active treatment period, and a follow-up period (4-6 weeks) ([Figure 1](#)). 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.

- 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.
- Limited ESA use is allowed around the time of dialysis initiation only (see [Section 5.3](#) for definition of “limited use”).
- The treatment period consists of :

- 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.
- 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.
- 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); all randomized treatments (Section 6.1) will be supplied by GSK.
- To ensure consistency of treatment across the study there are protocol-mandated algorithms for dose adjustments of daprodustat and rhEPO (Section 6.2), iron management (Section 6.10) and anemia rescue therapy (Section 6.11)
- An overview of the study design is provided in Figure 1.

Figure 1 Study Schematic



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

4.2. Type and Number of Subjects

The study will enroll the following types of subjects with anemia associated with CKD:

- **Planned:** Subjects who are planning to start dialysis (HD or PD) within the next 2-4 weeks (from the day of screening).
- **Unplanned (urgent):** For Subjects who have started chronic dialysis in an urgent manner, meaning they started HD with a temporary vascular access with no previous planning for chronic dialysis or have started PD with recent (< 2 weeks) PD catheter insertion and/or who have not been seen by a kidney specialist

(nephrologist) or other specialist with expertise in dialysis care within previous 4 months prior to screening.

Based on an assumed screen failure rate of 37%, approximately 475 subjects are expected to be screened in order to randomize approximately 300 subjects, or 150 subjects per treatment group. The study will be conducted globally.

4.3. Design Rationale

This study includes a screening period where iron supplementation is permitted, so that subjects who are not iron replete can meet iron status entry criteria prior to randomization.

The study will include subjects who are planning to start dialysis imminently, have already recently started dialysis in a planned manner, and those who start dialysis urgently. This broad range of subjects will provide data on the effects of daprodustat in subjects starting dialysis as well as data on whether there are differences between planned and unplanned (urgent) starts.

Although subjects will be rhEPO non-users, because it is routine medical practice to begin treatment with rhEPO around the time of dialysis initiation if subjects have anemia (Hgb <11 g/dL), the protocol will allow limited rhEPO use during the four weeks before or after starting dialysis (Section 5.2).

The stabilization period from Day 1 to Week 28 allows subjects to have their randomized treatment dose titrated to achieve the Hgb target range. This period of time provides the opportunity for subjects to be titrated to their optimal dose of randomized treatment prior to the efficacy EP (Weeks 28 to 52). Some subjects may still need dose titration during the EP.

The selection of the rhEPO control (darbepoetin alfa) is based on feasibility and clinical practice in the majority of participating countries.

The study is open-label (sponsor blind) because it would be complex to double-blind due to the differing number of dose steps and different modes of administration (oral vs. injection) between randomized treatments

4.4. Dose Justification

Starting doses, dose steps, and elements of the dose adjustment scheme are provided in Section 6.2 and [Appendix 3](#).

4.4.1. Daprodustat

Daprodustat starting doses are assigned based on Hgb at study entry, and were selected such that the target Hgb concentration would be reached after approximately one red blood cell lifespan of treatment (up to 90 days, pharmacodynamic steady-state). However, due to the between-subject variability in Hgb response to a given dose of daprodustat and the relatively narrow Hgb target range, individual dose adjustments of

daprodustat are expected during the first few months of treatment. If an individual dose adjustment is made, subjects will increase or decrease the daprodustat dose through a series of dose steps, one dose step at a time. The highest dose of daprodustat in the dose adjustment scheme is 24 mg once daily.

The daprodustat starting doses and dose steps were selected for this study based on exposure-response longitudinal modeling of Hgb data collected across the Phase 2 program. Covariate analyses elucidated that baseline Hgb, body-weight, and prior ESA dose (if applicable) were the most relevant covariates of Hgb response to daprodustat.

4.4.2. Randomized Treatment Dose Adjustment Scheme

A randomized treatment dose adjustment algorithm was designed to minimize unnecessary dose adjustments by allowing for visit-to-visit variability, and it is informed by the change in Hgb from the previous visit when evaluating the need for a dose adjustment (Section 6.2.3).

4.5. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with daprodustat can be found in the daprodustat Investigator's Brochure (IB) and IB supplement(s) (if applicable).

4.5.1. Risk Assessment

The potential risks of clinical significance, including adverse events of special interest (see Section 7.4.4 for details), and the mitigation strategies for this protocol taking into account the results of completed clinical and nonclinical studies with daprodustat are outlined in Appendix 4. In addition to the mitigation strategies outlined, an Independent Data Monitoring Committee (IDMC) will monitor accruing safety data for this trial (Section 10.8.1).

4.5.2. Benefit Assessment

In clinical trials of up to 24 weeks in duration, in subjects with anemia associated with CKD, daprodustat has been shown to treat Hgb to target range. Daprodustat may present several important advantages over rhEPO and other ESAs. It is an oral medication and does not require cold-chain storage as does rhEPO, thus increasing ease of use for patients and health care providers. After administration of daprodustat, data suggest that the increases in Hgb are achieved with EPO exposure lower than those observed with rhEPO. Treatment of anemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated supra-physiological increases in EPO exposure with rhEPO [Szczzech, 2008]; therefore, daprodustat has the potential to raise Hgb without the same CV risk associated with rhEPO. Other potential benefits include possibly improving iron availability for erythropoiesis, the potential to successfully treat rhEPO hyporesponders, and the potential to treat anemia without causing rhEPO-induced hypertension.

4.5.3. Overall Benefit:Risk Conclusion

Daprodustat demonstrates a positive benefit vs. risk based on the evidence as follows. In clinical trials up to 24 weeks in duration, daprodustat treats Hgb to target range, and there are no adverse events that have been identified as related to treatment with daprodustat.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (See [Appendix 4](#) for details). Given these precautions, as well as the potential benefit that daprodustat holds for the treatment of anemia associated with CKD compared to the current standard, the overall benefit risk balance is considered to be positive.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information about warnings, precautions, contraindications, AEs, and other pertinent information is provided in the daprodustat IB, IB supplement(s) (if applicable), the product label for darbepoetin alfa, and other pertinent documents (e.g., Study Reference Manual [SRM], informed consent).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply at screening and randomization (Day 1) unless otherwise specified.

1. **Age (confirm at screening):** 18 to 99 years of age inclusive
2. **Dialysis:** Planning to start chronic dialysis within the next 4 weeks (from the date of the screening visit) OR have started and received dialysis (as specified below) for end-stage renal disease for a maximum of ≤90 days immediately prior to randomization and is not expected to stop dialysis during the duration of the trial:
 - HD ≥2X/week, or
 - Daily PD (Including continuous and automated PD)
3. **Hemoglobin concentration as measured by HemoCue (range inclusive):** 8-10.5 g/dL (5-6.5 mmol/L) at screening and 8-11.0 g/dL (5-6.8 mmol/L) at randomization
4. **Informed consent:** capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol

Note: The country-specific requirements for France ONLY for the informed consent process is provided in [Appendix 11](#) (see Section 12.11.1, Item 3 for details)

5. **Other study eligibility criteria considerations:** The country-specific requirements for France ONLY for the eligibility for inclusion in this study is provided in [Appendix 11](#) (see Section 12.11.1, Item 1 for details)

5.2. Exclusion Criteria

A subject will not be eligible for participation in this study if any of the following criteria apply at screening or at randomization (Day 1), unless otherwise specified.

CKD-related criteria

1. **Kidney transplant:** Planned living-related donor kidney transplant during the study.

Anemia related criteria

2. **Ferritin:** ≤ 100 ng/mL (≤ 100 μ g/L) at screening or after IV iron supplementation.
3. **TSAT:** $\leq 20\%$ at screening or after IV iron supplementation.
4. **Vitamin B12:** Below the lower limit of the reference range at screening or after vitamin B12 supplementation
5. **Folate:** < 2.0 ng/mL (< 4.5 nmol/L) at screening
6. **Aplasias:** History of bone marrow aplasia or pure red cell aplasia (PRCA).
7. **Other causes of anemia:** Pernicious anemia, thalassemia major, sickle cell disease, or myelodysplastic syndrome.
8. **Gastrointestinal (GI) bleeding:** Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding ≤ 10 weeks prior to screening through to randomization (Day 1).

Erythropoiesis treatment criteria

9. Use of any **ESA** treatment within 8 weeks prior to screening except for limited use as part of dialysis initiation.

Limited use is defined as no more than 6 weeks of short acting ESA (rhEPO or biosimilars; maximum of 20000 U total) or long acting ESA (darbepoetin alfa [maximum of 100 μ g total] or methoxy polyethylene glycol-epoetin beta [maximum of 125 μ g total]) received before or after starting dialysis.

Cardiovascular disease-related criteria

10. **Myocardial infarction or acute coronary syndrome:** ≤ 10 weeks prior to screening through to randomization (Day 1).
11. **Stroke or transient ischemic attack:** ≤ 10 weeks prior to screening through to randomization (Day 1).
12. **Heart failure:** Chronic Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system.
13. **Current uncontrolled hypertension:** Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of rhEPO.

14. **QTcB (Day 1):** QTcB >500 msec, or QTcB >530 msec in subjects with bundle branch block. There is no QTc exclusion for subjects with a predominantly paced rhythm

Other disease-related criteria

15. **Liver disease (any one of the following):**

- Alanine transaminase (ALT) >2x upper limit of normal (ULN) (screening only)
- Bilirubin >1.5xULN (screening only)

NOTE: Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.

- Current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

NOTE: Stable chronic liver disease (including asymptomatic gallstones, chronic hepatitis B or C, or Gilbert's syndrome) are acceptable if subject otherwise meets entry criteria.

16. **Malignancy:** History of malignancy within the 2 years prior to screening through to randomization (Day 1), or currently receiving treatment for cancer, or complex kidney cyst (i.e. Bosniak Category II F, III or IV) > 3cm. The only exception is localized squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥10 weeks prior to screening.

Concomitant medications and other study treatment-related criteria

17. **Severe allergic reactions:** History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (refer to daprodustat IB) or to darbepoetin alfa (refer to product labelling)
18. **Drugs and supplements (randomization only):** Use of strong CYP2C8 inhibitors (e.g., gemfibrozil) or strong CYP2C8 inducers (e.g., rifampin/rifampicin).
19. **Prior investigational product exposure:** Use of an investigational drug (other than daprodustat – see next criterion) ≤30 days or within five half-lives of the investigational agent, whichever is longer prior to screening.
20. **Prior treatment with daprodustat:** Any prior treatment with daprodustat for treatment duration of > 30 days.

General health-related criteria

21. **Females ONLY:** Subject is pregnant [as confirmed by a positive serum human chorionic gonadotropin (hCG) test for females of reproductive potential (FRP) only], subject is breastfeeding, or subject is of reproductive potential and does not agree to follow one of the contraceptive options in the List of Highly Effective Methods for Avoiding Pregnancy listed in [Appendix 5](#).

22.Other Conditions: Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (e.g., intolerance to rhEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized. In this study, subjects can become a screen failure at any time from the screening visit to the Day 1 visit prior to randomization.

Documentation of a minimum set of information on screen failure subjects must be collected from subjects that fail screening, including demography, screen failure details, eligibility criteria, and serious adverse events (Section 7.4.3.4).

Subjects that fail screening are eligible to be rescreened once as soon as the investigator assesses they may meet study entry criteria. If subjects are rescreened, they must sign a new informed consent form.

5.4. Subject Retention

- Subjects will be educated on the importance of remaining in the study and attending scheduled study visits.
- Investigators should make every effort to keep subjects in the trial.
- Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject.

5.5. Permanent Discontinuation of Randomized Treatment

Every effort should be made to keep subjects in the study including those who permanently stop randomized treatment. A subject may permanently discontinue randomized treatment at any time at his/her own request, or at the discretion of the investigator for safety, or compliance reasons. A subject must permanently discontinue randomized treatment for the pre-specified reasons below:

- Kidney transplant
- Reaching criterion to receive rescue (Section 6.11)
- Becomes pregnant or intends to become pregnant during the study
- Liver chemistry abnormalities exceeding the threshold criteria (Section 7.4.12)

- Diagnosis of cancer (new or recurrent), with the exception of localized dermal squamous cell or basal cell carcinoma
- Need for chronic (more than 14 days) use of a prohibited medication (Section 6.9.2)

In all cases, the reason for randomized treatment discontinuation and the date of the last dose will be recorded in the subject's electronic case report form (eCRF) and the subject will continue in the study as described in Section 5.5.1.

5.5.1. Procedures for Subject Follow-up

Subjects who permanently discontinue randomized treatment will be asked to attend an Early Treatment Discontinuation visit and will be expected to attend in-clinic study visits through to Follow-up according to the study visit schedule, unless consent is actively withdrawn. Complete details are provided in Table 7 in Section 7.1.

- Early Treatment Discontinuation visit: This visit should occur within 2 weeks of the last dose of randomized treatment. This visit supersedes the scheduled study visit if the visit falls on the same date as a scheduled study visit.
- Remaining in-clinic visits*:
 - Day 1 through Week 52: Study visits every 12 weeks \pm 2 weeks post Early Treatment Discontinuation visit.
 - Follow-up: Study visit 2 to 4 weeks after Week 52.

*Phone visit acceptable in exceptional circumstances.

- In all cases, reasons for Early Treatment Discontinuation and the date of last dose will be recorded.
- If a subject does not agree to continue attending in-clinic or phone visits, other follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the subject, then the subject will be considered to have remained in the study and not to have withdrawn consent.

5.6. Withdrawal from Study

Every effort should be made to keep subjects in the study. For subjects that choose to withdraw consent or are lost to follow up, the reason for not completing the study will be recorded in the subject's eCRF.

If a subject withdraws from the study, he/she may request destruction of any clinical samples taken, and the investigator must document this in the site study records.

5.6.1. Withdrawal of Consent for Contact

Specific wording is included in the informed consent form which permits subjects to discontinue randomized treatment and study procedures, but states an expectation that follow up information will always be required. Subject will agree to this at the time of consenting.

Withdrawal of consent from the study is expected to be a rare occurrence. If a subject withdraws consent from the study, the Investigator will review the following contact options with the subject:

- In-clinic and phone visits
- Follow-up via medical records review and/or other treating physician
- Follow-up via family member or other third party contact

If all of these options are refused, then no further study visits or study-related telephone contact will be conducted and the subject will be considered to have withdrawn consent. The principal investigator will be required to document that all alternative options have been reviewed with the subject.

For these subjects, information regarding study outcomes or vital status will continue to be collected from available sources including those in the public domain based on accepted local laws and regulations. Where permitted, a third party may be used to obtain information.

5.6.2. Subjects Deemed Lost to Follow-up

- Investigators should make every effort to contact subjects who are deemed lost to follow-up and who have not withdrawn consent to follow-up contact.
- As permitted by local regulations, a third party may be used to locate alternative subject contact information that will be provided to the investigator. All attempts to contact subjects will be documented in the subject's eCRF and source notes and a final status contact will be recorded in the eCRF.

5.7. Subject and Study Completion

A completed subject is one who has completed all periods of the study through the End of Treatment visit.

6. RANDOMIZED TREATMENT

6.1. Investigational Product and Other Randomized Treatment

The term ‘randomized treatment’ is used throughout the protocol to describe any product (i.e., daprodustat or darbepoetin alfa during the treatment period) received by the subject as per the protocol design.

During the treatment period, iron therapy (supplied locally) will be administered as per the iron management criteria (Section 6.10).

Daprodustat will be supplied as film coated tablets for oral administration containing 1, 2, 4, 6, 8, or 10 mg of daprodustat. Doses of 12, 16, and 24 mg of daprodustat will be provided using multiples of these tablet strengths. The doses, tablet size, and description are provided in (Table 1).

Table 1 Description of Daprodustat Tablets

Tablet size	Dose	Description
7.0 mm	daprodustat 1 mg, 2 mg, 4 mg,	7.0 mm round, compound radius, white film coated tablets
9.0 mm	daprodustat 6 mg, 8 mg, 10 mg,	9.0 mm round, compound radius, white film coated tablets

Subjects will take daprodustat tablet(s) daily with water, and these tablets can be taken without regard to food.

GSK will supply rhEPO (darbepoetin alfa) for the control group. Darbepoetin alfa as prefilled syringes (PFS) for SC/IV injection. Doses from 20 µg to 400 µg will be administered using the strengths in Table 2.

Table 2 Description of Darbepoetin Alfa PFS

PFS Strengths	PFS Volume
40 µg	0.4 mL
60 µg	0.3 mL
100 µg	0.5 mL
150 µg	0.3 mL

6.2. Randomized Treatment Starting Dose, Dose Steps, and Dose Adjustments

6.2.1. Daprodustat Dosing Information

Daprodustat Starting Dose

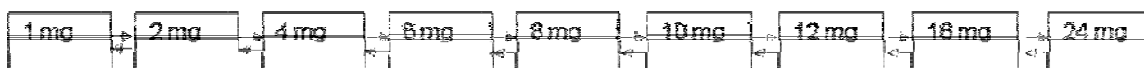
The starting dose of daprodustat will be assigned based on the HemoCue Hgb concentration at randomization (Day 1) (Table 3).

Table 3 Daprodustat Starting Dose (All Subjects)

HemoCue Hgb (g/dL) at Randomization (Day 1)	Daprodustat starting dose (mg, once daily)
≥8 to <9	4
≥9 to ≤10	2
>10	1

Daprodustat Dose Steps

The available dose steps of daprodustat are outlined below. Dose adjustments will result in the daprodustat dose being increased or decreased by one dose step at a time (see [Appendix 3](#), Section 12.3.2 for details). Those receiving the highest dose of daprodustat who require a dose increase will maintain the same dose, while those receiving the lowest dose of daprodustat that require a dose decrease will have doses withheld.



6.2.2. rhEPO Dosing Information

Darbepoetin alfa Starting Dose

For subjects starting HD or PD, the SC/IV darbepoetin alfa total weekly dose will be 0.75-1.0 µg/kg rounded to the nearest available dose. Detailed information is provided in [Table 4](#).

Table 4 Darbepoetin Alfa Starting Dose

Weight	Darbepoetin Alfa Starting Dose
<60 kg	40 µg every 4 weeks
≥ 60 kg to <90 kg	60 µg every 4 weeks
≥90 kg to < 120 kg	40 µg every 2 weeks
≥ 120 kg	60 µg every 2 weeks

Darbepoetin alfa Dose Steps

Dose adjustments will be made programmatically by the IRT system.

Dose-steps and frequency of administration of darbepoetin alfa are pre-defined in this study ([Appendix 3](#), Section 12.3.1). The SC or IV darbepoetin alfa dose adjustment increases and decreases are generally within 20% and 33% range, with a few increases of 50% based on available dose strengths.

Additional information about the delivery of the respective rhEPO doses is provided in the SRM. Those receiving the highest dose of rhEPO who require a dose increase will

maintain the same dose, while those receiving the lowest dose of rhEPO that require a dose decrease will have doses withheld as per the randomized treatment (daprodustat and darbepoetin alfa) dose adjustment algorithm in [Appendix 3](#).

6.2.3. Daprodustat and rhEPO Dose Adjustment Algorithm

Dose adjustments will be made programmatically by the Interactive Response Technology (IRT) system to maintain Hgb concentrations within the range of 10-11 g/dL based on the Hgb value measured every 2 to 4 weeks by the HemoCue value disclosed to the IRT system by the investigator.

The protocol-specified randomized treatment (daprodustat or rhEPO) dose adjustment algorithm is provided in [Appendix 3](#).

6.3. Blinding

This is an open-label study; however, the sponsor is blinded to randomized assignment. A detailed Blinding Plan will describe the procedures that will be implemented in order to minimize the extent to which this blind may be compromised.

6.4. Packaging and Product Labeling

Daprodustat tablets are packed in white, opaque high density polyethylene (HDPE) bottles with child-resistant closures. The contents of the label will be in accordance with all applicable regulatory requirements. Randomized treatment will have the dose strength on the label.

6.5. Preparation/Handling/Storage/Accountability

No special preparation of randomized treatment is required.

Only subjects enrolled in the study may receive randomized treatment and only authorized site staff may supply randomized treatment. All randomized treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for randomized treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

Further guidance and information for final disposition of unused randomized treatment are provided in the SRM.

Under normal conditions of handling and administration, randomized treatment is not expected to pose significant safety risks to site staff.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Randomized Treatment Administration

Randomized subjects who administer randomized treatment (daprodustat or rhEPO) at home will be instructed to return all unused randomized treatment at each clinic visit. A record of the number of daprodustat tablets or rhEPO doses dispensed to and taken by each subject will be maintained and reconciled with randomized treatment and compliance records. Randomized treatment start and stop dates and dosing details, including dates for randomized treatment interruptions and/or dose increases or reductions, will be recorded in the eCRF. At Week 2 and for unscheduled visits, compliance checking will not be performed if the dose of randomized treatment is not changed.

Subjects randomized to rhEPO, who have randomized treatment administered in the clinic, will have the details of each administered rhEPO dose maintained and reconciled with randomized treatment and compliance records. Randomized treatment start and stop dates and dosing details, including dates for randomized treatment interruptions and/or dose increases/reductions, will be recorded in the eCRF.

6.7. Treatment of Randomized Treatment Overdose

There is no specific antidote for overdose with daprodustat. The expected manifestations of daprodustat overdosage include signs and symptoms associated with an excessive and/or rapid increase in Hgb concentration.

Daprodustat is highly protein bound, thus clearance of daprodustat by HD or PD is very low so dialysis is not an effective method to enhance the elimination of daprodustat. Daprodustat metabolites are, in part, cleared via hemodialysis. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted, as dictated by the subject's clinical status. Additionally, subjects should be monitored closely for cardiovascular (CV) events, increased heart rate and hematologic abnormalities.

Consult the approved product label for information on overdose for rhEPOs.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study.

The investigator is responsible for ensuring that consideration has been given to post-study care of the subject's medical condition.

6.9. Concomitant Medications

Concomitant medications, including over-the-counter medications and supplements, taken during the study will be recorded in the eCRF. Start/stop dates and route of administration will be recorded for general concomitant medications. Additional details (e.g., changes in dose, reason for change, reason for addition and termination) will be

recorded for certain medications at each visit (i.e., iron and anti-hypertensive medications).

6.9.1. Permitted Medications

Unless specified as a prohibited medication in Section 6.9.2, all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferiasirox) should be performed with caution.

6.9.2. Prohibited Medications

Use of any of the following prescription drugs from screening until 7 days after the last dose of randomized treatment is prohibited and will constitute a protocol violation.

- Strong inhibitors of CYP2C8 (e.g., gemfibrozil)
- Strong inducers of CYP2C8 (e.g., rifampin/rifampicin)

6.10. Iron Management Criteria

Subjects must remain iron replete throughout the study.

Iron therapy will be administered if ferritin is ≤ 100 ng/mL and/or TSAT is $\leq 20\%$. The investigator should choose the route of administration and dose of iron based on the subject's iron status and local clinical practice.

All iron (excluding multivitamins) must be stopped and cannot be administered if:

- Ferritin > 800 ng/mL and TSAT $> 20\%$, or
- TSAT $> 40\%$

Investigators should be guided by local/regional guidelines and may stop administration of iron at a lower ferritin or TSAT level as long as subjects are maintained at a ferritin > 100 ng/mL and TSAT $> 20\%$.

The Steering Committee (Section 10.8.3) will monitor blinded subject iron data in an ongoing fashion to ensure compliance.

6.11. Anemia Rescue Therapy

A rescue algorithm is provided to minimize subjects having an inadequate response to the treatment for their anemia for an extended period of time and to enable consistency in the application of rescue therapy across the study. Details are provided in Table 5.

This rescue algorithm does not apply to subjects with a decrease in Hgb as a result of an acute or sub-acute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or vascular access). In these cases, treatment should be directed to the specific

cause AND randomized treatment will be continued. If a subject is transfused as part of the treatment, then the randomized treatment will be maintained at the current dose (unless Hgb is ≥ 12 g/dL which requires a dose hold).

Table 5 Rescue Algorithm for Anemia Management

Evaluate Subject for Rescue if: HemoCue Hgb remains <9 g/dL despite three ¹ consecutive dose increases above the starting dose or post-rescue ² (where HemoCue Hgb <9 g/dL prior to each dose increase) OR HemoCue Hgb is <7.5 g/dL despite a dose increase at the prior study visit.	
Step 1: Initial Intervention	While continuing randomized treatment (increase dose if HemoCue Hgb <7.5 g/dL; otherwise maintain current dose), intervene with one or more of the following as dictated by clinical comorbidities: <ul style="list-style-type: none"> -Single course of IV iron up to 1000 mg (in addition to the iron management criteria) -Transfusion of up to two units of packed red blood cells (PRBC) if clinically indicated -Allow additional 4 weeks on randomized treatment (NOTE: this is a required choice; can be combined with either or both of the above)
Step 2: Rescue	Check HemoCue Hgb 4 weeks ± 1 week from last study visit; earlier checks of Hgb may be obtained to advise further intervention as clinically indicated. Randomized treatment should be permanently discontinued and the subject should be rescued according to local clinical practice if either, <ul style="list-style-type: none"> -HemoCue Hgb remains <9 g/dL despite initial intervention based on the average of two HemoCue Hgb values³ OR - More than two units of PRBC were needed for transfusion (and was not related to acute bleeding).

1. Two consecutive dose increases if starting/post-rescue dose is daprodustat 12 mg or darbepoetin alfa 200 μ g over 4 weeks; one dose increase if starting/post-rescue dose is daprodustat 16 mg or darbepoetin alfa 300 μ g over 4 weeks; and no prior dose increase if starting/post-rescue dose is daprodustat 24 mg or darbepoetin alfa 400 μ g over 4 weeks (top dose).
2. For subjects who previously are evaluated for rescue and who are able to continue in the trial, "post-rescue" dose is the dose of randomized treatment that a subject is receiving at the study visit after initial intervention.
3. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample); take average of 2 values.

6.12. Subjects Changing Dialysis Modality

Subjects changing dialysis modality should not be withdrawn from the study, but should continue on the same randomized treatment (daprodustat or darbepoetin alfa).

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Time and Events Tables are provided for subjects receiving randomized treatment ([Table 6](#)) and for subjects who permanently discontinue randomized treatment ([Table 7](#)).

Because Hgb levels become more variable with increased time between dialysis sessions, the designated study visit should occur during the dialysis session with the shortest interval from the previous session. Study visit days should be scheduled as follows:

- For subjects on 3X/week HD: The designated study visit must not occur on the first dialysis session of the week. For example, if on a Monday-Wednesday-Friday schedule, the study visit should be on Wednesday or Friday.
- For subjects on PD: study visits can occur on any day of the week.
- For subjects on 2X/week HD: The visit should occur during the session that is closest to the previous HD session. For example, if a subject receives dialysis on a Monday and Thursday, the study visit should be on the Thursday (2 days from the previous dialysis session) rather than the Monday (3 days from the previous dialysis session).

Details regarding study-specific equipment are provided in [Appendix 7](#).

Post-randomization visits should be referenced back to the Randomization visit (Day 1). The visit window specified for those on randomized treatment is ± 1 week. However, to ensure continuity of randomized treatment, study visits should be no more than 5 weeks apart. In exceptional circumstances, minor changes to visit structure may be permitted after consultation with the PPD/GSK Medical Monitor.

Study assessments should preferably be done at dialysis centers, however, in some circumstances assessments can be performed at the research site.

Supplementary study conduct information is provided in the SRM. The SRM provides administrative and detailed technical information that does not impact subject safety.

7.1. Time and Events Tables and Procedures for Subject Follow-up

Table 6 TIME AND EVENTS TABLE FOR SUBJECTS ON RANDOMIZED TREATMENT

Protocol Activity (visits \pm 1 week) (Note: All visit timings are relative to Day 1)	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
IRT system call	X	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						
Ultrasound of kidneys and adrenal glands	X ⁴							
Randomized treatment dispensing		X		X	X	X	X ^{5,6}	
Randomized treatment compliance			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	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
Vitamin B12 ¹ , folate	X							
Hepcidin		X		X		X		X
iPTH		X		X		X		X
Storage biomarkers		X		Wk 28		X		
Kt/V _{urea} for dialysis adequacy ¹⁰				X		X		

Protocol Activity (visits \pm 1 week) (Note: All visit timings are relative to Day 1)	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
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		
Hospitalization / kidney transplant (record in eCRF, if applicable)			X	X		X		X
Non-serious AEs, SAEs, AEs of Special Interest, MACE	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 Section 5.2. HemoCue Hgb, ferritin, TSAT, and vitamin B₁₂ must be re-assessed 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 taken in triplicate. Measurements will be taken post-dialysis for subjects receiving in-center dialysis. See Section 7.4.8.
3. All ECGs assessments must be recorded pre dialysis.
4. Ultrasound of the kidneys and adrenal glands must be performed prior to randomization. The screening period may be extended up to 2 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 Section 7.4.10.
5. Additional visits to check Hgb and dispense randomized treatment are required under the circumstances described in 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 Appendix 5) during the study pregnancy tests are no longer required.
9. Testing panel in Table 8. 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 only from subjects randomized to the daprodustat arm, at 1 of these 3 visits, Details in 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.

Table 7 TIME AND EVENTS TABLE FOR SUBJECTS THAT PERMANENTLY DISCONTINUE RANDOMIZED TREATMENT

Protocol Activity	Early Treatment Discontinuation Visit (within 2 weeks of the last dose of randomized treatment)	Day 1 – Week 52 (every 12 weeks \pm 2 weeks)	Unscheduled	Follow-up (4 weeks post-study termination \pm 1 week)
Dialysis: In-clinic assessments done pre-dialysis.				
IRT SYSTEM call	X	X	X	X
SBP/DBP ¹ , HR ¹	X (triplicate)	X	X	X
Iron therapy, transfusions ²	X			
Rescue medication ^{2,3}	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, MACE	X	X	X	X
Review concomitant medications	X	X	X	X
CKD Anemia Symptoms Questionnaire (CKD-AQ) questionnaire ⁵ , PGI-S ⁵ , PGI-C ⁵	X			
SF-36 ⁵ , EQ-5D-5L ⁵	X			

1. See Section 7.4.8 for details.
2. Record in eCRF, if applicable
3. See details on Rescue in Section 6.11.
4. Subjects who are unable to or require assistance to read must not complete the questionnaires.

7.2. Screening and Critical Baseline Assessments

Before any study-specific procedure is performed, valid informed consent must be obtained.

Demography and medical history will be assessed at the initial screening visit.

Randomization requires an Hgb level within the specified range (Section 5.1) and levels of serum ferritin or TSAT as outlined in Section 5.2.

Full details of screening and baseline (Day 1) assessments are provided in the Time and Events Table (Table 6).

7.3. Efficacy

Planned time points for all Hgb efficacy assessments are listed in the Time and Events Table ([Table 6](#)).

GSK will supply a point-of-care Hgb analyzer (i.e., HemoCue) to each site for rapid measurement of Hgb.

Blood samples (not fingersticks) for measurement of Hgb via HemoCue and also by the central laboratory will be collected and specified in the Time and Events Table ([Table 6](#)) and the collection will be recorded in the eCRF.

7.4. Safety

Safety endpoints will include monitoring of deaths, AEs, SAEs, other CV events, AEs of special interest, AEs leading to discontinuation of randomized treatment, and laboratory parameters, blood pressure and heart rate (HR).

Planned time points for all safety assessments are listed in the Time and Events Table ([Table 6](#)). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

7.4.1. Events Referred to the Clinical Event Committee (CEC)

Investigators should refer any event suspected to be one the following MACE events to the CEC. The CEC will review and adjudicate the following clinical events:

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

Events referred to the CEC will be subjected to blinded adjudication using pre-specified diagnostic criteria.

When the investigator-reported event and the CEC assessment of the event differ, the CEC's decision will be considered final. The detailed descriptions of the endpoint definitions used for adjudication are contained within the CEC Charter (available on request).

Source documentation required to support the adjudication of the events is described in the SRM.

7.4.2. Other CV Events

GSK has identified other CV events of interest for all clinical studies. Investigators will be required to fill out the specific CV event page of the eCRF for the following categories of events:

- Arrhythmias
- Pulmonary hypertension*
- Valvulopathy
- Revascularization

(Pulmonary hypertension is also an AE of special interest for the current study, see Section 7.4.4 for details.)*

7.4.3. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE and SAE can be found in [Appendix 8](#).

The investigator or their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.3.1. Time period and Frequency for collecting AE and SAE information

Any SAE assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

AEs will be collected from the start of randomized treatment until the Follow-up visit, at the timepoints specified in the Time and Events Table ([Table 6](#)).

Medical occurrences that begin prior to the start of randomized treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF.

All SAEs will be recorded and reported to PPD within 24 hours, as indicated in [Appendix 8](#).

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the randomized treatment or study participation, the investigator must promptly notify PPD.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to PPD are provided in [Appendix 8](#).

7.4.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.4.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.6.2). Further information on follow-up procedures is given in [Appendix 8](#).

7.4.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to PPD of SAEs related to randomized treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.4. Adverse Events of Special Interest

The investigator or site staff will be responsible for detecting, documenting and reporting any event that may represent the AEs of special interest listed below (using preferred terms):

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis

- Death, myocardial infarction, stroke, heart failure, venous thromboembolism, 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

The results of any investigation should be recorded in the relevant sections of the subjects' eCRFs.

7.4.5. Possible Suicidality Related Adverse Events

If during the study there is an occurrence of an AE or SAE which in the investigator's opinion, is possibly related to suicidality, the Possible Suicidality Related Adverse Events (PSRAE) eCRF form should be completed (in addition to the AE and SAE pages, as appropriate).

This event may include, but is not limited to, one that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly related to suicidality.

7.4.6. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until 7 days after the last dose.

If a pregnancy is reported, the investigator should inform PPD within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 9](#).

7.4.7. Height and Weight

Height and weight will be measured as specified in the Time and Events Table ([Table 6](#)). Weight will be measured in clinic with the subject wearing indoor daytime clothing with no shoes. For HD subjects, this will be measured pre and post dialysis. For PD subjects these assessments will be done between treatments.

Estimated dry (target) weight will be calculated at each study visit as specified in the Time and Events Table ([Table 6](#)).

7.4.8. Blood Pressure and Heart Rate

Measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) will be taken at the time points specified in the Time and Events Table ([Table 6](#)).

- One measurement each of SBP, DBP and HR will be taken, except at Day 1, Week 52, and the Early Treatment Discontinuation visit (if applicable), when SBP, DBP and HR will be measured in triplicate.
- Measurements will be taken with the subject in a semi-supine or seated position in the dialysis chair after at least a 5-minute rest period (pre- and post-dialysis).

For HD subjects, SBP, DBP and HR will be measured pre and post-dialysis. For PD subjects these assessments will be done between treatments. Pre-dialysis measurements will be taken prior to blood sample collection.

7.4.9. Electrocardiogram (ECG)

ECG measurements will be taken at the time points specified in [Table 6](#) and must be recorded pre dialysis. Full 12-lead ECGs will be recorded with the subject in a supine position. Heart rate, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcB will be calculated (machine-read or manually).

At the Day 1 visit when ECGs are performed, two additional ECGs are required if the initial ECG indicates prolonged QTc using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility (Section [5.2](#), item [14](#) for detail). Additional details are provided in the SRM.

ECG data will be read locally.

All ECGs will be performed before measurement of SBP, DBP, HR (in-center HD only) and before collection of blood samples for laboratory testing.

7.4.10. Ultrasound

An ultrasound of the kidneys and adrenal glands will be performed prior to randomization (Day 1). It is understood that the adrenal glands will not always be able to be visualized. Non-visualization of the adrenals is NOT a reason to exclude subjects from randomization. Further details are provided in the SRM.

A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria (Section [5.2](#)), provided the size and cyst category has been reported. If a more sensitive imaging study (e.g., MRI, CT) has been performed within this timeframe and a report is available, this may be used in place of the ultrasound.

7.4.11. Clinical Laboratory Assessments

All protocol required laboratory assessments, as defined in [Table 8](#), must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule ([Table 6](#)). Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's eCRF.

Refer to the SRM for appropriate processing and handling of samples.

All study-required laboratory assessments will be performed by a central laboratory with the exception of HemoCue Hgb which will be performed at the clinical site. The results of each HemoCue Hgb must be entered into the subject's eCRF.

Table 8 Protocol Required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count	<i>RBC indices:</i>	<i>WBC count with Differential</i>
	RBC count	MCV	Neutrophils
	Reticulocyte count	MCH	Lymphocytes
	Hgb	MCHC	Monocytes
	Hematocrit	RDW	Eosinophils
			Basophils
Clinical Chemistry¹	ALT	AST	Bilirubin (total and direct/indirect)
	Potassium (serum)	Urea (serum)	Albumin (serum)
	Calcium (total and albumin-adjusted)	Inorganic phosphate	Creatinine (eGFR CKD-EPI) ^{4,5}
Iron parameters	Serum iron	Ferritin	UIBC
	Hepcidin	TSAT	TIBC
Lipid parameters	Total cholesterol	LDL-C (direct)	HDL-C
Other laboratory tests	Serum hCG pregnancy test ²	Follicle stimulating hormone ³	Estradiol ³
	HemoCue Hgb	hsCRP	iPTH
	Stored sample (blood)	Vitamin B12	Folate

Abbreviations: WBC, white blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width, AST, aspartate transaminase; ALT, alanine transaminase; LDL-C, low density lipoprotein-C; HDL-c high density lipoprotein-C; UIBC, unsaturated iron binding capacity; TIBC, Total iron binding capacity; TSAT, Transferrin saturation; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; hCG, human chorionic gonadotropin; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in [Appendix 6](#).
2. For females of reproductive potential only.
3. Screening only. As needed in postmenopausal women where their menopausal status is in doubt (see Inclusion Criteria Section [5.1](#))
4. Detail on the regional specific calculation will be summarized in the SPM.
5. Creatinine and eGFR will only be tested and calculated at screening and randomization

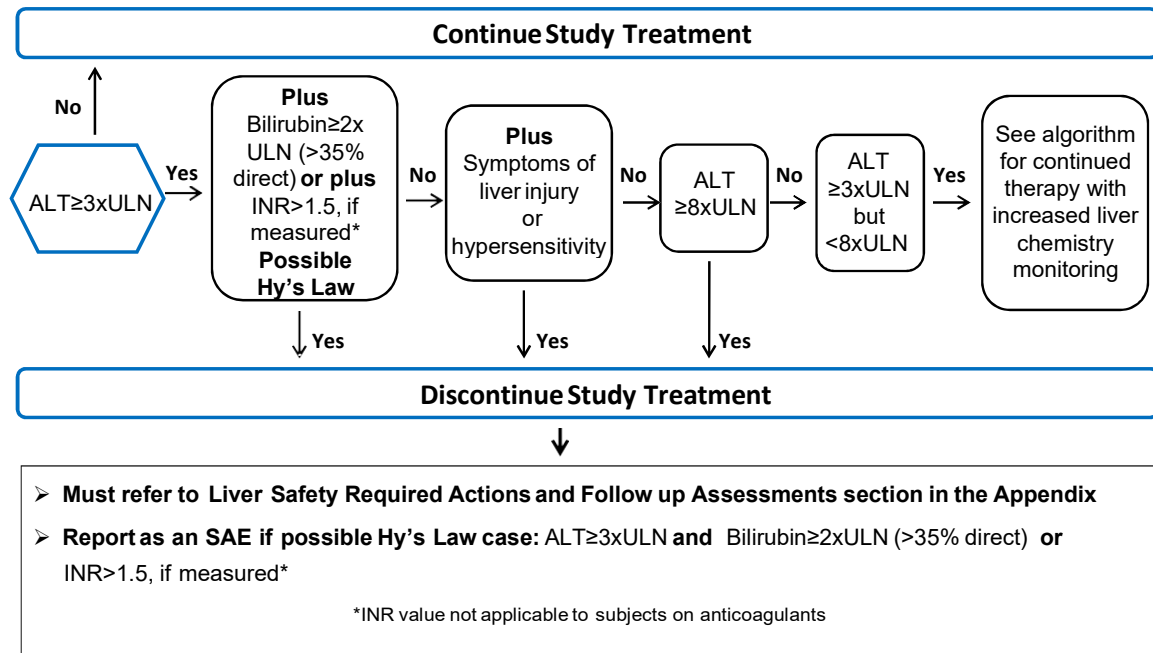
All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of randomized treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the Sponsor should be notified.

7.4.12. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

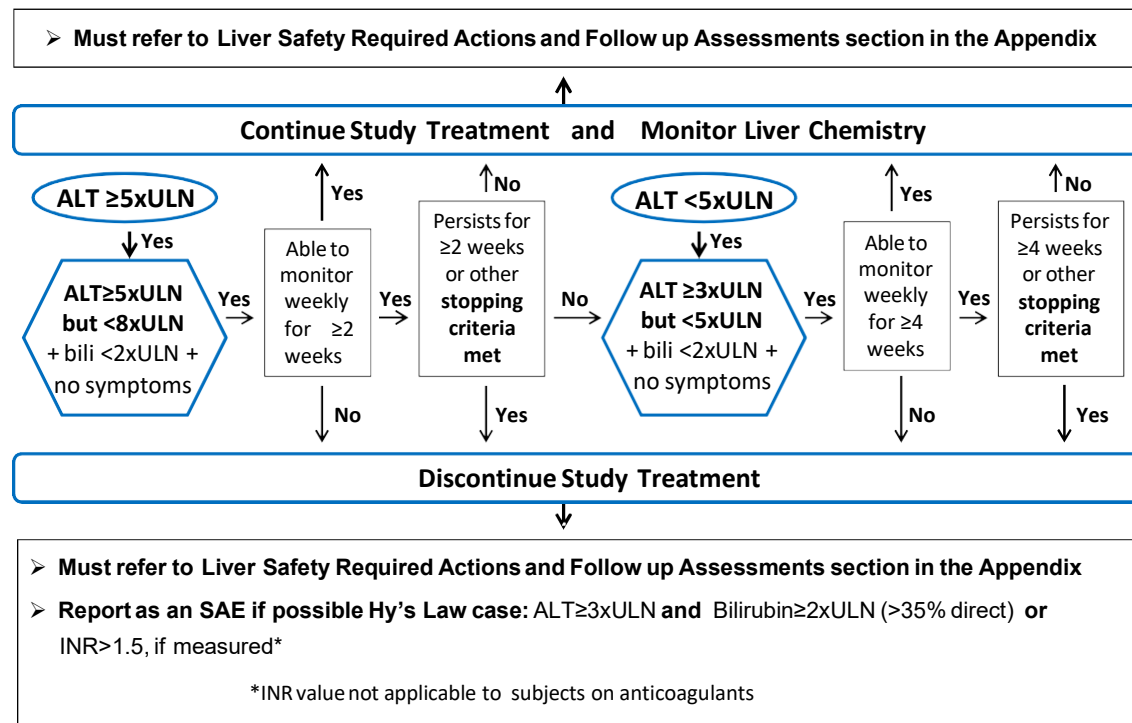
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Phase 3 Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 6](#).

Phase 3-4 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but < $8xULN$



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 6](#).

7.4.12.1. Randomized Treatment Restart

If a subject meets liver chemistry stopping criteria, do not restart randomized treatment unless there is a clear underlying cause for the liver stopping event other than drug-induced liver injury and:

- GSK Medical Governance approval **is granted in writing**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the subject

The full liver safety drug restart guideline is provided in [Appendix 6](#).

7.5. Pharmacokinetics (PK)

PK sampling will only be performed in in-center HD subjects randomized to the daprodustat arm.

Blood samples will be collected at the Week 4, Week 8 **or** Week 12 visit (i.e., PK is collected at one visit only, based on convenience for the subject/site). Samples will be collected at the following times relative to dosing of randomized treatment:

- Predose, 0.5, 1, 2, and 3 h post dose.

On the day of the scheduled PK visit:

- The subject is to be instructed **not** to take their dose at home before the visit, but to take the dose in the clinic after the predose sample is collected.
- The dose taken in the clinic should be from the same bottle(s) the subject has been using prior to the PK visit, **not** from any newly dispensed bottle(s) at the PK visit.
- Record the date and actual time of the dose taken in the clinic, and the date and actual time of all PK samples collected. Samples may be collected within ± 20 minutes of the planned collected time.
- Based on the time of dosing, samples may be obtained before, during, or after any dialysis procedure. The start and stop time of the dialysis procedure will also be recorded at this visit.

Plasma PK analysis will be performed under the control of GSK PTS-DMPK/Scinovo, the details of which will be included in the SRM. Concentrations of parent daprodustat and metabolites (GSK2391220 (M2), GSK2531403 (M3), and GSK2531401 (M13)) will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

7.6. Genetics

Information regarding genetic research is included in [Appendix 10](#). Samples for genetic analysis will be taken at the time points specified in the Time and Events Table ([Table 6](#)).

7.7. Patient Reported Outcomes

The patient-reported effect of daprodustat and rhEPO on symptoms, health-related quality of life (HR-QoL), and health status (e.g. utility) will be assessed. Symptoms will be assessed using a symptoms questionnaire which is specific to anemia of CKD (CKD-AQ). Overall symptom severity will be assessed using the patient global impression of severity (PGI-S) and overall symptom change using the patient global impression of change (PGI-C). Quality of life will be measured via SF-36, and health status via the EQ-5D-5L and EQ-5D-VAS.

All questionnaires used in this study have been translated and culturally adapted use in local country languages and will be administered electronically only. Specific instructions on how the subject is to complete the scales and the process for data entry is provided in the SRM. Details on patient reported outcomes are provided in the study procedure manual.

The CKD-AQ, PGI-S, PGI-C, HR-QoL, and Health Status questionnaires should be completed by subjects at a clinic visit, in the order specified: PGI-S, PGI-C, CKD-AQ, SF-36, EQ-5D 5L, and EQ-VAS. Subjects who are unable to or require assistance to read must not complete the questionnaires.

7.7.1. Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ)

A novel symptom questionnaire – CKD-AQ has been developed to collect concepts of interest for the anemia of CKD population over the past 24 hours. Unlike the Functional Assessment of Cancer Therapy – Anemia (FACT-AN) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) which have not demonstrated content validity specific for the anemia of CKD population, the novel CKD-AQ instrument was developed to verify and ensure that concepts specific for anemia of CKD were captured and measured. It will measure both the frequency and/or severity in anemia of CKD concepts such as weakness, energy, tiredness, shortness of breath, exertion, chest pain, memory, concentration, standing, sleep and distress over the past 7 days.

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

The Patient Global Impression of Severity (PGI-S) is a 1-item questionnaire designed to assess patient's impression of disease severity of their anemia of CKD. It is measured on a 5-point disease severity scale (absent, mild, moderate, severe, or very severe) during the past 24 hours.

The Patient Global Impression of Change (PGI-C) is a 1-item questionnaire designed to assess a subject's impression of symptom change of their anemia of CKD. It is measured 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) since they first started the study.

7.7.3. Health Related Quality of Life (SF-36)

The SF-36 acute version is a general health status questionnaire designed to elucidate the subject's perception of their health on several domains, including physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, and general health. The questionnaire contains 36 questions within these domains that ask the subject to recall how they felt during the past 7 days.

7.7.4. Health Status (EQ-5D-5L & EQ-VAS)

EQ-5D-5L consists of two concepts – the EQ-5D-5L descriptive system and the EQ-VAS. The EQ-5D-5L is a self-reported descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. Self-reported health status captured by EQ-5D-5L relates to the subject's situation at the time of completion. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'. This information is used as a quantitative measure of health outcome as judged by individual subjects.

7.7.5. Psychometric Analyses of the CKD Anemia Symptoms Questionnaire (CKD-AQ)

In order establish and evaluate the measurement properties of the CKD-AQ, a interim cut of blinded observations of the first 50 subjects who completed the week 52 visit will be taken. In order to establish content validity, the data cut will require a comparison to the following variables: PGI-C, PGI-S, Hgb, SF-36, demographic & baseline clinical characteristics. All data will be abstracted from screening until week 52.

The interim data cut will be used to conduct confirmatory factor analysis in order to establish a scoring algorithm for potential instrument domains and to evaluate the reliability, validity and responsiveness of the instrument without regard to treatment group. A full description of the data cut, variables of interest and analyses to establish the scoring and evaluate the measurement properties of the CKD-AQ will be specified *a priori* within the psychometric analysis plan.

7.8. Storage Biomarkers

Blood (serum and plasma) samples will be collected as outlined in the Time and Events Table ([Table 6](#)) for potential future analysis of CV risk and iron metabolism.

8. DATA MANAGEMENT

- For this study, subject data will be entered into eCRFs, transmitted electronically and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug, respectively.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Primary Hypotheses

The primary Hgb efficacy objective will assess the estimand defined as the comparative treatment effect in mean Hgb change between baseline and EP (i.e., Weeks 28 to 52 inclusive) in all randomized subjects; defined as those who remain in follow-up throughout the period of stabilization and have at least one Hgb assessment during the EP (i.e., Weeks 28 to 52) regardless of adherence to study treatment. The analysis will test whether daprodustat is non-inferior to rhEPO according to the following statistical hypotheses:

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

The non-inferiority margin is pre-defined as -0.75 g/dL; selected to be consistent across all clinical trials in the daprodustat Phase 3 clinical development program in subjects with anemia of chronic kidney disease, and 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 two-sided 5% level. An analysis of covariance (ANCOVA) model including randomization stratification factors, baseline hemoglobin and treatment will be used to obtain a point estimate and the 95% CI for the treatment difference (daprodustat-rhEPO) and generate the p-value for the non-inferiority test. The non-inferiority p-value will show strength of evidence against the null hypothesis. Non-inferiority will be established if the lower limit of the two-sided 95% CI for the treatment difference is greater than -0.75 g/dL.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The size of this study has been determined to be sufficient to meet the ICH E1 guideline for subject exposure, number and duration and to provide at least 90% power to test the primary non-inferiority hypothesis with a two-sided 95% CI.

Approximately 300 subjects are planned to be randomized (150 per arm) to receive daprodustat or rhEPO, to provide at least 100 subjects exposed to daprodustat for one year. Subjects will be treated to achieve and maintain Hgb between 10 and 11 g/dL. The expected difference in mean Hgb change from baseline and the EP, between arms, is 0 g/dL and the anticipated between subject standard deviation (SD) is 1.5 g/dL, based on historical rhEPO trials and daprodustat clinical trial experience to date. With a pre-specified non-inferiority margin of -0.75 g/dL, a two-sample T-test and assuming that up to approximately 30% of subjects will permanently stop randomized treatment before Week 28 (start of EP), 300 randomized subjects will provide >90% power to test the primary hypothesis.

With 300 randomized subjects, it is anticipated that the difference in mean Hgb change from baseline between arms will be estimated with a precision of 0.408 g/dL (half width of the 95% CI) and the largest (most negative) difference between arms that would meet the statistical criterion for non-inferiority would be -0.342 g/dL.

Note: The country-specific requirements for France ONLY for the sample size consideration is provided in [Appendix 11](#) (see Section 12.11.1, Item 2 for details).

9.2.2. Sample Size Sensitivity

The following table illustrates the impact on power for the primary efficacy analysis based on alternative assumptions for the between subject SD and the percentage of non-evaluable subjects.

Between subject Hgb SD (g/dL)	% non-evaluable (number of subjects per arm)				
	20%	25%	30%	35%	40%
	(n=120)	(n=113)	(n=105)	(n=98)	(n=90)
1	>99%	>99%	>99%	>99%	>99%
1.25	>99%	>99%	>99%	99%	98%
1.5	97%	96%	95%	94%	92%
1.75	91%	89%	87%	85%	82%
2	82%	80%	77%	74%	71%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The primary population for Hgb efficacy analyses will be the All Randomized (ITT) Population. Subjects will be analyzed according to the treatment to which they were randomized. In order to assess the sensitivity of the primary efficacy analysis, an analysis will be performed in a Per-Protocol (PP) Population defined as all ITT subjects who are not major protocol violators. Details will be defined in the RAP and subjects analyzed according to the treatment received.

For analyses of time to event endpoints such as all cause mortality, Major Adverse Cardiovascular Events (MACE) and hospitalizations, the All Randomized (ITT) Population will also be used. Subjects will be analyzed according to the treatment to which they were randomized.

The primary population for safety (Safety Population) will consist of all randomized subjects who receive at least one dose of randomized treatment. Subjects will be analyzed according to the treatment received.

Additional populations may be defined in the RAP.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Mean change in Hgb between baseline and EP (Weeks 28-52): The primary efficacy estimand is to compare the effect of treatment for the evaluation of mean change from baseline in Hgb during a 24 week evaluation period (Weeks 28 to 52 inclusive) in all ITT subjects with at least one Hgb during the EP. The analysis will use an analysis of covariance (ANCOVA) model. For each subject, the baseline Hgb will be the value obtained on Day 1, prior to taking randomized treatment, and Hgb during EP will be determined by calculating the mean of all available Hgb values between Weeks 28 to 52 inclusive regardless of adherence to randomized treatment. The ANCOVA model will include randomization stratification factors, baseline hemoglobin, and treatment. It will provide a point estimate and 95% CI for the treatment effect, together with the non-inferiority test p-value. Non-inferiority will be established if the lower limit of the two-sided 95% CI is greater than the margin of -0.75 g/dL. There will be no imputation for missing data but imputation will be explored via sensitivity analyses

Sensitivity Analyses: Sensitivity analyses for the primary estimand will include a multiple imputation-based “tipping point” analysis where assumptions are adjusted until non-inferiority is lost by imputing data for subjects who did not fully complete the EP. A further analysis will evaluate efficacy in those subjects who adhere to randomized treatment, defined as ITT subjects with at least one on-treatment Hgb during the EP (this approach corresponds to evaluating an efficacy estimand). A similar “tipping point” analysis as that described above for the primary analysis will be performed for this “on-drug” analysis. In addition, a per-protocol sensitivity analysis will estimate the treatment effect in subjects who strongly adhere to the protocol, and sensitivity analyses to explore

a shorter EP (Weeks 28 to 36) will be performed for the primary effectiveness estimand and “on-drug” efficacy estimand. Full details of all sensitivity analyses will be provided in the RAP.

9.4.2. Secondary Analyses

9.4.2.1. Principal Secondary Efficacy Analyses

Conditional on the primary endpoint achieving non-inferiority at the two-sided 5% level, statistical testing will progress to the principal secondary endpoint with a focus on superiority using a two-sided 5% significance level.

For the average monthly IV iron dose up to Week 52 endpoint: IV iron use for all subjects will be recorded in the eCRF and the average monthly IV iron dose up to week 52 while on treatment will be calculated. An ANCOVA model will be used to compare the difference in this average monthly IV iron dose per subject between arms, including factors for baseline dose, treatment and the randomization stratification factors.

Additional secondary/exploratory endpoints are listed in [Appendix 2](#). All analyses of secondary endpoints are of exploratory nature, summary statistical and nominal two-sided 5% significance levels will be used to describe the results and for any treatment comparisons.

9.4.2.2. Safety Analyses

Safety data, including all AEs (i.e., non-serious, serious and AEs of special interest), laboratory data, vital signs, concomitant medications and meeting protocol defined stopping criteria (e.g., liver chemistry) will be descriptively summarized by treatment arm. Reasons for stopping randomized treatment and for early study withdrawal will also be summarized by treatment group and time to stopping treatment or study will be presented graphically and assessed. Full details of all safety data reporting will be described in the RAP.

9.4.3. Multiplicity Strategy

The primary endpoint will be tested first for non-inferiority, using the lower limit of the 2-sided 95% confidence interval. Conditional on achieving statistical significance (i.e. passing the primary gate by establishing non-inferiority) the single principal secondary endpoint will be tested for superiority using a two-sided 5% significance level. This two-step hierarchical strategy will preserve the study-wise Type I error rate at a two-sided 5% level.

The additional secondary/exploratory endpoints as listed in [Appendix 2](#), if tested, will not be adjusted for multiplicity. A nominal 5% significance level will be applied per test.

9.4.4. Covariates and Subgroups of Interest

The primary and principal secondary endpoint will be evaluated for a set of pre-specified subgroups to support the proposed indication. Subgroup analyses are aimed to assess for

consistency with the overall result, they may have low power if the subgroup is small. Statistical models will be adjusted for baseline, subgroup, treatment and treatment by subgroup interaction. Point estimates and 95% CIs will be estimated (presented on Forest Plots) and the subgroup by treatment interaction p-value calculated. Subgroup analyses will not be adjusted for multiplicity. Further subgroups/covariates may be defined in the RAP.

Category	Subgroups
Age	<65 years , ≥65 years - <75, ≥75 years
Gender	Female, Male
Race group	American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race
Ethnicity	Hispanic, non-Hispanic
Region	US, EU, RoW (repeat using US, Non-US)
Dialysis type	HD, PD (repeat using HD, HDF/HF, PD)
Dialysis status	Planned, unplanned (urgent) start
Baseline Hgb	<9, 9 to <10, 10 to 11, >11 g/dL
BMI	<30, ≥30
Weight	< 75kg, ≥75kg
Baseline hsCRP	≤3 mg/L, >3 mg/L

Additional exploratory subgroups may be defined in the RAP.

9.4.4.1. Exploratory Cardiovascular Safety Analysis

This study is not designed or sufficiently powered for formal statistical analyses to assess cardiovascular safety. With fewer than 80 first MACE (defined as all-cause mortality, non-fatal MI, or non-fatal stroke) expected to occur during the trial, incidence rates and 95% CIs will be computed for the following mortality and CV composite or component endpoints: 1) MACE; 2) MACE or a thromboembolic event (vascular access thrombosis, a symptomatic deep vein thrombosis or a symptomatic pulmonary embolism); 3) MACE or hospitalization for heart failure; 4) all cause mortality; 5) CV mortality; 6) MI (fatal and non-fatal); 7) stroke (fatal and non-fatal); 8) CV mortality or non-fatal MI; 9) all cause hospitalization.

9.4.5. Interim Analysis

The IDMC will periodically receive unblinded safety reports containing MACE (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.

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

Further details will be specified in the IDMC charter and RAP.

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

The 'PK Population' is defined as subjects for whom a PK sample was obtained and analyzed. This will be the population used for all the PK displays.

The following plasma PK parameters will be determined for daprodustat and metabolites: C_{tau} (predose) and C_{max} .

Plasma daprodustat and metabolites concentration data will be listed and summarized by planned collection time and daprodustat dose administered at PK visit. PK parameter data will be listed and summarized by daprodustat dose administered at PK visit, and dose-normalized (per mg) PK parameter data will be summarized.

All PK data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

The following exploratory graphics will be created. Based on these, and the efficacy and safety results from other Phase 3 studies, post-hoc exploratory exposure-response/safety modelling may be conducted, including exploratory graphics with metabolites. Further details will be provided in the RAP.

- Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP.
- Scatter plots of average daprodustat dose during EP vs. percent time in range during EP.
- Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP vs. percent time in range during EP.
- Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) 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 (C_{tau} and C_{max}) dose normalized to average dose during EP vs. change from baseline of Hgb during EP.
- Boxplots of daprodustat PK parameters dose normalized to 1 mg by subjects with or without MACE or a combined safety endpoint of MACE + thromboembolic event + hospitalization for heart failure
- Boxplots of daprodustat PK parameters 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

9.4.7. Analysis of Patient Reported Outcomes Measures

Analysis to compare the patient reported effects of daprodustat and rhEPO on symptoms, severity, HR-QoL, and health status, as discussed in Section 7.7, will be described in the RAP. In order to establish and evaluate the measurement properties of the CKD-QA, an interim cut of blinded observations of at least 50 subjects who completed the Week 52 visit will be taken. The data cut will require the following variables through Week 52: PGI-C, PGI-S, Hgb, SF-36, demographic and baseline clinical characteristics.

The interim data cut will be used to conduct confirmatory factor analysis in order to establish a scoring algorithm for potential instrument domains and to evaluate the reliability, validity and responsiveness of the instrument without regard to treatment group. A full description of the data cut, variables of interest and analyses to establish the scoring and to evaluate the measurement properties of the CKD-QA will be specified *a priori* within a separate psychometric analysis plan.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion or approval of the study protocol and amendments as applicable
- Obtaining signed informed consent for each subject prior to participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.

- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, PPD monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

PPD will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, PPD may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the PPD monitor will conduct site closure activities with the investigator or site staff, as appropriate, in

accordance with applicable regulations including GCP, and PPD Standard Operating Procedures.

- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determine such action is needed, PPD will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, PPD will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, PPD will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK or PPD will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- PPD will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, PPD standards/procedures, and/or institutional requirements.

- The investigator must notify PPD of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.

GSK or PPD will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

10.8. Review Committees

In addition to GSK, medical governance will also be provided by the following independent committees:

10.8.1. Independent Data Monitoring Committee

An IDMC unblinded to treatment allocation will be utilized in this study to ensure external objective review of safety and efficacy data in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The analysis plan for IDMC review is described in the charter which is available upon request.

10.8.2. Clinical Endpoint Committee

An external independent CEC blinded to treatment allocation will adjudicate all clinical events reported during this study that are referred for adjudication, including major adverse cardiovascular events (MACE; composite of all-cause mortality [CV and non-CV mortality], non-fatal MI and non-fatal stroke) and additional components for a broader definition of MACE including thromboembolic events (vascular access thrombosis, symptomatic deep vein thrombosis, symptomatic pulmonary embolism), and hospitalization for heart failure (Section 7.4.1).

10.8.3. Steering Committees

The Executive Steering Committee is the primary external advisory group for GSK. The committee provides academic leadership, ensures proper study conduct and conformance to the protocol, advises and recommends changes to the protocol based on emerging scientific and/or clinical advances, advises on the selection of study sites, communicates with the media and external audiences when appropriate, and works with the sponsor to assist in patient identification strategies. Additional information about the committee is included in the Executive Steering Committee charter, which is available upon request.

The broader Steering Committee in collaboration with the Executive Steering Committee is responsible for the scientific content and integrity of all aspects of study conduct including participation in the study sub-committees and providing advice to the National Leader Committee if needed.

10.8.4. National Leader Committee

The National Leader Committee will provide clinical and operational leadership at the country and regional level to support the implementation and conduct of the studies.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse event
ALT	Alanine transaminase
ANOVA	Analysis of variance
ANSM	L'Agence nationale de sécurité du médicament et des produits de santé
AST	Aspartate transaminase
BP	Blood pressure
CEC	Clinical Event Committee
CI	Confidence interval
CNIL	Commission Nationale de l'Informatique et des Libertés
CKD	Chronic kidney disease
CKD-AQ	Chronic kidney disease anemia symptoms questionnaire
CKD-EPI	Chronic kidney disease epidemiology collaboration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRA	Clinical Research Assistant
CT	Computed tomography
CTR	Clinical Trials Register
CV	Cardiovascular
DBP	Diastolic blood pressure
DGF	Delayed graft function
DILI	Drug induced liver injury
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EP	Evaluation period
EPO	Erythropoietin
EQ-5D-5L	Dimension 5 Level Health Utility Index
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FRP	Females of reproductive potential
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
hCG	Human chorionic gonadotropin
HD	Hemodialysis
HDF	Hemodiafiltration
HDL-c	High density lipoprotein-C
HF	Hemofiltration
Hgb	Hemoglobin

HIF	Hypoxia-inducible factor
HR	Heart rate
HRT	Hormone replacement therapy
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
LDL-C	Low density lipoprotein-C
MACE	Major adverse cardiovascular event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
ND	Non-dialysis
NYHA	New York Heart Association
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PD	Peritoneal dialysis
PFS	Prefilled syringes
PHD	Prolyl hydroxylase domain enzymes
PHI	Prolyl hydroxylase inhibitor
PP	Per-protocol
PPD	Pharmaceutical Product Development, LLC
PRBC	Packed red blood cells
PRCA	Pure red cell aplasia
RAP	Reporting and Analysis Plan
PSRAE	Possible Suicidality Related Adverse Events
QD	Once daily
QoL	Quality of life
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RDW	Red blood cell distribution width
rhEPO	Recombinant human erythropoietin
RoW	Rest of world
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous

SD	Standard deviation
SDAC	Statistical Data Analysis Center
SRM	Study Reference Manual
TIW	Three times weekly
TSAT	Transferrin saturation
UIBC	Unsaturated iron binding capacity
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WBC	White blood cell

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
HemoCue

12.2. Appendix 2: Secondary, Exploratory, Patient Reported Outcomes, and Pharmacokinetics/Pharmacodynamics Objectives/ Endpoints

Objectives	Endpoints
Secondary Objectives	Secondary Endpoints (tested for superiority ¹ , no multiplicity adjustment)
To compare daprodustat to rhEPO on BP	<ul style="list-style-type: none"> Change from baseline in SBP, DBP, and MAP at Week 52 and at end of treatment Number of BP exacerbation events per 100 patient years N (%) with at least one BP exacerbation event during study
To compare daprodustat to rhEPO on Hgb variability	<ul style="list-style-type: none"> Hgb change from baseline to Week 52¹ 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 (<i>non-inferiority analysis that will use a margin of 15% less time in range</i>)¹
To compare daprodustat to rhEPO on the time to rescue (defined as permanently stopping randomized treatment due to meeting rescue criteria)	<ul style="list-style-type: none"> Time to stopping randomized treatment due to meeting rescue criteria
To compare daprodustat to rhEPO on HRQoL and Utility score	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Plasma daprodustat, M2, M3, and M13 PK parameters pre-dose trough (C_{tau}) and C_{max}
Exploratory Objectives	Exploratory Endpoints (statistical testing not planned)
To further compare daprodustat and rhEPO on Hgb variability	<ul style="list-style-type: none"> 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

Objectives	Endpoints
	<p>and below the Hgb analysis range during EP and at the end of treatment</p> <ul style="list-style-type: none"> • Number (%) of subjects with a Hgb <7.5 g/dL • 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 • N (%) of subjects with a Hgb value \geq 12 g/dL during the EP • Number of times Hgb \geq 12 g/dL during the EP • % of time Hgb \geq 12 g/dL during the EP
To compare daprodustat to rhEPO on measures of iron parameters	<ul style="list-style-type: none"> • 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 IV iron dose/subject • N (%) of subject who met iron management criteria • N (%) of subjects who reduced IV iron supplementation relative to baseline (defined as total iron (mg) over 4 weeks prior to randomization) to EP (defined as average monthly IV iron dose (mg) over Weeks 28-52)
To compare daprodustat to rhEPO on the need for RBC transfusions	<ul style="list-style-type: none"> • Number (%) of subjects who receive at least one RBC transfusion by Week 52 • Number of RBC transfusions per 100 patient years • Number of RBC units per 100 patient years
To evaluate the dose adjustment schemes	<ul style="list-style-type: none"> • Final (mean and median) dose at Week 28, Week 52, and at end of treatment • 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 – Week 52, Day 1 – the end of treatment. • Number of dose adjustments during the following periods: Day 1 - < Week 28, Week 28 – Week 52, Day 1 – Week 52, Day 1 – the end of treatment • Time dose held for Hgb \geq12 g/dL
To further compare daprodustat to rhEPO on BP and BP medication changes	<ul style="list-style-type: none"> • 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

Objectives	Endpoints
	medications from baseline by visit
To compare daprodustat to rhEPO on lipid parameters	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Change from Baseline at Wk 8, 12, 28, & 52, by item on the CKD-AQ Shift tables (Baseline to 8, 12, 28, & 52) in PGI-S N(%) of patients 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP. Scatter plots of average daprodustat dose during EP vs. percent time in range during EP. Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP vs. percent time in range during EP. Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) 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 (C_{tau} and C_{max}) 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	<ul style="list-style-type: none"> Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint. Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) 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.

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

- 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.

12.3. Appendix 3: Randomized Treatment Dose Steps and Dose Adjustment Scheme

12.3.1. Darbepoetin Alfa Dose Steps

Total 4-weekly Dose (µg)	PFS Dose and Frequency (PD/HD)
20 µg	20 µg (0.2 ml of 40 µg) Q4 weeks
30 µg	30 µg (0.3 ml of 40 µg) Q4 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 (0.4 ml of 100 µg) every 2 weeks
200 µg	100 µg every 2 weeks
300 µg	150 µg every 2 weeks
400 µg	100 µg every week

12.3.2. Randomized Treatment Dose Adjustment Scheme

HemoCue Hgb at current study visit ¹ (g/dL)	HemoCue Hgb change since last study visit ¹	Randomized Treatment Dose Adjustment ⁵
<7.5 ²	Any change	Repeat Hgb and average values ⁶ ; if confirmed, increase to the next higher dose step
7.5 to <9.5	Decreasing or No change	Increase to the next higher dose step
7.5 to <9.5	Increasing	Maintain dose
≥9.5 to <10 at two consecutive visits	Decreasing or No change	Increase to the next higher dose step
≥9.5 to ≤11.5	Any change	Maintain dose
>11 to ≤11.5 at two consecutive visits	Increasing or No change	Decrease to the next lower dose step
>11.5 to <12	Decreasing	Maintain dose
>11.5 to <12	Increasing or No change	Decrease to the next lower dose step
≥12 ³	Any change	Repeat Hgb and average values ⁶ ; if confirmed, temporary hold the dose and re-check Hgb at next study visit ¹ ; restart at one dose step lower when Hgb <11.5 g/dL and provided it has been at least 2 weeks from the prior study visit
Any	>2 g/dL increase over 4 weeks (>1 g/dL increase over 2 weeks ⁴)	Repeat Hgb and average values ⁶ ; if confirmed, decrease to the next lower dose step
Any	>2 g/dL decrease over 4 weeks (>1 g/dL decrease over 2 weeks ⁴)	Repeat Hgb and average values ⁶ ; if confirmed, increase to the next higher dose step

1. "Study visit" refers to scheduled study visits (every 4 weeks through Week 52).
2. This rule also applies to any mandated visit or an unscheduled visit, provided it has been at least 2 weeks from the prior study visit.
3. This rule applies to any mandated or unscheduled visit,
4. This rule applies to Weeks 2, 4, 6, and 8 visits only.
5. Those receiving the highest dose of randomized treatment who require a dose increase will maintain the same dose, while those receiving the lowest dose of randomized treatment that require a dose decrease will have doses withheld
6. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample) and take average.

12.4. Appendix 4: Benefit:Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Daprodustat		
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	<p>In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion, microthrombi, and tissue ischemia in a number of organs.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p> <p>Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose levels, and dose adjustment scheme to optimize Hgb management.</p>	<ul style="list-style-type: none"> • Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 5.1 • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb is provided in Section 6.2 and Section 6.11. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study .
Risk of death, MI, stroke, congestive heart failure, venous thromboembolism, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)	<p>Marketed rhEPO/ESAs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	<ul style="list-style-type: none"> • Specific eligibility criteria related to CV risk are outlined in Section 7.4.1. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) • Unblinded monitoring of safety data by an IDMC in-stream throughout the study
Esophageal and gastric erosions	<p>In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ulcers with hemorrhage were observed with daprodustat.</p> <p>In rodents stomach erosions observed with intravenous and oral administration of daprodustat.</p> <p>Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat).</p>	<ul style="list-style-type: none"> • Suspected GI bleeding or significant symptoms consistent with erosion should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted • Unblinded monitoring of safety data by an IDMC in-stream throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported adverse event, however causal association has not been established.</p> <p>Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.</p>	
Cancer-related mortality and tumor progression and recurrence	<p>In clinical trials, use of rhEPO in patients with cancer has been associated with increased risk of cancer related morbidity and mortality.</p> <p>Administration of 60mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p> <p>In clinical studies with daprodustat up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations, an angiogenic factor that has been implicated in tumor growth, was observed at doses ranging from 10 to 150 mg. In clinical studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentrations were variable but similar relative to control.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	<ul style="list-style-type: none"> • Specific eligibility criteria related to personal history of malignancy or subjects with complex kidney cyst are outlined in Section 5.2.. • Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.5. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study
Pulmonary artery hypertension (PAH)	<p>A role for HIF-regulated pathways in the pathophysiology of PAH has been suggested based on well established effects of acute and chronic hypoxia in man on the pulmonary vasculature (vasoconstriction), and by findings in patients with naturally occurring mutations that result in decreased HIF degradation [Smith, 2006; Formenti, 2011].</p> <p>There have been no histopathologic findings suggestive of PAH in pre-clinical safety studies with daprodustat (up to 13-weeks duration in mice and dog, up to 26-weeks in rat, and up to 39-weeks in monkeys).</p> <p><u>Acute hypoxic challenge (rats):</u> daprodustatA produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. These hypoxia-induced PRVP changes fall within the range of PRVP differences noted among non-treated rats.</p>	<ul style="list-style-type: none"> • Unblinded monitoring of safety data by an IDMC in-stream throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with daprodustat 5mg or 100mg has no clinically significant effect on echocardiographically estimated systolic pulmonary artery pressure (sPAP) under either normoxic or hypoxic conditions. ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in sPAP in subjects not on dialysis for daprodustat. In hemodialysis subjects, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (daprodustat Total: 8 [7%]; Control 0) in subjects reaching the sPAP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 subjects with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study drug; and there was no dose relationship for subjects meeting the sPAP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	
Cardiomyopathy	<p>Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized.</p> <p>Small increases in cardiac troponin in 6 month rat study with daprodustat were consistent with the background finding of spontaneous rodent cardiomyopathy. There were no elevations observed in cardiac troponin in 9 month monkey study with daprodustat.</p> <p>Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization.</p> <p>ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in LVEF with daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified</p>	<ul style="list-style-type: none"> • Unblinded monitoring of safety data by an IDMC in-stream throughout the study .

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	as a safety concern for daprodustat.	
Proliferative retinopathy, macular edema, choroidal neovascularization	<p>Increases in local (ocular) VEGF production with retinal neovascularization and macular edema observed in diabetic retinopathy and to choroidal leakage, edema and neovascularization seen in age-related macular degeneration [Campochiaro, 2006].</p> <p>Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p> <p>No ocular abnormalities with daprodustat were seen in non-clinical studies of up to 13 weeks duration in mice and dogs, 26 weeks in rats, and 39-weeks in monkeys.</p> <p>In clinical studies with daprodustat up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg. In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentrations were variable but similar relative to control.</p> <p>Ophthalmologic assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization from daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	<ul style="list-style-type: none"> • Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Exacerbation of rheumatoid arthritis	<p>In inflamed rheumatic joints, activation of HIF- related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra, 2010; Muz, 2009].</p> <p>No abnormalities seen in non-clinical studies conducted to date for daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	<ul style="list-style-type: none"> • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Drug-drug interactions	<p>Co-administration of daprodustat with a strong CYP2C8 inhibitor increased the Cmax and AUC of daprodustat, 4- and 19-fold, respectively, while co-administration of a weak inhibitor increased the Cmax and AUC of</p>	<ul style="list-style-type: none"> • Co-administration of daprodustat with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>daprodustat by 1.3- and 1.5-fold, respectively. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with a moderate CYP2C8 inhibitor, leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response.</p> <p>daprodustat is an inhibitor of CYP2C8 <i>in vitro</i>, with an IC₅₀ value of 21 µM. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with clopidogrel (a moderate CYP2C8 inhibitor) leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution.</p> <p>Co-administration of daprodustat with potent BCRP inhibitors has the potential to increase exposure of daprodustat. Use of BCRP inhibitors (mostly weak) was found to result in a small change in metabolite exposure (20% increase in AUC).</p> <p>Daprodustat is an inhibitor of OATP1B1/1B3 <i>in vitro</i>, with IC₅₀ values of 6 µM and 11 µM, respectively. A clinical drug interaction study between 25mg daprodustat with either a CYP2C8 substrate or an OATP1B1/1B3 substrate showed that there is no PK interaction at this dose of daprodustat.</p>	<p>outlined in Section 6.9.2 and Appendix 3</p> <ul style="list-style-type: none"> • Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 6.9.1. Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.9.. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb is provided in Section 6.2.1 and Appendix 3. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Other		
rhEPO risks (Control)	<p>See risks outlined in table for daprodustat for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia, Death, MI, stroke, venous thromboembolism, thrombosis of vascular access, and for Increased cancer-related mortality and tumor progression.</p> <p>Uncontrolled hypertension</p> <p>Pure red cell aplasia</p>	<ul style="list-style-type: none"> • See mitigation strategies outlined in table for daprodustat for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia, Risk of death, MI, stroke, venous thromboembolism, thrombosis of vascular access, and for Increased cancer-related mortality and tumor progression. • Specific eligibility criteria related to current uncontrolled hypertension are outlined in Section 5.2. • Specific eligibility criteria related to personal history of pure red cell aplasia are outlined in Section 5.2.

References:

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Formenti F, Beer PA, Croft QP, Dorrington KL, Gale DP, Robbins PA, *et al*. Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2alpha gain-of-function mutation. *FASEB J*. 2011;25(6):2001-11.

Muz B, Khan MN, Kiriakidis S, Paleolog EM. Hypoxia. The role of hypoxia and HIF-dependent signalling events in rheumatoid arthritis. *Arthritis Res Ther*. 2009;11(1):201.

Smith TG, Brooks JT, Balanos GM, Lappin TR, Layton DM, Robbins PA. *et al*. Mutation of von Hippel-Lindau tumour suppressor and human cardiopulmonary physiology. *PLoS Med*. 2006 Jul;3(7):e290.

Westra J, Molema G, Kallenberg CG. Hypoxia-inducible factor-1 as regulator of angiogenesis in rheumatoid arthritis - therapeutic implications. *Curr Med Chem*. 2010;17(3):254-63.

12.5. Appendix 5: Female Eligibility Criteria

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum hCG test for females of reproductive potential only), not breastfeeding, or at least one of the following conditions applies:

- Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP from 30 days prior to the first dose of randomized treatment and until completion of the Follow-up visit (4-6 weeks after the end of randomized treatment); those who permanently discontinue randomized treatment prior to the end of the study should continue contraceptive methods following the Early Treatment Discontinuation Visit until the final pregnancy test assessment at a subsequent study visit (at least 4 weeks after the end of randomized treatment) as described in the Time and Events Table (Section 7.1).

1. Contraceptive subdermal implant.
2. Intrauterine device or intrauterine system.
3. Combined estrogen and progestogen oral contraceptive [Trussell, 2011]
4. Injectable progestogen [Trussell, 2011]
5. Contraceptive vaginal ring [Trussell, 2011]
6. Percutaneous contraceptive patches [Trussell, 2011]
7. Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject [Trussell, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Non-reproductive potential defined as either:
 1. Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;
 2. Postmenopausal defined as 12 months of spontaneous amenorrhea. In questionable cases, a blood sample with simultaneous FSH and estradiol consistent with

menopause is confirmatory (FSH 23-116.3 MIU/L and estradiol ≤ 10 pg/mL (or ≤ 37 pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

References

Trussell J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, and Policar M (editors). Contraceptive Technology: Twentieth Revised Edition. New York: Ardent Media, 2011. Table 26-1

12.6. Appendix 6: Liver Chemistry Stopping Criteria

12.6.1. Liver Safety Required Actions and Follow up Assessments

Phase 3-4 liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT \geq 8xULN
ALT Increase	ALT \geq 5xULN but $<$ 8xULN persists for \geq 2 weeks ALT \geq 3xULN but $<$ 5xULN persists for \geq 4 weeks
Bilirubin^{1,2}	ALT \geq 3xULN and bilirubin \geq 2xULN ($>$ 35% direct bilirubin)
INR²	ALT \geq 3xULN and INR $>$ 1.5, if INR measured
Cannot Monitor	ALT \geq 5xULN but $<$ 8xULN and cannot be monitored weekly for \geq 2 weeks ALT \geq 3xULN but $<$ 5xULN and cannot be monitored weekly for \geq 4 weeks
Symptomatic³	ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> • Immediately discontinue randomized treatment • Report the event to PPD within 24 hours • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE² • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) • Do not restart subject with randomized treatment unless allowed per protocol and GSK Medical Governance approval is granted (Section 12.6.2) • If restart not allowed or not granted, permanently discontinue randomized treatment and may continue subject in the study for any protocol specified follow up 	<ul style="list-style-type: none"> • Viral hepatitis serology⁴ • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody⁵. • Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hr after last dose⁶ • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin \geq 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

<p>assessments</p> <p>MONITORING:</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended <p><u>For All other criteria:</u></p> <ul style="list-style-type: none"> • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline 	<ul style="list-style-type: none"> • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: not required in China • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.
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1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue randomized treatment for that subject if ALT \geq 3xULN **and** bilirubin \geq 2xULN.
2. All events of ALT \geq 3xULN **and** bilirubin \geq 2xULN (>35% direct bilirubin) or ALT \geq 3xULN **and** INR > 1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of randomized treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase 3-4 liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT \geq5xULN and $<$8xULN and bilirubin $<$2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT \geq3xULN and $<$5xULN and bilirubin $<$2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety. • Subject can continue randomized treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT \geq5xULN and $<$8xULN to \geq3xULN but $<$5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT $<$3xULN and bilirubin $<$2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363–2369.

12.6.2. Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart randomized treatment unless there is a clear underlying cause for the liver stopping event other than drug-induced liver injury and:

- GSK Medical Governance approval **is granted** in writing (as described below),
- Ethics and/or IRB approval is obtained, if required, and

- Separate consent for treatment restart is signed by the subject

If GSK Medical Governance approval to restart subject with randomized treatment **is not granted**, then subject must permanently discontinue randomized treatment and may continue in the study for protocol-specified follow up assessments.

Restart Following Transient Resolving Liver Stopping Events Not Related to randomized Treatment

Restart refers to resuming randomized treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the randomized treatment should not be associated with HLA markers of liver injury.

Approval by GSK for randomized treatment restart can be considered where:

- Investigator requests consideration for randomized treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible randomized treatment-induced liver injury) or randomized treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or Institutional Review Board approval of randomized treatment restart must be obtained, as required.
- If restart of randomized treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of randomized treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the randomized treatment restart. Documentation of informed consent must be recorded in the study chart.
- Randomized treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting randomized treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after randomized treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- PPD Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following randomized treatment restart.
- PPD to be notified of any AEs, as per Section 7.4 and [Appendix 8](#).

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Saf*. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. *Hepatology*. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009;54:84-90.

12.7. Appendix 7: Study Specific Equipment

Study specific equipment required:

- Refrigerator
- Freezer (-20°C or lower)
- Centrifuge
- Point-of-care HemoCue Hgb analyzer - to be provided as part of the study

12.8. Appendix 8: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.8.1. Definition of Adverse Events

Adverse Event Definition:

- An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting AE definition include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after randomized treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either randomized treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.8.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday

life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: <ul style="list-style-type: none"> • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: <ul style="list-style-type: none"> • ALT \geq 3xULN and total bilirubin* \geq 2xULN (>35% direct), or • ALT \geq 3xULN and INR** > 1.5. <p>* Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable and ALT \geq 3xULN and total bilirubin \geq 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>

12.8.3. Recording of AEs and SAEs

AEs and SAE Recording:
<ul style="list-style-type: none"> • When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is not acceptable for the investigator to send photocopies of the subject's medical records to PPD in lieu of completion of the PPD/GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by PPD. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to PPD. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be

documented as the AE/SAE and not the individual signs/symptoms.

- Subject-completed Patient Reported Outcomes questionnaires and the collection of AE data are independent components of the study.

12.8.4. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between randomized treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the randomized treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to PPD. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to PPD.**

- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by PPD to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.8.5. Reporting of SAEs to PPD

SAE reporting to PPD via electronic data collection tool

- Primary mechanism for reporting SAEs to PPD will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt will be provided in a separate document .

12.9. Appendix 9: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to PPD within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the randomized treatment by the investigator, will be reported to PPD as described in Section 12.8.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating must permanently discontinue randomized treatment. Subjects will be asked to attend an Early Treatment Discontinuation visit and expected to attend study visits through the End of Study visit, according to the study visit schedule, unless consent is actively withdrawn.

12.10. Appendix 10: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [[Gorin, 2012](#)] with certain variants reported to influence treatment response [[Chen, 2012](#)]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;

Anemia associated with CKD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Informed consent for genetic research must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

Continue to participate in the genetic research in which case the genetic DNA sample is retained

Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample

destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.

Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

References

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.11. Appendix 11 - Country Specific Requirements

12.11.1. French Administrative Considerations and Specifics Requirements

This appendix includes all the requirements of the French law (n° 2004-806 of 9th August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol and includes specifics GSK requirements.

1. Concerning the « STUDY POPULATION»

In line with the local regulatory requirements, the following text in section «**OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS** » is added: A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category.

It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

2. Concerning the “DATA ANALYSIS AND STATISTICAL CONSIDERATIONS” and specially in the “SAMPLE SIZE ASSUMPTION”

The expected number of patients to be recruited in France is declared to the French regulatory authority.

3. Concerning the “STUDY CONDUCT CONSIDERATIONS”

In section “Regulatory and Ethical Considerations, Including the Informed Consent Process”

Concerning **the process for informing the patient** or his/her legally authorized representative, the following text is added :

French Patient Informed Consent form is a document which summarizes the main features of the study and allows collection of the patient's written consent in duplicate. It also contains a reference to the authorisation of L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) and the approval from the French Ethic committee.

Concerning the management of the Patient Informed Consent forms, the following text is added:

The first copy of the Patient Informed Consent form is kept by the investigator. The second is given to the patient or his/her legally authorized representative

- In section concerning the “**NOTIFICATION TO THE HOSPITAL DIRECTOR**” the following text is added:

In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

- In section concerning the **“INFORMATION TO THE HOSPITAL PHARMACIST”** the following text is added:

In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- In section **“DATA MANAGEMENT”** the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

4. Monitoring visits

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc.). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the eCRF, in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

5. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's eCRF use here below:

The Health Institution and the Investigator undertake:

- 1) That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
- 2) That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
- 3) That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
- 4) To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
- 5) That the Investigator and the staff of the investigator center enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.
- 6) That the Investigator resolves and returns to GLAXOSMITHKLINE the data queries issued by GLAXOSMITHKLINE or a service provider designated by GLAXOSMITHKLINE within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GLAXOSMITHKLINE and/or a company designated by GLAXOSMITHKLINE.
- 7) To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
- 8) To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

6. CTR publication

It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Register (CTR) including the registration of all the clinical trials conduct by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

7. Data Protection French Law of 6 January 1978 (CNIL)

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GLAXOSMITHKLINE to monitor and follow the implementation and the progress of the Study are declared with the Commission Nationale de l'Informatique et des Libertés (CNIL) by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This

information can be transferred or be accessed to other entities of GLAXOSMITHKLINE Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

TITLE PAGE**Division:** Worldwide Development**Information Type:** Protocol Amendment

Title:	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
Short Title:	<u>A</u> nemia <u>S</u> tudies in <u>C</u> KD: <u>E</u> rythropoiesis via a <u>N</u> ovel PHI <u>D</u> aprodustat-in Incident <u>D</u> ialysis (ASCEND-ID)

Compound Number: GSK1278863**Development Phase:** III**Effective Date:** 06-OCT-2017**Protocol Amendment Number:** 01

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N234534_00	2016-OCT-18	Original
2015N234534_01	2017-OCT-06	Amendment No. 1
<p>Amendment 1 applies to all countries</p> <ul style="list-style-type: none"> Updated the time period of planning to start dialysis from the day of screening to 6 weeks to be consistent with the extended screening period, when appropriate Removed number of screening subjects required and stated only an approximate number of randomized subjects required in the study Modified peritoneal dialysis (PD) inclusion criteria to allow participants on 2:4 times/week PD including an incremental schedule Removed France country specific requirement for Informed Consent process from inclusion criteria Broadened exclusion to include participation in an interventional study with an investigational agent or device Removed option to have Early Treatment Discontinuation visit supersede the scheduled study visit Added a provision that in unexpected circumstances where the supply to the site is interrupted, then local standard of care for anemia management during this time period may be considered Added direction regarding randomized treatment and study continuation for subjects who will be away from the research site for an extended period of time Added new darbepoetin alfa dose strengths (not available in all countries) Clarified timeframe for iron management criteria Clarified timing of designated study visits for subjects who have not yet initiated dialysis and for subjects on dialysis Shortened visit window for the Week 2 and 4 visits Modified Time and Events Table 6 'Schedule of Assessments. Main changes include addition of Informed Consent activity; footnotes to allow for more time for ECG before randomization visit, more clarity around randomized treatment dispensing and compliance; removed capture of rescue medications from unscheduled visit (rescue evaluation is triggered at scheduled visits); added healthcare resource data collection, added footnote to clarify biomarkers storage requirements and added Argentina only pregnancy requirement Added direction to CEC Site Manual for full scope of reporting requirements Clarified timing of weight, blood pressure and heart rate in relation to laboratory assessments and dialysis Clarified PK sampling in relation to subjects on dose hold Updated PRO section to add healthcare resource utilization data being collected for completeness Changed time point for blinded data cut need for psychometric validation of the Chronic Kidney Disease Questionnaire 		

- Revised statistical section to change from two-sided testing at the 5% level to one-sided testing at the 2.5% level; for secondary endpoints, to change significance levels to p-values and to correct the time point for various Patient Reported Outcomes
- Updated wording around exploratory endpoints in Appendix 2
- Updated Darbepoetin alfa dose steps table in Appendix 3 to remove partial doses and clarify booster dosing to be consistent with Interactive Response Technology (IRT) system
- Provision for possible adjustment to the Dose Adjustment Algorithm triggers for Hgb values 7.5 g/dL to <9.5 g//dL based on review of blinded instream Hgb data
- Edited Risk Assessment information in Appendix 4 to align with version 8 of the Investigator's Brochure
- Updated FSH level to confirm menopause in Appendix 5, Female Eligibility Criteria
- Removed Appendix 11- France country specific requirement
- Other changes include minor edits, corrections of typos and administrative changes throughout.

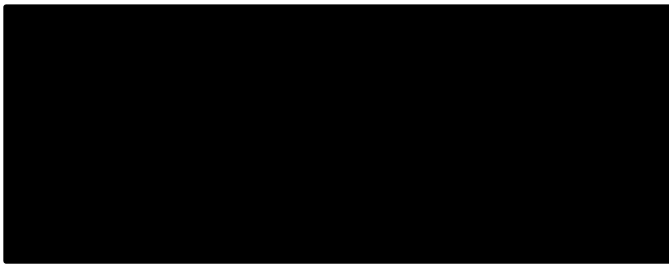
SPONSOR SIGNATORY



October 6, 2017

Date

Executive Director Clinical Development
Metabolic Pathways & Cardiovascular Unit
GlaxoSmithKline



MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

As this is a multinational study medical monitor/SAE contact information will be provided as a separate document.

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

PPD is the contract research organization for this study.

In some countries, the clinical trial Sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s):

IND Number: 101,291

EudraCT: 2016-000507-86

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201410

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature	Date	

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1. PROTOCOL SYNOPSIS

This Phase 3 study will evaluate the efficacy and safety of daprodustat (GSK1278863) compared to recombinant human erythropoietin (rhEPO) in the treatment of anemia associated with chronic kidney disease (CKD) in subjects who are planning to start or who have recently started dialysis. This study will also provide information on daprodustat dosing initiation and titration in subjects initiating dialysis.

Primary Objective/Primary Efficacy Endpoint

The primary objective of the study is to compare daprodustat to rhEPO for hemoglobin (Hgb) efficacy (non-inferiority).

The primary efficacy endpoint will be the mean change in Hgb between baseline and the evaluation period (EP, mean over Weeks 28-52).

Overall 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).

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

- 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); all randomized treatments (Section 6.1) 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 rhEPO, iron management, and rescue.

Type and Number of Subjects

- The study will enroll the following types of subjects with anemia associated with CKD: Planned initiation of dialysis: Subjects who are planning to start chronic dialysis (HD or PD) within the next 6 weeks (from the day of screening).

- **Unplanned (urgent) initiation of dialysis:** For Subjects who have started chronic dialysis in an urgent manner, meaning they started HD with a temporary vascular access with no previous planning for chronic dialysis or have started PD with recent (< 2 weeks) PD catheter insertion and/or who have not been seen by a kidney specialist (nephrologist) or other specialist with expertise in dialysis care within previous 4 months prior to screening.

This study will randomize approximately 300 subjects, or 150 subjects per treatment group.

Primary Efficacy Analysis

The primary Hgb efficacy analysis will assess whether daprodustat is non-inferior to rhEPO for change from baseline. The analysis will be based on the mean change in Hgb between baseline and the efficacy EP (defined as Weeks 28 to 52) using a non-inferiority margin of -0.75 g/dL (two-sided 95% CI). An analysis of the ITT Population, comprising all subjects with at least one Hgb measurement (on or off-treatment) during the EP and an analysis of covariance (ANCOVA) model will be used. The model will include randomization stratification factors, and factors for baseline Hgb and treatment.

2. INTRODUCTION

2.1. Brief Background

Daprodustat (GSK1278863) is an oral hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI) currently being investigated as a treatment for anemia associated with CKD in both subjects on dialysis and not on dialysis. Safety and efficacy have been investigated in clinical trials up to 24 weeks' duration. Both pre-clinical and clinical data show that daprodustat stimulates endogenous erythropoietin (EPO) production and increased erythropoiesis, resulting in elevation of Hgb concentrations. These increases in Hgb are achieved with peak plasma EPO levels substantially lower than those observed with IV rhEPO. Data from completed clinical and preclinical studies are provided in the current daprodustat Investigator Brochure (IB) and IB supplement(s) (if applicable).

2.2. Study Rationale

Based on its mechanism of action to stimulate erythropoiesis via inhibition of HIF-prolyl hydroxylase enzymes, daprodustat is postulated to be associated with fewer major adverse cardiovascular events (MACE) by raising Hgb without the supraphysiologic EPO concentrations associated with IV rhEPO therapy, potentially avoiding blood pressure (BP) elevations and other adverse effects of high EPO levels.

A Phase 2B clinical trial (PHI133633) in dialysis subjects with anemia associated with CKD demonstrated that daprodustat can maintain Hgb up to 24 weeks with minimal effects on plasma EPO concentration. Daprodustat treatment for up to 24 weeks demonstrated an adverse event (AE) profile consistent with the patient population.

This Phase 3 study will evaluate the safety and efficacy of daprodustat compared to rhEPO for treatment of anemia associated with CKD in subjects who are starting dialysis

or who have recently started dialysis. Data from this trial are intended to support the use of daprodustat for the treatment of anemia in subjects initiating chronic dialysis.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
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 (tested for superiority, adjusted for multiplicity)	
To compare daprodustat to rhEPO on the use of intravenous (IV) iron	1. Average monthly IV iron dose (mg)/subject from baseline to Week 52
Safety	
To compare the safety and tolerability of daprodustat to rhEPO	<ul style="list-style-type: none"> Incidence and severity of AEs and SAEs including those AEs of special interest Reasons for discontinuation of randomized treatment Absolute values and changes from baseline in laboratory parameters, blood pressure, and heart rate

Secondary and exploratory objectives/endpoints are listed in [Appendix 2](#).

4. STUDY DESIGN

4.1. Overall Design

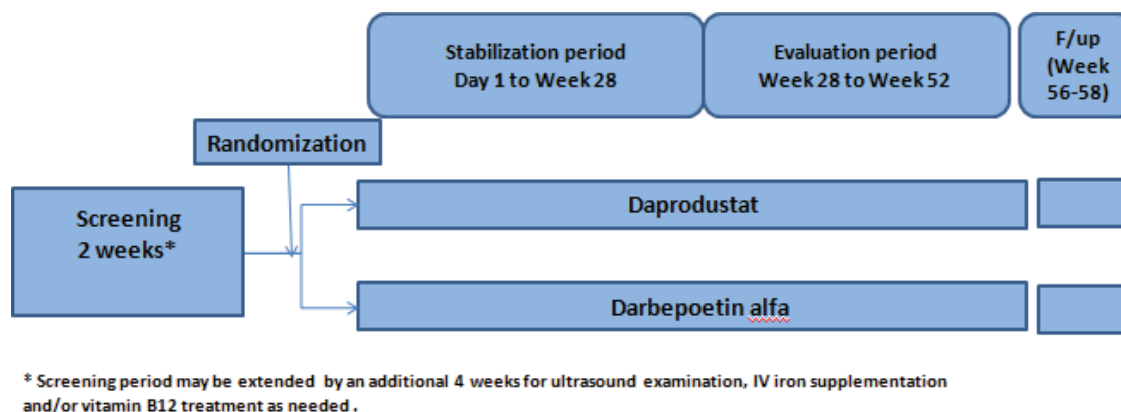
- This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center study in subjects with anemia associated with CKD who are not regularly using routine erythropoiesis-stimulating agent (ESA) users and who are initiating dialysis.
- The study will comprise three study periods: a screening period (2 weeks*), a 52-week active treatment period, and a follow-up period (4-6 weeks) ([Figure 1](#)). 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.

- 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.
- Limited ESA use is allowed around the time of dialysis initiation only (see [Section 5.2](#) for definition of “limited use”).
- The treatment period consists of:

- 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.
- 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.
- 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); all randomized treatments (Section 6.1) will be supplied by GSK.
- To ensure consistency of treatment across the study there are protocol-mandated algorithms for dose adjustments of daprodustat and rhEPO (Section 6.2), iron management (Section 6.10) and anemia rescue therapy (Section 6.11)
- An overview of the study design is provided in Figure 1.

Figure 1 Study Schematic



4.2. Type and Number of Subjects

The study will enroll the following types of subjects with anemia associated with CKD:

- **Planned:** Subjects who are planning to start dialysis (HD or PD) within the next 6 weeks (from the day of screening).
- **Unplanned (urgent):** For Subjects who have started chronic dialysis in an urgent manner, meaning they started HD with a temporary vascular access with no previous planning for chronic dialysis or have started PD with recent (< 2 weeks) PD catheter insertion and/or who have not been seen by a kidney specialist (nephrologist) or other specialist with expertise in dialysis care within previous 4 months prior to screening.

This study will randomize approximately 300 subjects, or 150 subjects per treatment group. The study will be conducted globally.

4.3. Design Rationale

This study includes a screening period where iron supplementation is permitted, so that subjects who are not iron replete can meet iron status entry criteria prior to randomization.

The study will include subjects who are planning to start dialysis imminently, have already recently started dialysis in a planned manner, and those who start dialysis urgently. This broad range of subjects will provide data on the effects of daprodustat in subjects starting dialysis as well as data on whether there are differences between planned and unplanned (urgent) starts.

Although subjects will be rhEPO non-users, because it is routine medical practice to begin treatment with rhEPO around the time of dialysis initiation if subjects have anemia (Hgb <11 g/dL), the protocol will allow limited rhEPO use during the four weeks before or after starting dialysis (Section 5.2).

The stabilization period from Day 1 to Week 28 allows subjects to have their randomized treatment dose titrated to achieve the Hgb target range. This period of time provides the opportunity for subjects to be titrated to their optimal dose of randomized treatment prior to the efficacy EP (Weeks 28 to 52). Some subjects may still need dose titration during the EP.

The selection of the rhEPO control (darbepoetin alfa) is based on feasibility and clinical practice in the majority of participating countries.

The study is open-label (sponsor blind) because it would be complex to double-blind due to the differing number of dose steps and different modes of administration (oral vs. injection) between randomized treatments

4.4. Dose Justification

Starting doses, dose steps, and elements of the dose adjustment scheme are provided in Section 6.2 and [Appendix 3](#).

4.4.1. Daprodustat

Daprodustat starting doses are assigned based on Hgb at study entry, and were selected such that the target Hgb concentration would be reached after approximately one red blood cell lifespan of treatment (up to 90 days, pharmacodynamic steady-state).

However, due to the between-subject variability in Hgb response to a given dose of daprodustat and the relatively narrow Hgb target range, individual dose adjustments of daprodustat are expected during the first few months of treatment. If an individual dose adjustment is made, subjects will increase or decrease the daprodustat dose through a series of dose steps, one dose step at a time. The highest dose of daprodustat in the dose adjustment scheme is 24 mg once daily.

The daprodustat starting doses and dose steps were selected for this study based on exposure-response longitudinal modeling of Hgb data collected across the Phase 2 program. Covariate analyses elucidated that baseline Hgb, body-weight, and prior ESA dose (if applicable) were the most relevant covariates of Hgb response to daprodustat.

4.4.2. Randomized Treatment Dose Adjustment Scheme

A randomized treatment dose adjustment algorithm was designed to minimize unnecessary dose adjustments by allowing for visit-to-visit variability, and it is informed by the change in Hgb from the previous visit when evaluating the need for a dose adjustment (Section 6.2.3).

4.5. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with daprodustat can be found in the daprodustat Investigator's Brochure (IB) and IB supplement(s) (if applicable).

4.5.1. Risk Assessment

The potential risks of clinical significance, including adverse events of special interest (see Section 7.4.4 for details), and the mitigation strategies for this protocol taking into account the results of completed clinical and nonclinical studies with daprodustat are outlined in Appendix 4 (Section 12.4). In addition to the mitigation strategies outlined, an Independent Data Monitoring Committee (IDMC) will monitor accruing safety data for this trial (Section 10.8.1).

4.5.2. Benefit Assessment

In clinical trials of up to 24 weeks in duration, in subjects with anemia associated with CKD, daprodustat has been shown to treat Hgb to target range. Daprodustat may present several important advantages over rhEPO and its analogs. It is an oral medication and does not require cold-chain storage as does rhEPO, thus increasing ease of use for patients and health care providers. After administration of daprodustat, data suggest that the increases in Hgb are achieved with EPO exposure lower than those observed with rhEPO. Treatment of anemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated supra-physiological increases in EPO exposure with rhEPO [Szczuch, 2008]; therefore, daprodustat has the potential to raise Hgb without the same CV risk associated with rhEPO and its analogs. Other potential benefits include possibly improving iron availability for erythropoiesis, the potential to successfully treat rhEPO hyporesponders, and the potential to treat anemia without causing rhEPO-induced hypertension.

4.5.3. Overall Benefit:Risk Conclusion

Daprodustat demonstrates a positive benefit vs. risk based on the evidence as follows. In clinical trials up to 24 weeks in duration, daprodustat treats Hgb to target range, and there are no adverse events that have been identified as related to treatment with daprodustat.

This protocol employs precautions to mitigate known and potential risks to enrolled subjects (See [Appendix 4](#), Section 12.4, for details). Given these precautions, as well as the potential benefit that daprodustat holds for the treatment of anemia associated with CKD compared to the current standard, the overall benefit risk balance is considered to be positive.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information about warnings, precautions, contraindications, AEs, and other pertinent information is provided in the daprodustat IB, IB supplement(s) (if applicable), the product label for darbepoetin alfa, and other pertinent documents (e.g., Study Reference Manual [SRM], informed consent).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply at screening and randomization (Day 1) unless otherwise specified.

1. **Age (confirm at screening):** 18 to 99 years of age inclusive.
2. **Dialysis:** Planning to start chronic dialysis within the next 6 weeks (from the date of the screening visit) OR have started and received dialysis (as specified below) for end-stage renal disease for a maximum of 90 days immediately prior to randomization and is not expected to stop dialysis during the duration of the trial:
 - HD ≥2X/week
 - PD: 2-4 times/week including incremental schedule; subjects on continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) are eligible.
3. **Hemoglobin concentration as measured by HemoCue (range inclusive):** 8-10.5 g/dL (5-6.5 mmol/L) at screening and 8-11.0 g/dL (5-6.8 mmol/L) at randomization.
4. **Informed consent (at screening):** capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for participation in this study if any of the following criteria apply at screening or at randomization (Day 1), unless otherwise specified.

CKD-related criteria

1. **Kidney transplant:** Planned living-related or living-unrelated kidney transplant during the study.

Anemia related criteria

2. **Ferritin:** ::100 ng/mL (::100 µg/L) at screening or after IV iron supplementation.
3. **TSAT:** ::20% at screening or after IV iron supplementation.
4. **Vitamin B12:** Below the lower limit of the reference range at screening or after vitamin B12 supplementation.
5. **Folate:** <2.0 ng/mL (<4.5 nmol/ L) at screening.
6. **Aplasias:** History of bone marrow aplasia or pure red cell aplasia (PRCA).
7. **Other causes of anemia:** Untreated pernicious anemia, thalassemia major, sickle cell disease, or myelodysplastic syndrome.
8. **Gastrointestinal (GI) bleeding:** Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GT bleeding :SIO weeks prior to screening through to randomization (Day 1).

Erythropoiesis treatment criteria

9. Use of any **ESA** treatment within 8 weeks prior to screening except for limited use as part of dialysis initiation.

Limited use is defined as no more than 6 weeks of short acting ESA (rhEPO or biosimilars; maximum of 20000 U total) or long acting ESA (darbepoetin alfa [maximum of 100 µg total] or methoxy polyethylene glycol-epoetin beta [maximum of 125 µg total]) received before or after starting dialysis.

Cardiovascular disease-related criteria

10. **Myocardial infarction or acute coronary syndrome:** :SIO weeks prior to screening through to randomization (Day 1).
11. **Stroke or transient ischemic attack:** :SIO weeks prior to screening through to randomization (Day 1).
12. **Heart failure:** Chronic Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system.
13. **Current uncontrolled hypertension:** Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of rhEPO.
14. **QTcB (Day 1):** QTcB >500 msec, or QTcB >530 msec in subjects with bundle branch block. There is no QTc exclusion for subjects with a predominantly ventricular paced rhythm.

Other disease-related criteria

15. **Liver disease (any one of the following):**
 - Alanine transaminase (ALT) >2x upper limit of normal (ULN) (screening only)
 - Bilirubin >1.5xULN (screening only)

NOTE: Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%

- Current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice, or cirrhosis

NOTE: Stable chronic liver disease (including asymptomatic gallstones, chronic hepatitis B or C, or Gilbert's syndrome) are acceptable if subject otherwise meets entry criteria.

16. **Malignancy:** History of malignancy within the 2 years prior to screening through to randomization (Day 1), or currently receiving treatment for cancer, or complex kidney cyst (i.e. Bosniak Category II F, III or IV) > 3cm. The only exception is localized squamous cell or basal cell carcinoma of the skin that has been definitively treated \geq 10 weeks prior to screening.

Concomitant medications and other study treatment-related criteria

17. **Severe allergic reactions:** History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (refer to daprodustat IB) or to darbepoetin alfa (refer to product labelling).
18. **Drugs and supplements (randomization only):** Use of strong CYP2C8 inhibitors (e.g., gemfibrozil) or strong CYP2C8 inducers (e.g., rifampin/rifampicin).
19. **Other study participation:** Use of **other** investigational agent or device prior to screening through to randomization (Day 1).

NOTE: at screening, this exclusion applies to use of the investigational agent within 30 days or within five half-lives (whichever is longer).

20. **Prior treatment with daprodustat:** Any **prior** treatment with daprodustat for treatment duration of > 30 days.

General health-related criteria

21. **Females ONLY:** Subject is pregnant [as confirmed by a positive serum human chorionic gonadotropin (hCG) test for females of reproductive potential (FRP) only], subject is breastfeeding, or subject is of reproductive potential and does not agree to follow one of the contraceptive options in the List of Highly Effective Methods for Avoiding Pregnancy listed in [Appendix 5](#).
22. **Other Conditions:** Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (e.g., intolerance to rhEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized. In this study, subjects can become a screen failure at any time from the screening visit to the Day 1 visit prior to randomization.

Documentation of a minimum set of information on screen failure subjects must be collected from subjects that fail screening, including demography, screen failure details, eligibility criteria, and serious adverse events (Section [7.4.3.4](#)).

Subjects that fail screening are eligible to be rescreened once as soon as the investigator assesses they may meet study entry criteria. If subjects are rescreened, they must sign a new informed consent form.

5.4. Subject Retention

- Subjects will be educated on the importance of remaining in the study and attending scheduled study visits.
- Investigators should make every effort to keep subjects in the trial.
- Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject.

5.5. Permanent Discontinuation of Randomized Treatment

Every effort should be made to keep subjects in the study including those who permanently stop randomized treatment. A subject may permanently discontinue randomized treatment at any time at his/her own request, or at the discretion of the investigator for safety, or compliance reasons. A subject must permanently discontinue randomized treatment for the pre-specified reasons below:

- Kidney transplant
- Reaching criterion to receive rescue (Section 6.11)
- Becomes pregnant or intends to become pregnant during the study
- Liver chemistry abnormalities exceeding the threshold criteria (Section 7.4.12)
- Diagnosis of cancer (new or recurrent), with the exception of localized dermal squamous cell or basal cell carcinoma
- Need for more than 14 days use of a prohibited medication (Section 6.9.2)

In all cases, the reason for randomized treatment discontinuation and the date of the last dose will be recorded in the subject's electronic case report form (eCRF) and the subject will continue in the study as described in Section 5.5.1.

Subjects may be re-approached about restarting randomized treatment in certain circumstances if the Sponsor and the investigator agree.

5.5.1. Procedures for Subject Follow-up

Subjects who permanently discontinue randomized treatment will be asked to attend an Early Treatment Discontinuation visit and will be expected to attend in-clinic study visits

through to Follow-up according to the study visit schedule, unless consent is actively withdrawn. Complete details are provided in [Table 7](#) in Section 7.1.

- Early Treatment Discontinuation visit: This visit should occur within 2 weeks of the last dose of randomized treatment.
- Remaining in-clinic visits*:
 - Day 1 through Week 52: Study visits every 12 weeks \pm 2 weeks post Early Treatment Discontinuation visit.
 - Follow-up: Study visit 4 weeks after Week 52.

*Phone visit acceptable in exceptional circumstances.

- In all cases, reasons for Early Treatment Discontinuation and the date of last dose will be recorded.
- If a subject does not agree to continue attending in-clinic or phone visits, other follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the subject, then the subject will be considered to have remained in the study and not to have withdrawn consent.

5.6. Withdrawal from Study

Every effort should be made to keep subjects in the study. For subjects that choose to withdraw consent or are lost to follow up, the reason for not completing the study will be recorded in the subject's eCRF.

If a subject withdraws from the study, he/she may request destruction of any clinical samples taken, and the investigator must document this in the site study records.

5.6.1. Withdrawal of Consent for Contact

Specific wording is included in the informed consent form which permits subjects to discontinue randomized treatment and study procedures, but states an expectation that follow up information will always be required. Subject will agree to this at the time of consenting.

Withdrawal of consent from the study is expected to be a rare occurrence. If a subject withdraws consent from the study, the Investigator will review the following contact options with the subject:

- In-clinic and phone visits
- Follow-up via medical records review and/or other treating physician
- Follow-up via family member or other third party contact

If all of these options are refused, then no further study visits or study-related telephone contact will be conducted and the subject will be considered to have withdrawn consent. The principal investigator will be required to document that all alternative options have been reviewed with the subject.

For these subjects, information regarding study outcomes or vital status will continue to be collected from available sources including those in the public domain based on accepted local laws and regulations. Where permitted, a third party may be used to obtain information.

5.6.2. Subjects Deemed Lost to Follow-up

- Investigators should make every effort to contact subjects who are deemed lost to follow-up and who have not withdrawn consent to follow-up contact.
- As permitted by local regulations, a third party may be used to locate alternative subject contact information that will be provided to the investigator. All attempts to contact subjects will be documented in the subject's eCRF and source notes and a final status contact will be recorded in the eCRF.

5.7. Subject and Study Completion

A completed subject is one who has completed all periods of the study through the End of Treatment visit with the following exception: subjects who die while on study are also considered as having completed the study.

6. RANDOMIZED TREATMENT

6.1. Investigational Product and Other Randomized Treatment

The term ‘randomized treatment’ is used throughout the protocol to describe any product (i.e., daprodustat or darbepoetin alfa during the treatment period) received by the subject as per the protocol design. Randomized treatment will be provided by GSK.

During the treatment period, iron therapy (supplied locally) will be administered as per the iron management criteria (Section 6.10).

Daprodustat will be supplied as film coated tablets for oral administration containing 1, 2, 4, 6, 8, or 10 mg of daprodustat. Doses of 12, 16, and 24 mg of daprodustat will be provided using multiples of these tablet strengths. The doses, tablet size, and description are provided in (Table 1).

Table 1 Description of Daprodustat Tablets

Tablet size	Dose	Description
7.0 mm	daprodustat 1 mg, 2 mg, 4 mg,	7.0 mm round, compound radius, white film coated tablets
9.0 mm	daprodustat 6 mg, 8 mg, 10 mg,	9.0 mm round, compound radius, white film coated tablets

Subjects will take daprodustat tablet(s) daily with water, and these tablets can be taken without regard to food.

GSK will supply rhEPO (darbepoetin alfa) for the control group as prefilled syringes (PFS) for SC/IV injection. If the supply to the site is interrupted due to unexpected circumstances (e.g., natural disaster), local standard of care for anemia management may be considered during that time-period, without the need to withdraw the subject from the study or to permanently discontinue randomized treatment.

Darbepoetin alfa doses from 20 µg to 400 µg will be administered using the strengths in Table 2. See also Appendix 3, Section 12.3.1 for darbepoetin alfa dose steps and dosing frequency. Additional details to deliver the total dose are also captured in the SRM.

Table 2 Description of Darbepoetin Alfa PFS

PFS Strengths	PFS Volume
20 µg*	0.5 mL
30 µg*	0.3 mL
40 µg	0.4 mL
60 µg	0.3 mL
80 µg*	0.4 mL
100 µg	0.5 mL
150 µg	0.3 mL

* Not available in all countries.

6.2. Randomized Treatment Starting Dose, Dose Steps, and Dose Adjustments

6.2.1. Daprodustat Dosing Information

Daprodustat Starting Dose

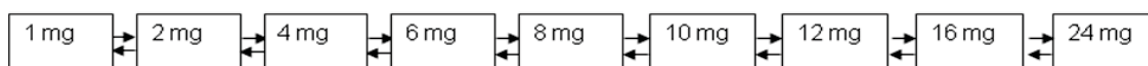
The starting dose of daprodustat will be assigned based on the HemoCue Hgb concentration at randomization (Day 1) ([Table 3](#)).

Table 3 Daprodustat Starting Dose (All Subjects)

HemoCue Hgb (g/dL) at Randomization (Day 1)	Daprodustat starting dose (mg, once daily)
8 to <9	4
9 to <10	2
>10	1

Daprodustat Dose Steps

The available dose steps of daprodustat are outlined below. Dose adjustments will result in the daprodustat dose being increased or decreased by one dose step at a time (see [Appendix 3](#), Section 12.3.2 for details). Those receiving the highest dose of daprodustat who require a dose increase will maintain the same dose, while those receiving the lowest dose of daprodustat that require a dose decrease will have doses withheld.



6.2.2. rhEPO Dosing Information

Darbepoetin alfa Starting Dose

For subjects starting HD or PD, the SC/IV darbepoetin alfa dose will be 0.75-1.0 µg/kg rounded to the nearest available dose. Detailed information is provided in [Table 4](#).

Table 4 Darbepoetin Alfa Starting Dose

Weight	Darbepoetin Alfa Starting Dose
<60 kg	40 µg every 4 weeks
60 kg to <90 kg	60 µg every 4 weeks
90 kg to < 120 kg	40 µg every 2 weeks
120 kg	60 µg every 2 weeks

Darbepoetin alfa Dose Steps

Dose adjustments will be made programmatically by the Interactive Response Technology (IRT) system.

Dose-steps and frequency of administration of darbepoetin alfa are pre-defined in this study ([Appendix 3, Section 12.3.1](#)). The SC or IV darbepoetin alfa dose adjustment increases and decreases are generally within 20% and 33% range, with a few increases of 50% based on available dose strengths.

Additional information about the delivery of the respective rhEPO doses is provided in the SRM. Those receiving the highest dose of rhEPO who require a dose increase will maintain the same dose, while those receiving the lowest dose of rhEPO that require a dose decrease will have doses withheld as per the randomized treatment (daprodustat and darbepoetin alfa) dose adjustment algorithm in [Appendix 3](#).

6.2.3. Daprodustat and rhEPO Dose Adjustment Algorithm

Dose adjustments will be made programmatically by the IRT system to maintain Hgb concentrations within the range of 10-11 g/dL based on the Hgb value measured every 2 to 4 weeks by the HemoCue value disclosed to the IRT system by the investigator.

The protocol-specified randomized treatment (daprodustat or rhEPO) dose adjustment algorithm is provided in [Appendix 3, Section 12.3.2](#).

In order to mitigate subjects remaining below the Hgb target range for an extended period of time, adjustments to the algorithm may be implemented by the Sponsor as outlined in [Appendix 3](#) based on the review of aggregate blinded instream Hgb data.

6.3. Blinding

This is an open-label study; however, the sponsor is blinded to randomized assignment. A detailed Blinding Plan will describe the procedures that will be implemented in order to minimize the extent to which this blind may be compromised.

6.4. Packaging and Product Labeling

Daprodustat tablets are packed in white, opaque high density polyethylene (HDPE) bottles with child-resistant closures. The contents of the label will be in accordance with all applicable regulatory requirements. Randomized treatment will have the dose strength on the label.

6.5. Preparation/Handling/Storage/Accountability

No special preparation of randomized treatment is required.

Only subjects enrolled in the study may receive randomized treatment and only authorized site staff may supply randomized treatment. All randomized treatments must be stored in a secure environmentally controlled and monitored (manual or automated)

area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for randomized treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

Further guidance and information for final disposition of unused randomized treatment are provided in the SRM.

Under normal conditions of handling and administration, randomized treatment is not expected to pose significant safety risks to site staff.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Randomized Treatment Administration

Randomized subjects who administer randomized treatment (daprodustat or rhEPO) at home will be instructed to return all unused randomized treatment at each clinic visit. A record of the number of daprodustat tablets or rhEPO doses dispensed to and taken by each subject will be maintained and reconciled with randomized treatment and compliance records. Randomized treatment start and stop dates and dosing details, including dates for randomized treatment interruptions and/or dose increases or reductions, will be recorded in the eCRF. At Week 2 and for unscheduled visits, compliance checking will not be performed if the dose of randomized treatment is not changed.

Subjects randomized to rhEPO, who have randomized treatment administered in the clinic, will have the details of each administered rhEPO dose maintained and reconciled with randomized treatment and compliance records. Randomized treatment start and stop dates and dosing details, including dates for randomized treatment interruptions and/or dose increases/reductions, will be recorded in the eCRF.

6.6.1. Randomized Treatment Extended Interruption

Every effort must be made to continue randomized treatment and to complete study visits, where able; however, sites should contact their PPD study team member if a subject cannot return to the research site on a temporary basis for any one of the following situations:

- Subjects who are hospitalized for any duration.
- Subjects who cannot return to the site for a period >5 weeks.

In exceptional circumstances, standard of care for anemia management during this time period may be considered based on consultation with the PPD medical monitor. If non-study ESAs are administered, doses should be recorded on the Prior/Concomitant Medications – ESA eCRF page.

6.7. Treatment of Randomized Treatment Overdose

There is no specific antidote for overdose with daprodustat. The expected manifestations of daprodustat overdosage include signs and symptoms associated with an excessive and/or rapid increase in Hgb concentration.

Daprodustat is highly protein bound, thus clearance of daprodustat by HD or PD is very low so dialysis is not an effective method to enhance the elimination of daprodustat. Daprodustat metabolites are, in part, cleared via hemodialysis. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted, as dictated by the subject's clinical status. Additionally, subjects should be monitored closely for cardiovascular (CV) events, increased heart rate and hematologic abnormalities.

Consult the approved product label for information on overdose for rhEPOs.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study.

The investigator is responsible for ensuring that consideration has been given to post-study care of the subject's medical condition.

6.9. Concomitant Medications

Concomitant medications, including over-the-counter medications and supplements, taken during the study will be recorded in the eCRF. Start/stop dates and route of administration will be recorded for general concomitant medications. Additional details (e.g., changes in dose, reason for change, reason for addition and termination) will be recorded for certain medications at each visit (i.e., iron and anti-hypertensive medications).

6.9.1. Permitted Medications

Unless specified as a prohibited medication in Section 6.9.2, all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferiasirox) should be performed with caution.

6.9.2. Prohibited Medications

Use of any of the following prescription drugs from screening until 7 days after the last dose of randomized treatment is prohibited and will constitute a protocol violation.

- Strong inhibitors of CYP2C8 (e.g., gemfibrozil)
- Strong inducers of CYP2C8 (e.g., rifampin/rifampicin)

Except for study randomized treatment, no other investigational agents or devices are permitted from study entry through completion of the study.

6.10. Iron Management Criteria

Subjects must remain iron replete throughout the study. The investigator will follow the iron management criteria from randomization (Day 1) through the end of the study treatment period for subjects receiving randomized treatment.

Iron therapy will be administered if ferritin is ≥ 100 ng/mL and/or TSAT is $\geq 20\%$. The investigator should choose the route of administration and dose of iron based on the subject's iron status and local clinical practice.

All iron (excluding multivitamins) must be stopped and cannot be administered if:

- Ferritin >800 ng/mL and TSAT $>20\%$, or
- TSAT $>40\%$

Investigators should be guided by local/regional guidelines and may stop administration of iron at a lower ferritin or TSAT level as long as subjects are maintained at a ferritin >100 ng/mL and TSAT $>20\%$.

The Steering Committee (Section 10.8.3) will monitor blinded subject iron data in an ongoing fashion to ensure compliance.

6.11. Anemia Rescue Therapy

A rescue algorithm is provided to minimize subjects having an inadequate response to the treatment for their anemia for an extended period of time and to enable consistency in the application of rescue therapy across the study. Details are provided in Table 5.

This rescue algorithm does not apply to subjects with a low Hgb as a result of an acute or sub-acute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or vascular access). In these cases, treatment should be directed to the specific cause AND randomized treatment will be continued. If a subject is transfused as part of the treatment, then the randomized treatment will be maintained at the current dose (unless Hgb is ≥ 12 g/dL which requires a dose hold).

Table 5 Rescue Algorithm for Anemia Management

Evaluate Subject for Rescue if: HemoCue Hgb remains <9 g/dL (at a scheduled visit, Week 4 onwards) despite three ¹ consecutive dose increases above the starting dose or post-rescue ² (where HemoCue Hgb<9 g/dL prior to each dose increase) OR HemoCue Hgb is <7.5 g/dL despite a dose increase at the prior study visit.	
Step 1: Initial Intervention	While continuing randomized treatment (increase dose if HemoCue Hgb <7.5 g/dL; otherwise maintain current dose), intervene with one or more of the following as dictated by clinical comorbidities: <ul style="list-style-type: none"> - Single course of IV iron up to 1000 mg (in addition to the iron management criteria) - Transfusion of up to two units of packed red blood cells (PRBC) if clinically indicated - Allow additional 4 weeks on randomized treatment (NOTE: this is a required choice; can be combined with either or both of the above)
Step 2: Rescue	Check HemoCue Hgb 4 weeks \pm 1 week from last study visit; earlier checks of Hgb may be obtained to advise further intervention as clinically indicated. Randomized treatment should be permanently discontinued and the subject should be rescued according to local clinical practice if either, <ul style="list-style-type: none"> - HemoCue Hgb remains <9 g/dL despite initial intervention based on the average of two HemoCue Hgb values³ OR <ul style="list-style-type: none"> - More than two units of PRBC were needed for transfusion (and was not related to acute bleeding).

1. Two consecutive dose increases if starting/post-rescue dose is daprodustat 12 mg or darbepoetin alfa 200 µg over 4 weeks; one dose increase if starting/post-rescue dose is daprodustat 16 mg or darbepoetin alfa 300 µg over 4 weeks; and no prior dose increase if starting/post-rescue dose is daprodustat 24 mg or darbepoetin alfa 400 µg over 4 weeks (top dose).
2. For subjects who previously are evaluated for rescue and who are able to continue in the trial, “post-rescue” dose is the dose of randomized treatment that a subject is receiving at the study visit after initial intervention.
3. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample); take average of 2 values.

6.12. Subjects Changing Dialysis Modality

Subjects changing dialysis modality should not be withdrawn from the study, but should continue on the same randomized treatment (daprodustat or darbepoetin alfa).

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Time and Events Tables are provided for subjects receiving randomized treatment (Table 6) and for subjects who permanently discontinue randomized treatment (Table 7).

Because Hgb levels become more variable with increased time between dialysis sessions,

the designated study visit should occur during the dialysis session with the shortest interval from the previous session.

Designated study visits for subjects in the screening period or study treatment period who have not yet initiated dialysis can occur on any day of the week.

Designated study visits for subjects on dialysis should be scheduled as follows from the screening assessment to the end of the study:

- For subjects on 3X/week HD: The designated study visit must not occur on the first dialysis session of the week. For example, if on a Monday-Wednesday-Friday schedule, the study visit should be on Wednesday or Friday.
- For subjects on 2X/week HD: The visit should occur during the session that is closest to the previous HD session. For example, if a subject receives dialysis on a Monday and Thursday, the study visit should be on the Thursday (2 days from the previous dialysis session) rather than the Monday (3 days from the previous dialysis session).
- For subjects on PD: study visits can occur on any day of the week.

Details regarding study-specific equipment are provided in [Appendix 7](#).

Post-randomization visits should be referenced back to the Randomization visit (Day 1). The visit window for those on randomized treatment for the Week 2 and Week 4 visits is ± 3 days. The visit window specified for those on randomized treatment from Week 6 onwards is ± 1 week. However, to ensure continuity of randomized treatment, study visits should be no more than 5 weeks apart. In exceptional circumstances, minor changes to visit structure may be permitted after consultation with the PPD/GSK Medical Monitor.

Study assessments should preferably be done at dialysis centers, however, in some circumstances assessments can be performed at the research site.

Supplementary study conduct information is provided in the SRM. The SRM provides administrative and detailed technical information that does not impact subject safety.

7.1. Time and Events Tables and Procedures for Subject Follow-up

Table 6 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
Vitamin B12 ¹ , folate	X							
Hepcidin		X		X		X		X

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
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 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 taken in triplicate. Measurements will be taken post-dialysis for subjects receiving in-center dialysis. See 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 (Day1).
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 Section 7.4.10.
5. Additional visits to check Hgb and dispense randomized treatment are required under the circumstances described in 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 Appendix 5) during the study pregnancy tests are no longer required.
9. Testing panel in Table 8. 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 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 \geq 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.

Table 7 TIME AND EVENTS TABLE FOR SUBJECTS THAT PERMANENTLY DISCONTINUE RANDOMIZED TREATMENT

Protocol Activity	Early Treatment Discontinuation Visit (within 2 weeks of the last dose of randomized treatment)	Day 1 – Week 52 (every 12 weeks \pm 2 weeks)	Unscheduled	Follow-up (4 weeks post-study termination \pm 1 week)
Dialysis: In-clinic assessments done pre-dialysis.				
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 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.

7.2. Screening and Critical Baseline Assessments

Before any study-specific procedure is performed, valid informed consent must be obtained.

Demography and medical history will be assessed at the initial screening visit.

Randomization requires an Hgb level within the specified range (Section 5.1) and levels of serum ferritin or TSAT as outlined in Section 5.2.

Full details of screening and baseline (Day 1) assessments are provided in the Time and Events Table (Table 6).

7.3. Efficacy

Planned time points for all Hgb efficacy assessments are listed in the Time and Events Table (Table 6).

GSK will supply a point-of-care Hgb analyzer (i.e., HemoCue) to each site for rapid measurement of Hgb.

Blood samples (not fingersticks) for measurement of Hgb via HemoCue, and also by the central laboratory will be collected as specified in the Time and Events Table (Table 6).

7.4. Safety

Safety endpoints will include monitoring of deaths, AEs, SAEs, other CV events, AEs of special interest, AEs leading to discontinuation of randomized treatment, and laboratory parameters, blood pressure and heart rate (HR).

Planned time points for all safety assessments are listed in the Time and Events Table (Table 6). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

7.4.1. Events Referred to the Clinical Event Committee (CEC)

Investigators should refer any event suspected to be one of the events below to the CEC. The CEC will review and adjudicate the following clinical events. See CEC Site Manual for full scope of reporting requirements.

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

Events referred to the CEC will be subjected to blinded adjudication using pre-specified diagnostic criteria.

When the investigator-reported event and the CEC assessment of the event differ, the CEC's decision will be considered final. The detailed descriptions of the endpoint definitions used for adjudication are contained within the CEC Charter (available on request).

Source documentation required to support the adjudication of the events is described in the CEC Site Manual.

7.4.2. Other CV Events

GSK has identified other CV events of interest for all clinical studies. Investigators will be required to fill out the specific CV event page of the eCRF for the following categories of events:

- Arrhythmias
- Pulmonary hypertension*
- Valvulopathy
- Revascularization

(Pulmonary hypertension is also an AE of special interest for the current study, see Section 7.4.4 for details.)*

7.4.3. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE and SAE can be found in [Appendix 8](#).

The investigator or their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.3.1. Time period and Frequency for collecting AE and SAE information

- Any SAE assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of randomized treatment until the Follow-up visit, at the timepoints specified in the Time and Events Table ([Table 6](#)).
- Medical occurrences that begin prior to the start of randomized treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to PPD within 24 hours, as indicated in [Appendix 8](#).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the randomized treatment or study participation, the investigator must promptly notify PPD.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to PPD are provided in [Appendix 8](#).

7.4.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.4.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.6.2). Further information on follow-up procedures is given in [Appendix 8](#).

7.4.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to PPD of SAEs related to randomized treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.4. Adverse Events of Special Interest

The investigator or site staff will be responsible for detecting, documenting and reporting any event that may represent the AEs of special interest listed below (using preferred terms):

- 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

The results of any investigation should be recorded on the AE page and in the relevant AE of special interest page of the subjects' eCRFs.

7.4.5. Possible Suicidality Related Adverse Events

If during the study there is an occurrence of an AE or SAE which in the investigator's opinion, is possibly related to suicidality, the Possible Suicidality Related Adverse Events (PSRAE) eCRF form should be completed (in addition to the AE and SAE pages, as appropriate).

This event may include, but is not limited to, one that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly related to suicidality.

7.4.6. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until 7 days after the last dose.

- If a pregnancy is reported, the investigator should inform PPD within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 9](#).

7.4.7. Height and Weight

Height and weight will be measured as specified in the Time and Events Table ([Table 6](#)). Weight will be measured in clinic with the subject wearing indoor daytime clothing with no shoes. For HD subjects, this will be measured pre and post dialysis when possible, or at study visits between dialysis sessions. For PD subjects these assessments will be done at study visits, as per standard of care.

Estimated dry (target) weight will be calculated at each study visit as specified in the Time and Events Table ([Table 6](#)).

7.4.8. Blood Pressure and Heart Rate

Measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) will be taken at the time points specified in the Time and Events Table (Table 6).

- One measurement each of SBP, DBP and HR will be taken, except at Day 1, Week 52, and the Early Treatment Discontinuation visit (if applicable), when SBP, DBP and HR will be measured in triplicate.
- For HD subjects, measurements will be taken pre-and post dialysis with the subject in a semi-supine or seated position in the dialysis chair after at least a 5-minute rest period.
- For PD subjects, this assessment will be done at study visits, as per standard of care.

SBP, DBP, and HR will be performed before collection of blood samples for laboratory testing, where applicable.

7.4.9. Electrocardiogram (ECG)

ECG measurements will be taken at the time points specified in Table 6 and must be recorded pre-dialysis. Full 12-lead ECGs will be recorded with the subject in a supine position. Heart rate, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcB will be calculated (machine-read or manually).

For the Day 1 ECG, two additional ECGs are required if the initial ECG indicates prolonged QTc using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility (Section 5.2 for detail). Additional details are provided in the SRM.

ECG data will be read locally by a physician with experience in reading and interpreting ECGs. The over-read of the Day 1 ECG is required to confirm eligibility. Additional details are provided in the SRM.

All ECGs will be performed before measurement of SBP, DBP, HR (in-center HD only) and before collection of blood samples for laboratory testing.

7.4.10. Ultrasound

An ultrasound of the kidneys and adrenal glands will be performed prior to randomization (Day 1). It is understood that the adrenal glands will not always be able to be visualized. Non-visualization of the adrenals is NOT a reason to exclude subjects from randomization. Further details are provided in the SRM.

A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria (Section 5.2), provided the size and cyst category has been

reported. If a more sensitive imaging study (e.g., MRI, CT) has been performed within this timeframe and a report is available, this may be used in place of the ultrasound.

7.4.11. Clinical Laboratory Assessments

All protocol required laboratory assessments, as defined in [Table 8](#), must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule ([Table 6](#)). Laboratory assessments will be done pre-dialysis for HD subjects and at the study visits for PD subjects, as per standard of care.

Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's source notes.

Refer to the SRM for appropriate processing and handling of samples.

All study-required laboratory assessments will be performed by a central laboratory with the exception of HemoCue Hgb which will be performed at the clinical site. The results of each HemoCue Hgb must be entered into the subject's eCRF.

Table 8 Protocol Required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count	<i>RBC indices:</i>	<i>WBC count with Differential</i>
	RBC count	MCV	Neutrophils
	Reticulocyte count	MCH	Lymphocytes
	Hgb	MCHC	Monocytes
	Hematocrit	RDW	Eosinophils
			Basophils
Clinical Chemistry¹	ALT	AST	Bilirubin (total and direct/indirect)
	Potassium (serum)	Urea (serum)	Albumin (serum)
	Calcium (total and albumin-adjusted)	Inorganic phosphate	Creatinine (eGFR CKD-EPI) ^{4,5}
Iron parameters	Serum iron	Ferritin	UIBC
	Hepcidin	TSAT (calculated)	TIBC (calculated)
Lipid parameters	Total cholesterol	LDL-C (direct)	HDL-C
Other laboratory tests	Serum hCG pregnancy test ²	Follicle stimulating hormone ³	Estradiol ³
	HemoCue Hgb	hsCRP	iPTH
	Stored sample (blood)	Vitamin B12	Folate

Abbreviations: WBC, white blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width, AST, aspartate transaminase; ALT, alanine transaminase; LDL-C, low density lipoprotein-C; HDL-c high density lipoprotein-C; UIBC, unsaturated iron binding capacity; TIBC, Total iron binding capacity; TSAT, Transferrin saturation; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; hCG, human chorionic gonadotropin; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in [Appendix 6](#).
2. For females of reproductive potential only.
3. Screening only. As needed in postmenopausal women where their menopausal status is in doubt (see Inclusion Criteria Section [5.1](#))
4. Detail on the regional specific calculation will be summarized in the SPM.
5. Creatinine and eGFR will only be tested and calculated at screening and randomization

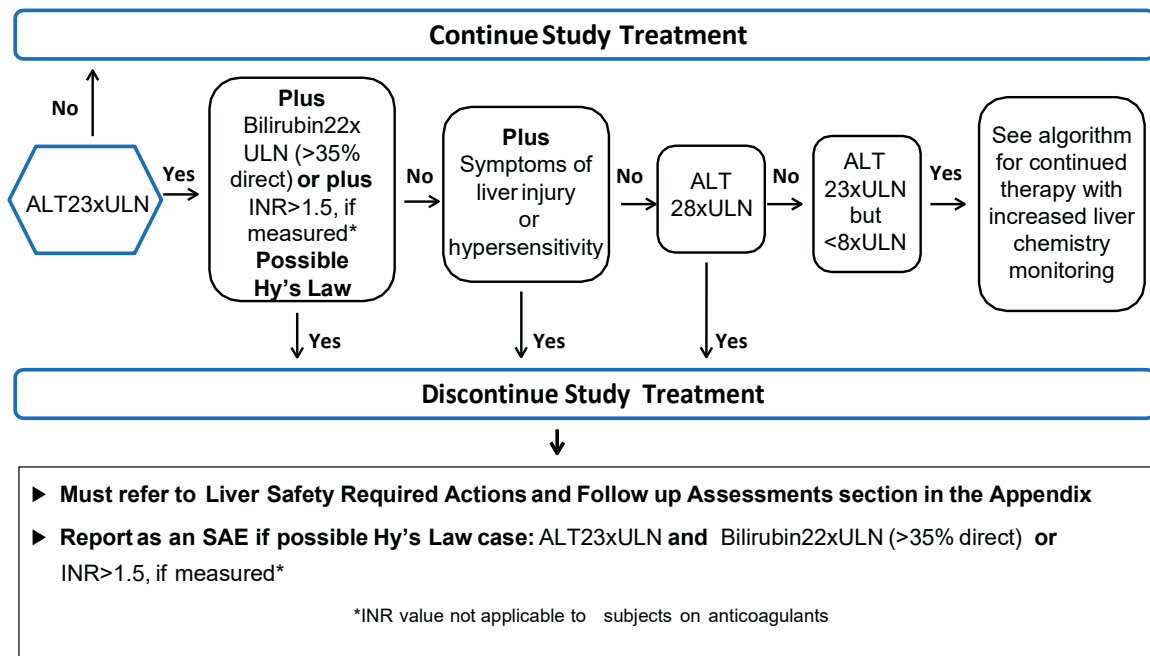
All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of randomized treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the Sponsor should be notified.

7.4.12. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

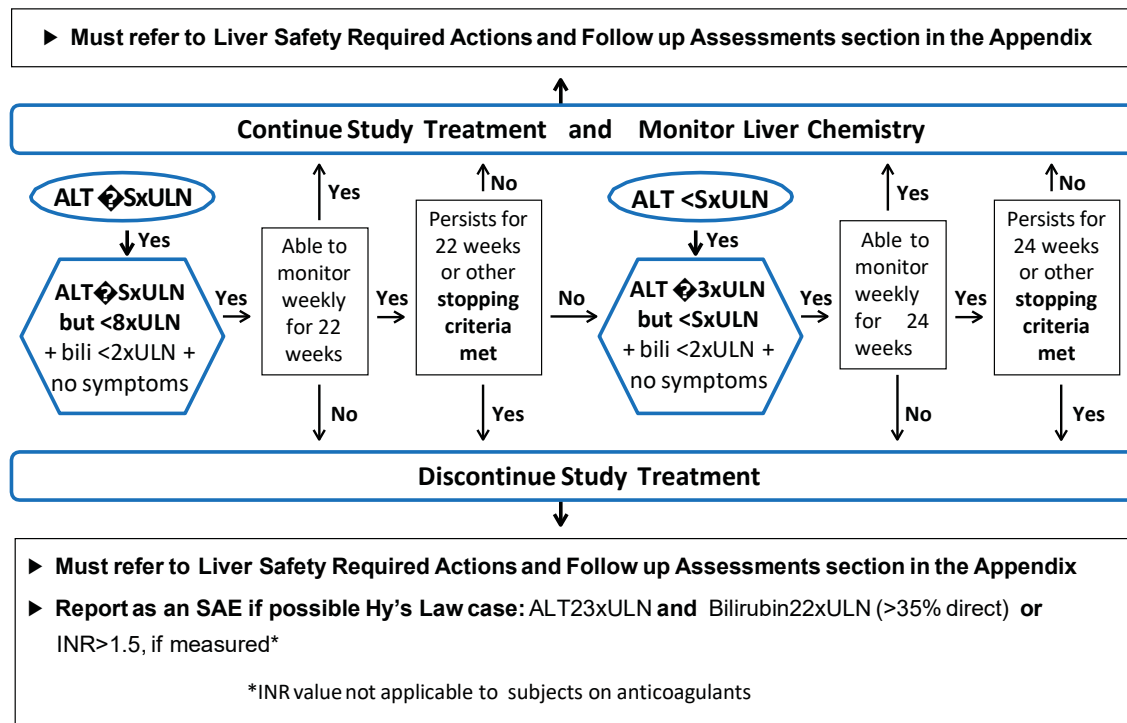
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Phase 3 Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 6](#).

Phase 3-4 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥ 3 xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 6](#).

7.4.12.1. Randomized Treatment Restart

If a subject meets liver chemistry stopping criteria, do not restart randomized treatment unless there is a clear underlying cause for the liver stopping event other than drug-induced liver injury and:

- GSK Medical Governance approval **is granted in writing**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the subject

The full liver safety drug restart guideline is provided in [Appendix 6](#).

7.5. Pharmacokinetics (PK)

PK sampling will be performed in all in-center HD subjects randomized to the daprodustat arm.

Blood samples will be collected at the Week 4, Week 8 **or** Week 12 visit (i.e., PK is collected at one visit only, based on convenience for the subject/site). Samples will be collected at the following times relative to dosing of randomized treatment:

- Predose, 0.5, 1, 2, and 3 h post dose.

On the day of the scheduled PK visit:

- The subject is to be instructed **not** to take their dose at home before the visit, but to take the dose in the clinic after the pre-dose sample is collected.
- The dose taken in the clinic should be from the same bottle(s) the subject has been using prior to the PK visit, **not** from any newly dispensed bottle(s) at the PK visit. [Note: a subject placed on a dose hold at the previous visit should not have PK samples taken; PK collection should be delayed until the visit after the subject has restarted study treatment.]
- Record the date and actual time of the dose taken in the clinic and three doses prior to the visit, and the date and actual time of all PK samples collected. Samples may be collected within ± 20 min of the planned collected time.
- Based on the time of dosing, samples may be obtained before, during, or after any dialysis procedure. The start and stop time of the dialysis procedure will also be recorded at this visit.

Plasma PK analysis will be performed under the control of GSK PTS-DMPK/Scinovo, the details of which will be included in the SRM. Concentrations of parent daprodustat

and metabolites (GSK2391220 (M2), GSK2531403 (M3), and GSK2531401 (M13)) will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

7.6. Genetics

Information regarding genetic research is included in [Appendix 10](#). Samples for genetic analysis will be taken at the time points specified in the Time and Events Table ([Table 6](#)).

7.7. Patient Reported Outcomes

The patient-reported effect of daprodustat and rhEPO on symptoms, health-related quality of life (HR-QoL), and health status (e.g. utility) will be assessed. Symptoms will be assessed using a symptoms questionnaire which is specific to anemia of CKD (CKD-AQ). Overall symptom severity will be assessed using the patient global impression of severity (PGI-S) and overall symptom change using the patient global impression of change (PGI-C). Quality of life will be measured via SF-36, and health status via the EQ-5D-5L and EQ-5D-VAS. In addition, healthcare resource utilization will be assessed including out-patient visits.

All questionnaires used in this study have been translated and culturally adapted use in local country languages and will be administered electronically only. Specific instructions on how the subject is to complete the scales and the process for data entry is provided in the SRM. Details on patient reported outcomes are provided in the study reference manual.

The CKD-AQ, PGI-S, PGI-C, HR-QoL, and Health Status questionnaires should be completed by subjects at a clinic visit, in the order specified: PGI-S, PGI-C, CKD-AQ, SF-36, EQ-5D 5L, and EQ-VAS. Subjects who are unable to or require assistance to read must not complete the questionnaires. If there are other exceptional circumstances whereby the Patient Reported Outcomes assessments cannot be conducted, the completion of these assessments will be discussed with the Sponsor on a case-by-case basis.

7.7.1. Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ)

A novel symptom questionnaire – CKD-AQ has been developed to collect concepts of interest for the anemia of CKD population over the past 24 hours. Unlike the Functional Assessment of Cancer Therapy – Anemia (FACT-AN) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) which have not demonstrated content validity specific for the anemia of CKD population, the novel CKD-AQ instrument was developed to verify and ensure that concepts specific for anemia of CKD were captured and measured. It will measure both the frequency and/or severity in anemia of CKD concepts such as weakness, energy, tiredness, shortness of breath, exertion, chest pain, memory, concentration, standing, sleep and distress over the past seven days.

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

The Patient Global Impression of Severity (PGI-S) is a 1-item questionnaire designed to assess patient's impression of disease severity of their anemia of CKD. It is measured on a 5-point disease severity scale (absent, mild, moderate, severe, or very severe) during the past 24 hours.

The Patient Global Impression of Change (PGI-C) is a 1-item questionnaire designed to assess a subject's impression of symptom change of their anemia of CKD. It is measured 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) since they first started the study.

7.7.3. Health Related Quality of Life (SF-36)

The SF-36 acute version is a general health status questionnaire designed to elucidate the subject's perception of their health on several domains, including physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, mental health, and general health. The questionnaire contains 36 questions within these domains that ask the subject to recall how they felt during the past seven days.

7.7.4. Health Status (EQ-5D-5L & EQ-VAS)

EQ-5D-5L consists of two concepts – the EQ-5D-5L descriptive system and the EQ-VAS. The EQ-5D-5L is a self-reported descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. Self-reported health status captured by EQ-5D-5L relates to the subject's situation at the time of completion. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'the best health you can imagine' and 'the worst health you can imagine'. This information is used as a quantitative measure of health outcome as judged by individual subjects.

7.7.5. Psychometric Analyses of the CKD Anemia Symptoms Questionnaire (CKD-AQ)

In order to establish and evaluate the measurement properties of the CKD-AQ, an interim cut of blinded observations of the first 50 subjects who completed the week 28 visit will be taken. In order to establish content validity, the data cut will require a comparison to the following variables: PGI-C, PGI-S, Hgb, SF-36, demographic & baseline clinical characteristics. All data will be abstracted from screening until week 28.

The interim data cut will be used to conduct confirmatory factor analysis in order to establish a scoring algorithm for potential instrument domains and to evaluate the reliability, validity and responsiveness of the instrument without regard to treatment group. A full description of the data cut, variables of interest and analyses to establish

the scoring and evaluate the measurement properties of the CKD-AQ will be specified *a priori* within the psychometric analysis plan.

7.8. Storage Biomarkers

Blood (serum and plasma) samples will be collected as outlined in the Time and Events Table (Table 6) for potential future analysis of CV risk and iron metabolism.

8. DATA MANAGEMENT

- For this study, subject data will be entered into eCRFs, transmitted electronically and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug, respectively.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Primary Hypotheses

The primary Hgb efficacy objective will assess the estimand defined as the comparative treatment effect in mean Hgb change between baseline and EP (i.e., Weeks 28 to 52 inclusive) in all randomized subjects; defined as those who remain in follow-up throughout the period of stabilization and have at least one Hgb assessment during the EP (i.e., Weeks 28 to 52) regardless of adherence to study treatment. The analysis will test whether daprodustat is non-inferior to rhEPO according to the following statistical hypotheses:

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

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

Statistical significance of non-inferiority will be assessed at the one-sided 2.5% level. An analysis of covariance (ANCOVA) model including randomization stratification factors, baseline hemoglobin and treatment will be used to obtain a point estimate and the two-sided 95% CI for the treatment difference (daprodustat-rhEPO) and generate the p-value for the non-inferiority test. The non-inferiority p-value will show strength of evidence against the null hypothesis. Non-inferiority will be established if the lower limit of the two-sided 95% CI for the treatment difference is greater than -0.75 g/dL.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The size of this study has been determined to be sufficient to meet the ICH E1 guideline for subject exposure, number and duration and to provide at least 90% power to test the primary non-inferiority hypothesis with a two-sided 95% CI.

Approximately 300 subjects are planned to be randomized (150 per arm) to receive daprodustat or rhEPO, to provide at least 100 subjects exposed to daprodustat for one year. Subjects will be treated to achieve and maintain Hgb between 10 and 11 g/dL. The expected difference in mean Hgb change from baseline and the EP, between arms, is 0 g/dL and the anticipated between subject standard deviation (SD) is 1.5 g/dL, based on historical rhEPO trials and daprodustat clinical trial experience to date. With a pre-specified non-inferiority margin of -0.75 g/dL, a two-sample T-test and assuming that up to approximately 30% of subjects will permanently stop randomized treatment before Week 28 (start of EP), 300 randomized subjects will provide >90% power to test the primary hypothesis.

With 300 randomized subjects, it is anticipated that the difference in mean Hgb change from baseline between arms will be estimated with a precision of 0.408 g/dL (half width of the two-sided 95% CI) and the largest (most negative) difference between arms that would meet the statistical criterion for non-inferiority would be -0.342 g/dL.

9.2.2. Sample Size Sensitivity

The following table illustrates the impact on power for the primary efficacy analysis based on alternative assumptions for the between subject SD and the percentage of non-evaluable subjects.

Between subject Hgb SD (g/dL)	% non-evaluable (number of subjects per arm)				
	20%	25%	30%	35%	40%
	(n=120)	(n=113)	(n=105)	(n=98)	(n=90)
1	>99%	>99%	>99%	>99%	>99%
1.25	>99%	>99%	>99%	99%	98%
1.5	97%	96%	95%	94%	92%
1.75	91%	89%	87%	85%	82%
2	82%	80%	77%	74%	71%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The primary population for Hgb efficacy analyses will be the All Randomized (ITT) Population. Subjects will be analyzed according to the treatment to which they were randomized. In order to assess the sensitivity of the primary efficacy analysis, an analysis will be performed in a Per-Protocol (PP) Population defined as all ITT subjects who are not major protocol violators. Details will be defined in the RAP and subjects analyzed according to the treatment received.

For analyses of time to event endpoints such as all-cause mortality, Major Adverse Cardiovascular Events (MACE) and hospitalizations, the All Randomized (ITT) Population will also be used. Subjects will be analyzed according to the treatment to which they were randomized.

The primary population for safety (Safety Population) will consist of all randomized subjects who receive at least one dose of randomized treatment. Subjects will be analyzed according to the treatment received.

Additional populations may be defined in the RAP.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Mean change in Hgb between baseline and EP (Weeks 28-52): The primary efficacy estimand is to compare the effect of treatment for the evaluation of mean change from baseline in Hgb during a 24-week evaluation period (Weeks 28 to 52 inclusive) in all ITT subjects with at least one Hgb during the EP. The analysis will use an analysis of covariance (ANCOVA) model. For each subject, the baseline Hgb will be the value obtained on Day 1, prior to taking randomized treatment, and Hgb during EP will be determined by calculating the mean of all available Hgb values between Weeks 28 to 52 inclusive regardless of adherence to randomized treatment. The ANCOVA model will include randomization stratification factors, baseline hemoglobin, and treatment. It will provide a point estimate and two-sided 95% CI for the treatment effect, together with the one-sided non-inferiority test p-value. Non-inferiority will be established if the lower limit of the two-sided 95% CI is greater than the margin of -0.75 g/dL. There will be no imputation for missing data but imputation will be explored via sensitivity analyses

Sensitivity and Supplementary Analyses: Sensitivity analyses for the primary estimand will include a multiple imputation-based “tipping point” analysis where assumptions are adjusted until non-inferiority is lost by imputing data for subjects who did not fully complete the EP. A further supplementary analysis will evaluate efficacy in those subjects who adhere to randomized treatment, defined as ITT subjects with at least one

on-treatment Hgb during the EP (this approach corresponds to evaluating an efficacy estimand). A similar “tipping point” analysis as that described above for the primary analysis will be performed for this “on-drug” analysis. In addition, a supplementary per-protocol analysis will estimate the treatment effect in subjects who strongly adhere to the protocol, and sensitivity analyses to explore a shorter EP (Weeks 28 to 36) will be performed for the primary effectiveness estimand and “on-drug” efficacy estimand. Full details of all sensitivity and supplementary analyses will be provided in the RAP.

9.4.2. Secondary Analyses

9.4.2.1. Principal Secondary Efficacy Analyses

Conditional on the primary endpoint achieving non-inferiority at the one-sided 2.5% level, statistical testing will progress to the principal secondary endpoint with a focus on superiority using a one-sided 2.5% significance level.

For the average monthly IV iron dose up to Week 52 endpoint: IV iron use for all subjects will be recorded in the eCRF and the average monthly IV iron dose up to week 52 while on treatment will be calculated. An ANCOVA model will be used to compare the difference in this average monthly IV iron dose per subject between arms, including factors for baseline dose, treatment and the randomization stratification factors.

Additional secondary/exploratory endpoints are listed in [Appendix 2](#). All analyses of secondary endpoints are of exploratory nature, summary statistical and nominal one-sided -p values will be used to describe the results and for any treatment comparisons.

9.4.2.2. Safety Analyses

Safety data, including all AEs (i.e., non-serious, serious and AEs of special interest), laboratory data, vital signs, concomitant medications and meeting protocol defined stopping criteria (e.g., liver chemistry) will be descriptively summarized by treatment arm. Reasons for stopping randomized treatment and for early study withdrawal will also be summarized by treatment group and time to stopping treatment or study will be presented graphically and assessed. Full details of all safety data reporting will be described in the RAP.





9.4.3. Multiplicity Strategy

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

The additional secondary/exploratory endpoints as listed in [Appendix 2](#), if tested, will not be adjusted for multiplicity. A nominal one-sided 2.5% significance level will be applied per test.

9.4.4. Covariates and Subgroups of Interest

The primary and principal secondary endpoint will be evaluated for a set of pre-specified subgroups to support the proposed indication. Subgroup analyses are aimed to assess for consistency with the overall result, they may have low power if the subgroup is small. Statistical models will be adjusted for the covariates used in the original analysis, baseline, subgroup, treatment and treatment by subgroup interaction. Point estimates and two-sided 95% CIs will be estimated (presented on Forest Plots) and the subgroup by treatment interaction p-value calculated. Subgroup analyses will not be adjusted for multiplicity. Further subgroups/covariates may be defined in the RAP.

Category	Subgroups
Age	<65 years,  65 years - <75,  75 years
Gender	Female, Male
Race group	American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race
Ethnicity	Hispanic, non-Hispanic
Region	US, EU, RoW (repeat using US, Non-US)
Dialysis type	HD, PD (repeat using HD, HDF/HF, PD)
Dialysis status	Planned, unplanned (urgent) start
Baseline Hgb	<9, 9 to <10, 10 to 11, >11 g/dL
BMI	<30,  30
Weight	< 75kg,  75kg
Baseline hsCRP	s;3 mg/l, >3 mg/l

Additional exploratory subgroups may be defined in the RAP.

9.4.4.1. Exploratory Cardiovascular Safety Analysis

This study is not designed or sufficiently powered for formal statistical analyses to assess cardiovascular safety. With fewer than 80 first MACE (defined as all-cause mortality, non-fatal MI, or non-fatal stroke) expected to occur during the trial, incidence rates and two-sided 95% CIs will be computed for the following mortality and CV composite or component endpoints: 1) MACE; 2) MACE or a thromboembolic event (vascular access thrombosis, a symptomatic deep vein thrombosis or a symptomatic pulmonary embolism); 3) MACE or hospitalization for heart failure; 4) all cause mortality; 5) CV mortality; 6) MI (fatal and non-fatal); 7) stroke (fatal and non-fatal); 8) CV mortality or non-fatal MI; 9) all cause hospitalization.

9.4.5. Interim Analysis

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.

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

Further details will be specified in the IDMC charter and RAP.

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

The 'PK Population' is defined as subjects for whom a PK sample was obtained and analyzed. This will be the population used for all the PK displays.

The following plasma PK parameters will be determined for daprodustat and metabolites: C_{τ} (pre-dose) and C_{\max} .

Plasma daprodustat and metabolites concentration data will be listed and summarized by planned collection time and daprodustat dose administered at PK visit. PK parameter data will be listed and summarized by daprodustat dose administered at PK visit, and dose-normalized (per mg) PK parameter data will be summarized.

All PK data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

The following exploratory graphics will be created. Based on these, and the efficacy and safety results from other Phase 3 studies, post-hoc exploratory exposure-response/safety modelling may be conducted, including exploratory graphics with metabolites. Further details will be provided in the RAP.

- Scatter plots of daprodustat PK parameters (C_{τ} and C_{\max}) dose normalized to 1 mg vs. percent time in range during EP.
- Scatter plots of average daprodustat dose during EP vs. percent time in range during EP.
- Scatter plots of daprodustat PK parameters (C_{τ} and C_{\max}) dose normalized to average dose during EP vs. percent time in range during EP.
- Scatter plots of daprodustat PK parameters (C_{τ} and C_{\max}) 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 (C_{τ} and C_{\max}) dose normalized to average dose during EP vs. change from baseline of Hgb during EP.
- Boxplots of daprodustat PK parameters dose normalized to 1 mg by subjects with or without MACE or a combined safety endpoint of MACE + thromboembolic event + hospitalization for heart failure

- Boxplots of daprodustat PK parameters 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

9.4.7. Analysis of Patient Reported Outcomes Measures

Analysis to compare the patient reported effects of daprodustat and rhEPO on symptoms, severity, HR-QoL, and health status, as discussed in Section 7.7, will be described in the RAP. In order to establish and evaluate the measurement properties of the CKD-QA, an interim cut of blinded observations of at least 50 subjects who completed the Week 28 visit will be taken. The data cut will require the following variables through Week 28: PGI-C, PGI-S, Hgb, SF-36, demographic and baseline clinical characteristics.

The interim data cut will be used to conduct confirmatory factor analysis in order to establish a scoring algorithm for potential instrument domains and to evaluate the reliability, validity and responsiveness of the instrument without regard to treatment group. A full description of the data cut, variables of interest and analyses to establish the scoring and to evaluate the measurement properties of the CKD-QA will be specified *a priori* within a separate psychometric analysis plan.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion or approval of the study protocol and amendments as applicable
- Obtaining signed informed consent for each subject prior to participation in the study

- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, PPD monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

PPD will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, PPD may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the PPD monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and PPD Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determine such action is needed, PPD will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, PPD will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, PPD will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK or PPD will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- PPD will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, PPD standards/procedures, and/or institutional requirements.
- The investigator must notify PPD of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.

GSK or PPD will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

10.8. Review Committees

In addition to GSK, medical governance will also be provided by the following independent committees:

10.8.1. Independent Data Monitoring Committee

An IDMC unblinded to treatment allocation will be utilized in this study to ensure external objective review of safety and efficacy data in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The analysis plan for IDMC review is described in the charter which is available upon request.

10.8.2. Clinical Endpoint Committee

An external independent CEC blinded to treatment allocation will adjudicate all clinical events reported during this study that are referred for adjudication, including major adverse cardiovascular events (MACE; composite of all-cause mortality [CV and non-CV mortality], non-fatal MI and non-fatal stroke) and additional components for a broader definition of MACE including thromboembolic events (vascular access thrombosis, symptomatic deep vein thrombosis, symptomatic pulmonary embolism), and hospitalization for heart failure (Section 7.4.1).

10.8.3. Steering Committees

The Executive Steering Committee is the primary external advisory group for GSK. The committee provides academic leadership, ensures proper study conduct and conformance to the protocol, advises and recommends changes to the protocol based on emerging scientific and/or clinical advances, advises on the selection of study sites, communicates with the media and external audiences when appropriate, and works with the sponsor to assist in patient identification strategies. Additional information about the committee is included in the Executive Steering Committee charter, which is available upon request.

The broader Steering Committee in collaboration with the Executive Steering Committee is responsible for the scientific content and integrity of all aspects of study conduct including participation in the study sub-committees and providing advice to the National Leader Committee if needed.

10.8.4. National Leader Committee

The National Leader Committee will provide clinical and operational leadership at the country and regional level to support the implementation and conduct of the studies.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse event
AESI	Adverse event of Special Interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APD	Automated peritoneal dialysis
AST	Aspartate transaminase
AUC	Area under curve
BCRP	Breast cancer resistant protein
BP	Blood pressure
CAPD	Continuous ambulatory peritoneal dialysis
CEC	Clinical Event Committee
CI	Confidence interval
CKD	Chronic kidney disease
CKD-AQ	Chronic kidney disease anemia symptoms questionnaire
CKD-EPI	Chronic kidney disease epidemiology collaboration
C _{max}	Maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRA	Clinical Research Assistant
CT	Computed tomography
CTR	Clinical Trials Register
CV	Cardiovascular
DBP	Diastolic blood pressure
DGF	Delayed graft function
DILI	Drug induced liver injury
dL	Deciliter
ECG	Electrocardiogram
ECHO	Echocardiography
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EP	Evaluation period
EPO	Erythropoietin
EQ-5D-5L	Dimension 5 Level Health Utility Index
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FRP	Females of reproductive potential
FSH	Follicle stimulating hormone
g	Grams
GCP	Good Clinical Practice

GI	Gastrointestinal
GSK	GlaxoSmithKline
hCG	Human chorionic gonadotropin
HD	Hemodialysis
HDF	Hemodiafiltration
HDL-c	High density lipoprotein-C
HF	Hemofiltration
Hgb	Hemoglobin
HIF	Hypoxia-inducible factor
HR	Heart rate
HRT	Hormone replacement therapy
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IU	International Units
IV	Intravenous
Kg	Kilograms
LDL-C	Low density lipoprotein-C
MACE	Major adverse cardiovascular event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MIU	Milliinternational units
mL	milliliter
mmHg	Millimeter of mercury
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
ND	Non-dialysis
NYHA	New York Heart Association
PAH	Pulmonary artery hypertension
PASP	Pulmonary artery systolic pressure
PCM	Progressive cardiomyopathy
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PD	Peritoneal dialysis
PFS	Prefilled syringes
pg	Picogram
PHD	Prolyl hydroxylase domain enzymes

PHI	Prolyl hydroxylase inhibitor
PP	Per-protocol
PPD	Pharmaceutical Product Development, LLC
PRBC	Packed red blood cells
PRCA	Pure red cell aplasia
PRVP	Peak right ventricular pressure
RAP	Reporting and Analysis Plan
RSM-L	Remote Site Monitor-Lead
PSRAE	Possible Suicidality Related Adverse Events
QD	Once daily
QoL	Quality of life
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RDW	Red blood cell distribution width
rhEPO	Recombinant human erythropoietin
RoW	Rest of world
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDAC	Statistical Data Analysis Center
SRM	Study Reference Manual
TIW	Three times weekly
TSAT	Transferrin saturation
UIBC	Unsaturated iron binding capacity
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WBC	White blood cell

Trademark Information

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HemoCue

12.2. Appendix 2: Secondary, Exploratory, Patient Reported Outcomes, and Pharmacokinetics/Pharmacodynamics Objectives/ Endpoints

Objectives	Endpoints
<ul style="list-style-type: none"> Secondary Objectives 	<ul style="list-style-type: none"> Secondary Endpoints (tested for superiority¹, no multiplicity adjustment)
To compare daprodustat to rhEPO on BP	<ul style="list-style-type: none"> Change from baseline in SBP, DBP, and MAP at Week 52 and at end of treatment Number of BP exacerbation events per 100 patient years N (%) with at least one BP exacerbation event during study
To compare daprodustat to rhEPO on Hgb variability	<ul style="list-style-type: none"> Hgb change from baseline to Week 52¹ 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 (<i>non-inferiority analysis that will use a margin of 15% less time in range</i>)¹
To compare daprodustat to rhEPO on the time to rescue (defined as permanently stopping randomized treatment due to meeting rescue criteria)	<ul style="list-style-type: none"> Time to stopping randomized treatment due to meeting rescue criteria
To compare daprodustat to rhEPO on HRQoL and Utility score	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Plasma daprodustat, M2, M3, and M13 PK parameters pre-dose trough (C_{tau}) and C_{max}
Exploratory Objectives	Exploratory Endpoints (statistical testing not planned)
To further compare daprodustat and rhEPO on Hgb variability	<ul style="list-style-type: none"> 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

Objectives	Endpoints
	<p>and below the Hgb analysis range during EP and at the end of treatment</p> <ul style="list-style-type: none"> • 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 >1g/dL decrease in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL decrease in Hgb within any 4-week period from Week 4 to Week 52 • N (%) of subjects with a Hgb value $\nless 12$ g/dL during the EP • Number of times Hgb $\nless 12$ g/dL during the EP • % of time Hgb $\nless 12$ g/dL during the EP
To compare daprodustat to rhEPO on measures of iron parameters	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Assigned dose by visit and at Day 1, Week 28, Week 52 • Most recent dose prior to Week 28 and Week 52 • Number (%) of patients with 0, 1, 2, or >2 dose adjustments during the following periods: <ul style="list-style-type: none"> ○ Day 1 - <Week 28 ○ Week 28 - <Week 52 • Number of dose adjustments during the following periods: <ul style="list-style-type: none"> ○ Day 1 - <Week 28 ○ Week 28 - <Week 52 • Time dose held for Hgb $\nless 12$ g/dL
To further compare daprodustat to rhEPO on BP	<ul style="list-style-type: none"> • Observed and change from baseline in SBP, DBP

Objectives	Endpoints
and BP medication changes	and MAP by visit <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Change from Baseline at Wk 8, 12, 28, & 52, by item on the CKD-AQ • Shift tables (Baseline to 8, 12, 28, & 52) in PGI-S • N(%) of patients 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP. • Scatter plots of average daprodustat dose during EP vs. percent time in range during EP. • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP vs. percent time in range during EP. • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) 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 (C_{tau} and C_{max}) 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	<ul style="list-style-type: none"> • Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint. • Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) 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.

- Conversion from g/dL to g/L is 1:10 and from g/dL to mmol/L is 0.6206. For example, Hgb of 10 to 11 g/dL is equivalent to 100-110 g/L or 6.2 to 6.8 mmol/L.
- 1. Hgb change from baseline to Wk 52 is tested for non-inferiority, using the -0.75 g/dL margin used in the primary analysis. % time in range is tested first for non-inferiority, then for superiority.

12.3. Appendix 3: Randomized Treatment Dose Steps and Dose Adjustment Scheme

12.3.1. Darbepoetin Alfa Dose Steps

Total 4-weekly Dose (µg)	PFS Dose and Frequency (PD/HD)
20 µg	20 µg Q4 weeks
30 µg	30 µg Q4 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

* Subjects starting on these doses at the Randomization (Day1) who have >1 g/dL Hgb decrease or Hgb < 7.5 g/dL at Week 2 or Week 6 from the last visit will receive a “booster” dose of 20 µg in addition to their previous dose.

12.3.2. Randomized Treatment Dose Adjustment Scheme

HemoCue Hgb at current study visit ¹ (g/dL)	HemoCue Hgb change since last study visit ¹	Randomized Treatment Dose Adjustment ⁵
<7.5 ²	Any change	Repeat Hgb and average values ⁶ ; if confirmed, increase to the next higher dose step
7.5 to <9.5	Decreasing or No change	Increase to the next higher dose step
7.5 to <9.5	Increasing	Maintain dose
◀ 9.5 to <10 at two consecutive visits	Decreasing or No change	Increase to the next higher dose step
◀ 9.5 to ≤11.5	Any change	Maintain dose
>11 to ≤11.5 at two consecutive visits	Increasing or No change	Decrease to the next lower dose step
>11.5 to <12	Decreasing	Maintain dose
>11.5 to <12	Increasing or No change	Decrease to the next lower dose step
≥12 ³	Any change	Repeat Hgb and average values ⁶ ; if confirmed, temporary hold the dose and re-check Hgb at next study visit ¹ ; restart at one dose step lower when Hgb <11.5 g/dL and provided it has been at least 2 weeks from the prior study visit
Any	>2 g/dL increase over 4 weeks (>1 g/dL increase over 2 weeks ⁴)	Repeat Hgb and average values ⁶ ; if confirmed, decrease to the next lower dose step
Any	>2 g/dL decrease over 4 weeks (>1 g/dL decrease over 2 weeks ⁴)	Repeat Hgb and average values ⁶ ; if confirmed, increase to the next higher dose step

1. "Study visit" refers to scheduled study visits (every 4 weeks through Week 52).
2. This rule also applies to any mandated visit or an unscheduled visit, provided it has been at least 2 weeks from the prior study visit.
3. This rule applies to any mandated or unscheduled visit,
4. This rule applies to Weeks 2, 4, 6, and 8 visits only.
5. Those receiving the highest dose of randomized treatment who require a dose increase will maintain the same dose, while those receiving the lowest dose of randomized treatment that require a dose decrease will have doses withheld
6. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample) and take average.

12.4. Appendix 4: Benefit:Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Daprodustat		
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	<p>In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion/inflammation, microthrombi, and tissue ischemia in a number of organs.</p> <p>Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose levels, and dose adjustment scheme to optimize Hgb management.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	<ul style="list-style-type: none"> • Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 5.1 • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb (including rate of change) is provided in Section 6.2 and Section 6.11 • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)	<p>Marketed rhEPO and its analogs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD.</p> <p>In non-clinical studies conducted to date, not observed at tolerated doses when hemoglobin/hematocrit within normal range for species.</p> <p>The clinical data received to date are insufficient to conclude or refute this risk.</p>	<ul style="list-style-type: none"> • Specific eligibility criteria related to CV risk are outlined in Section 5.2 • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) • Unblinded monitoring of safety data by an IDMC in-stream throughout the study
Esophageal and gastric erosions	<p>In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ulcers with hemorrhage were observed with daprodustat.</p> <p>In rats stomach erosions were observed with intravenous and oral administration of daprodustat.</p> <p>Stomach erosions/ulcers also reported in rats with some marketed rhEPO and</p>	<ul style="list-style-type: none"> • Suspected GI bleeding or significant symptoms consistent with erosions or ulcers should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>its analogs .</p> <p>In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported adverse event, however causal association has not been established.</p> <p>Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.</p>	
Cancer-related mortality and tumor progression and recurrence	<p>In clinical trials, use of rhEPO and its analogs in patients with cancer has been associated with increased risk of cancer related morbidity and mortality.</p> <p>Administration of 60mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p> <p>There were no test article-related neoplastic findings in 2-year rat (oral daprodustat) or mouse (daprodustat + subcutaneous injection of the 3 major human metabolites; M2, M3 and M13) carcinogenicity studies.</p> <p>In clinical studies conducted to date, administration of daprodustat has been associated with:</p> <p><u>Once daily administration:</u></p> <ul style="list-style-type: none"> • In studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg. • In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentration were variable but similar relative to control. • Systemic EPO concentrations within the physiologic range. <p><u>Three times weekly administration:</u></p> <ul style="list-style-type: none"> • In studies up to 4 weeks duration at doses of 10 to 30 mg: <ul style="list-style-type: none"> ○ Dose dependent increases in plasma VEGF and EPO 	<ul style="list-style-type: none"> • Specific eligibility criteria related to personal history of malignancy or subjects with complex kidney cyst are outlined in Section 5.2.. • Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.5. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>concentrations were observed.</p> <ul style="list-style-type: none">○ Pre-dose concentrations of EPO and VEGF were near or below baseline indicating no accumulation of EPO or VEGF after three times weekly dosing <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pulmonary artery hypertension (PAH)	<p>A role for HIF-regulated pathways in the pathophysiology of PAH has been suggested based on well-established effects of acute and chronic hypoxia in man on the pulmonary vasculature (vasoconstriction), and by findings in patients with naturally occurring mutations that result in decreased HIF degradation [Smith, 2006; Formenti, 2011].</p> <p>There have been no histopathologic findings suggestive of PAH in pre-clinical safety studies with daprodustat up to 13-weeks duration in dogs, up to 2-years in rats and mice, and up to 39-weeks in monkeys.</p> <p><u>Acute hypoxic challenge (rats)</u>: Daprodustat produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. However, these hypoxia-induced PRVP changes were within the range of PRVP changes noted among un-treated rats.</p> <p>Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with daprodustat 5mg or 100mg had no clinically significant effect on transthoracic echocardiographic (ECHO) estimates of pulmonary artery systolic pressure (PASP) under either normoxic or hypoxic conditions.</p> <p>ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in PASP in subjects not on dialysis for daprodustat. In hemodialysis subjects, mean absolute change from baseline in PASP was similar for both treatment groups; however, there was a numeric imbalance (daprodustat Total: 8 [7%]; Control 0) in subjects reaching the PASP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 subjects with resolution of PASP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study drug; and there was no dose relationship for subjects meeting the PASP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with</p>	<ul style="list-style-type: none"> • Unblinded monitoring of safety data by an IDMC in-stream throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	
Cardiomyopathy	<p>Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized.</p> <p>With lifetime exposure to daprodustat in a 2-year rat oral carcinogenicity study, an exacerbation of rat spontaneous, progressive cardiomyopathy (PCM)(focal myofiber degeneration/necrosis with inflammatory infiltrates) was observed at doses of 0.8 mg/kg/day and above, although total incidence and severity distribution within any daprodustat-group were within historical control ranges. This is consistent with an equivocal threshold for exacerbation of spontaneous, progressive cardiomyopathy at 0.8 mg/kg/day which is also the threshold dose for observing increased Hct values in individual rats.</p> <p>Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization.</p> <p>ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in LVEF with daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	<ul style="list-style-type: none"> • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Proliferative retinopathy, macular edema, choroidal neovascularization	<p>Increases in local (ocular) VEGF production with retinal neovascularization and macular edema observed in diabetic retinopathy and to choroidal leakage, edema and neovascularization seen in age-related macular degeneration [Campochiaro, 2006].</p> <p>Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p>	<ul style="list-style-type: none"> • Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>Aside from congestion of retinal vessels and optic disc hyperemia secondary to markedly increased red cell mass, there were no ocular abnormalities observed in non-clinical studies.</p> <p>In clinical studies with daprodustat up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg administered once daily and from 10 to 30mg administered three times weekly. In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentrations were variable but similar relative to control.</p> <p>Ophthalmologic assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization for daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Exacerbation of rheumatoid arthritis	<p>In inflamed rheumatic joints, activation of HIF- related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra, 2010; Muz, 2009].</p> <p>No abnormalities were seen in non-clinical studies conducted to date for daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	<ul style="list-style-type: none"> • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Drug-drug interactions	<p><u>Daprodustat is a substrate of CYP2C8</u>: Co-administration of daprodustat with a strong CYP2C8 inhibitor (gemfibrozil) increased the Cmax and AUC of daprodustat, 4- and 19-fold, respectively, while co-administration of a weak inhibitor (trimethoprim) increased the Cmax and AUC of daprodustat by 1.3- and 1.5-fold, respectively. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with a moderate CYP2C8 inhibitor (clopidogrel), leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Although CYP2C8 induction studies were not performed, co-administration of daprodustat with an inducer of CYP2C8 (e.g., rifampin/rifampicin) may decrease the exposure of daprodustat.</p> <p>Even though co-administration of daprodustat with strong inhibitors and inducers of CYP2C8 is prohibited, inadvertent co-administration may occur. Due to the known time delay in enhancing erythropoiesis by daprodustat, co-administration with strong CYP2C8 inhibitors for up to 14 days is not anticipated to lead to immediate marked increases in hemoglobin levels. Therefore, there is adequate time to change to alternate therapy that does not inhibit CYP2C8.</p> <p>Additionally, as the time for maximum induction of CYP2C8 occurs after approximately 10-14 days of dosing with rifampin (Brodie, 2013 and Ohnhaus, 1989), daprodustat systemic exposure will decrease over time which will result in a lag period before an effect on Hgb is recognized and is of clinical concern.</p>	<ul style="list-style-type: none"> • Co-administration of daprodustat with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.9.2. • Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 6.9.1. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.9.. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb is provided in Section 6.2.1 and Appendix 3. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p><u>Daprodustat is an inhibitor of CYP2C8</u>: A clinical drug interaction study between 25mg and 100mg daprodustat with a CYP2C8 substrate (pioglitazone) showed that there is no PK interaction at these doses of daprodustat.</p> <p><u>Daprodustat is a substrate of BCRP</u>: Population PK analysis from Phase 2 studies suggested that while BCRP inhibitors were a covariate for daprodustat CL/F (8.6% lower clearance) the predicted change in exposure was not considered to be of clinical relevance.</p> <p><u>Daprodustat is an inhibitor of OATP1B1/1B3</u>: A clinical drug interaction study between 25mg and 100mg daprodustat with an OATP1B1/1B3 substrate (rosuvastatin) showed that there is no PK interaction at these doses of daprodustat</p>	
Other		
rhEPO risks (Control)	<ul style="list-style-type: none"> See risks outlined in table for daprodustat for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia, Death, MI, stroke, thromboembolic events, thrombosis of vascular access, and for Increased cancer-related mortality and tumor progression. Uncontrolled hypertension Pure red cell aplasia 	<ul style="list-style-type: none"> See mitigation strategies outlined in table for daprodustat for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia, Risk of death, MI, stroke, thromboembolic events, thrombosis of vascular access, and for Increased cancer-related mortality and tumor progression. Specific eligibility criteria related to current uncontrolled hypertension are outlined in Section 5.2. Specific eligibility criteria related to personal history of pure red cell aplasia are outlined in Section 5.2.

References:

Campochiaro PA. Ocular versus extraocular neovascularization: mirror images or vague resemblances. *Invest Ophthalmol Vis Sci*. 2006;47(2):462-74.

Formenti F, Beer PA, Croft QP, Dorrington KL, Gale DP, Robbins PA, *et al*. Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2alpha gain-of-function mutation. *FASEB J*. 2011;25(6):2001-11.

Muz B, Khan MN, Kiriakidis S, Paleolog EM. Hypoxia. The role of hypoxia and HIF-dependent signalling events in rheumatoid arthritis. *Arthritis Res Ther*. 2009;11(1):201.

Smith TG, Brooks JT, Balanos GM, Lappin TR, Layton DM, Robbins PA. *et al*. Mutation of von Hippel-Lindau tumour suppressor and human cardiopulmonary physiology. *PLoS Med*. 2006 Jul;3(7):e290.

Westra J, Molema G, Kallenberg CG. Hypoxia-inducible factor-1 as regulator of angiogenesis in rheumatoid arthritis - therapeutic implications. *Curr Med Chem*. 2010;17(3):254-63.

12.5. Appendix 5: Female Eligibility Criteria

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum hCG test for females of reproductive potential only), not breastfeeding, or at least one of the following conditions applies:

- Reproductive potential and agrees to follow one of the options listed below in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP **from 30 days prior to the first dose of randomized treatment and until completion of the Follow-up visit (4-6 weeks after the end of randomized treatment)**; those who permanently discontinue randomized treatment prior to the end of the study should continue contraceptive methods following the Early Treatment Discontinuation Visit until the final pregnancy test assessment at a subsequent study visit (at least 4 weeks after the end of randomized treatment) as described in the Time and Events Table (Section 7.1).
 1. Contraceptive subdermal implant.
 2. Intrauterine device or intrauterine system.
 3. Combined estrogen and progestogen oral contraceptive [Trussell, 2011]
 4. Injectable progestogen [Trussell, 2011]
 5. Contraceptive vaginal ring [Trussell, 2011]
 6. Percutaneous contraceptive patches [Trussell, 2011]
 7. Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject [Trussell, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Non-reproductive potential defined as either:
 1. Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;
 2. Postmenopausal defined as 12 months of spontaneous amenorrhea. In questionable cases, a blood sample with simultaneous FSH and estradiol

consistent with menopause is confirmatory (FSH ≥ 23 MIU/mL (2:23.0 TU/L) and estradiol ≤ 10 pg/mL (or ≤ 37 pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

References

Trussell J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, and Policar M (editors). Contraceptive Technology: Twentieth Revised Edition. New York: Ardent Media, 2011. Table 26-1

12.6. Appendix 6: Liver Chemistry Stopping Criteria

12.6.1. Liver Safety Required Actions and Follow up Assessments

Phase 3-4 liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT \geq 8xULN
ALT Increase	ALT \geq 5xULN but $<$ 8xULN persists for \geq 2 weeks ALT \geq 3xULN but $<$ 5xULN persists for \geq 4 weeks
Bilirubin^{1,2}	ALT \geq 3xULN and bilirubin \geq 2xULN ($>$ 35% direct bilirubin)
INR²	ALT \geq 3xULN and INR $>$ 1.5, if INR measured
Cannot Monitor	ALT \geq 5xULN but $<$ 8xULN and cannot be monitored weekly for \geq 2 weeks ALT \geq 3xULN but $<$ 5xULN and cannot be monitored weekly for \geq 4 weeks
Symptomatic³	ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> Immediately discontinue randomized treatment Report the event to PPD within 24 hours Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE² Perform liver event follow up assessments Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) Do not restart subject with randomized treatment unless allowed per protocol and GSK Medical Governance approval is granted (Section 12.6.2) If restart not allowed or not granted, permanently discontinue randomized treatment and may continue subject in the 	<ul style="list-style-type: none"> Viral hepatitis serology⁴ Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody⁵. Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hr after last dose⁶ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Fractionate bilirubin, if total bilirubin \geq 2xULN Obtain complete blood count with differential to assess eosinophilia Record the appearance or worsening of clinical symptoms of liver injury, or

<p>study for any protocol specified follow up assessments</p> <p>MONITORING:</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline A specialist or hepatology consultation is recommended <p><u>For All other criteria:</u></p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline 	<p>hypersensitivity, on the AE report form</p> <ul style="list-style-type: none"> Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. Record alcohol use on the liver event alcohol intake case report form <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: not required in China Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms.
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1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue randomized treatment for that subject if ALT 2: 3xULN **and** bilirubin 2: 2xULN.
2. All events of ALT 2: 3xULN **and** bilirubin 2: 2xULN (>35% direct bilirubin) or ALT 2: 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of randomized treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase 3-4 liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT 2:5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT 2:3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety. • Subject can continue randomized treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT 2:5xULN and <8xULN to \geq 3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363–2369.

12.6.2. Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart randomized treatment unless there is a clear underlying cause for the liver stopping event other than drug-induced liver injury and:

- GSK Medical Governance approval **is granted** in writing (as described below),
- Ethics and/or IRB approval is obtained, if required, and

- Separate consent for treatment restart is signed by the subject

If GSK Medical Governance approval to restart subject with randomized treatment **is not granted**, then subject must permanently discontinue randomized treatment and may continue in the study for protocol-specified follow up assessments.

Restart Following Transient Resolving Liver Stopping Events Not Related to randomized Treatment

Restart refers to resuming randomized treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the randomized treatment should not be associated with HLA markers of liver injury.

Approval by GSK for randomized treatment restart can be considered where:

- Investigator requests consideration for randomized treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible randomized treatment-induced liver injury) or randomized treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or Institutional Review Board approval of randomized treatment restart must be obtained, as required.
- If restart of randomized treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of randomized treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the randomized treatment restart. Documentation of informed consent must be recorded in the study chart.
- Randomized treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting randomized treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after randomized treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- PPD Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following randomized treatment restart.
- PPD to be notified of any AEs, as per Section 7.4 and [Appendix 8](#).

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Saf*. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. *Hepatology*. 2010;52:2216-2222.

Papay JJ, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009;54:84-90.

12.7. Appendix 7: Study Specific Equipment

Study specific equipment required:

- Refrigerator
- Freezer (-20°C or lower)
- Centrifuge
- Point-of-care HemoCue Hgb analyzer - to be provided as part of the study

12.8. Appendix 8: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.8.1. Definition of Adverse Events

Adverse Event Definition:

- An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting AE definition include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after randomized treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either randomized treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.8.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday

life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: <ul style="list-style-type: none"> Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: <ul style="list-style-type: none"> ALT 2: 3xULN and total bilirubin* 2: 2xULN (>35% direct), or ALT 2: 3xULN and INR** > 1.5. <p>* Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable and ALT 2: 3xULN and total bilirubin 2: 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>

12.8.3. Recording of AEs and SAEs

AEs and SAE Recording:
<ul style="list-style-type: none"> When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the CRF It is not acceptable for the investigator to send photocopies of the subject's medical records to PPD in lieu of completion of the PPD/GSK, AE/SAE CRF page. There may be instances when copies of medical records for certain cases are requested by PPD. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to PPD. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be

documented as the AE/SAE and not the individual signs/symptoms.

- Subject-completed Patient Reported Outcomes questionnaires and the collection of AE data are independent components of the study.

12.8.4. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between randomized treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the randomized treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to PPD. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to PPD.**

- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by PPD to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.8.5. Reporting of SAEs to PPD

SAE reporting to PPD via electronic data collection tool

- Primary mechanism for reporting SAEs to PPD will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt will be provided in a separate document.

12.9. Appendix 9: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to PPD within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the randomized treatment by the investigator, will be reported to PPD as described in Section 12.8.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating must permanently discontinue randomized treatment. Subjects will be asked to attend an Early Treatment Discontinuation visit and expected to attend study visits through the End of Study visit, according to the study visit schedule, unless consent is actively withdrawn.

12.10. Appendix 10: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- Anemia associated with CKD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Informed consent for genetic research must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

References

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.11. Appendix 11 – Protocol Changes

12.11.1. Changes Resulting from Protocol Amendment 1

This is an amendment to the original protocol dated 18-Oct-2016

This amendment applies to all countries.

12.11.1.1. Summary of Changes

- Updated the time period of planning to start dialysis from the day of screening to 6 weeks to be consistent with the extended screening period, when appropriate
- Removed number of screening subjects required and stated only an approximate number of randomized subjects required in the study
- Modified peritoneal dialysis (PD) inclusion criteria to allow participants on 2:4 times/week PD including an incremental schedule
- Removed France country specific requirement for Informed Consent process from inclusion criteria
- Broadened exclusion to include participation in an interventional study with an investigational agent or device
- Removed option to have Early Treatment Discontinuation visit supersede the scheduled study visit
- Added a provision that in unexpected circumstances where the supply to the site is interrupted, then local standard of care for anemia management during this time period may be considered
- Added direction regarding randomized treatment and study continuation for subjects who will be away from the research site for an extended period of time
- Added new darbepoetin alfa dose strengths (not available in all countries)
- Clarified timeframe for iron management criteria
- Clarified timing of designated study visits for subjects who have not yet initiated dialysis and for subjects on dialysis
- Shortened visit window for the Week 2 and 4 visits
- Modified Time and Events Table 6 ‘Schedule of Assessments. Main changes include addition of Informed Consent activity; footnotes to allow for more time for ECG before randomization visit, more clarity around randomized treatment dispensing and compliance; removed capture of rescue medications from unscheduled visit (rescue evaluation is triggered at scheduled visits); added healthcare resource data collection, added footnote to clarify biomarkers storage requirements and added Argentina only pregnancy requirement
- Added direction to CEC Site Manual for full scope of reporting requirements
- Clarified timing of weight, blood pressure and heart rate in relation to laboratory assessments and dialysis
- Clarified PK sampling in relation to subjects on dose hold
- Updated PRO section to add healthcare resource utilization data being collected for completeness
- Changed time point for blinded data cut need for psychometric validation of the Chronic Kidney Disease Questionnaire

- Revised statistical section to change from two-sided testing at the 5% level to one-sided testing at the 2.5% level; for secondary endpoints, to change significance levels to p-values and to correct the time point for various Patient Reported Outcomes
- Updated wording around exploratory endpoints in Appendix 2
- Updated Darbepoetin alfa dose steps table in Appendix 3 to remove partial doses and clarify booster dosing to be consistent with Interactive Response Technology (IRT) system
- Provision for possible adjustment to the Dose Adjustment Algorithm triggers for Hgb values 7.5 g/dL to <9.5 g/dL based on review of blinded instream Hgb data
- Edited Risk Assessment information in Appendix 4 to align with version 8 of the Investigator's Brochure
- Updated FSH level to confirm menopause in Appendix 5, Female Eligibility Criteria
- Removed Appendix 11- France country specific requirement
- Other changes include minor edits, corrections of typos and administrative changes throughout.

12.11.1.2. List of Specific Changes

Section 1. Protocol Synopsis, type and Number of Subjects, updated time period of start of chronic dialysis (HD or PD) to within the 6 weeks from the day of screening to be consistent with extended screening period.

Revised Text:

The study will enroll the following types of subjects with anemia associated with CKD: Planned initiation of dialysis: Subjects who are planning to start chronic dialysis (HD or PD) within the next ~~2-4 weeks~~ 6 weeks (from the day of screening).

Section 1. Protocol Synopsis, type and number of subjects, changed the number of subjects that need to be screened.

Revised Text:

~~Approximately 600 subjects are expected to be screened in order to randomize approximately 300 subjects, or 150 subjects per treatment group~~

This study will randomize approximately 300 subjects, or 150 subjects per treatment group

Section 4.2 Type and Number of Subjects, updated the time period of planning to start dialysis from the day of screening to be consistent with the extended screening period, when appropriate.

Revised Text:

- Planned: Subjects who are planning to start dialysis (HD or PD) within the next ~~2-4~~ 6 weeks (from the day of screening).

Section 4.2 Type and Number of Subjects, changed the screen failure rate and the number of subjects that need to be screened.

Revised Text:

~~Based on an assumed screen failure rate of 50%, approximately 600 subjects are expected to be screened in order to randomize approximately 300 subjects, or 150 subjects per treatment group.~~

This study will randomize approximately 300 subjects, or 150 subjects per treatment group.

Section 4.5.2. Benefit Assessment. Clarified wording around other ESAs.

Revised Text:

Daprodustat may present several important advantages over rhEPO ~~and other ESAs~~ **its analogs**.

Treatment of anemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated supra-physiological increases in EPO exposure with rhEPO [Szczzech, 2008]; therefore, daprodustat has the potential to raise Hgb without the same CV risk associated with rhEPO **and its analogs**.

Section 5.1. Inclusion Criteria, Inclusion #2: updated updated the time period of planning to start dialysis from the day of screening to be consistent with the extended screening period, when appropriate.

Revised Text

2. Dialysis: Planning to start chronic dialysis within the next ~~4~~ **6** weeks (from the date of the screening visit) OR have started and received dialysis (as specified below) for end-stage renal disease for a maximum of ~~90~~ **90** days immediately prior to randomization and is not expected to stop dialysis during the duration of the trial

Section 5.1. Inclusion Criteria; inclusion #2: Updated frequency of dialysis descriptions.

Revised Text:

~~Daily PD (Including continuous and automated PD):~~ PD 2:4 times/week including incremental schedule; subjects on continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) are eligible

Section 5.1. Inclusion Criteria; inclusion #4. Clarified study visit this is confirmed.

Revised Text:

- a. Informed consent (**at screening**): capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol

Section 5.1 Inclusion Criteria: Inclusion #5 and Section 12.11.1: Removed country specific requirements for France, as the study is not being conducted there.

Revised Text:

4. **Informed consent:** capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol

~~Note: The country-specific requirements for France ONLY for the informed consent process is provided in Appendix 11 (see Section 12.11.1, Item 3 for details)~~

5. ~~**Other study eligibility criteria considerations:** The country-specific requirements for France ONLY for the eligibility for inclusion in this study is provided in Appendix 11 (see Section 12.11.1, Item 1 for details)~~

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Section 5.2. Exclusion Criteria; exclusion #1. Added or living-unrelated to clarify.

Revised Text:

1. **Kidney transplant:** Planned living-related **or living-unrelated donor** kidney transplant within 52 weeks after study start (Day 1).

Section 5.2. Exclusion Criteria; exclusion #7. Added Untreated to clarify.

Revised Text:

7. **Other causes of anemia: Untreated** pernicious anemia, thalassemia major, sickle cell disease or myelodysplastic syndrome.

Section 5.2. Exclusion Criteria; exclusion #14. Clarified QTcB exclusion criteria

Revised Text:

14. QTcB (Day 1): QTcB >500 msec, or QTcB >530 msec in subjects with bundle branch block. There is no QTc exclusion for subjects with a predominantly **ventricular** paced rhythm

Section 5.2. Exclusion Criteria; exclusion #19. Broadened exclusion to include participation in an interventional study with an investigational agent or device.

Revised Text:

~~**19. Prior investigational product exposure:** Use of an investigational drug (other than daprodustat – see next criterion) : 30 days or within five half-lives of the investigational agent, whichever is longer prior to screening.~~

19. Other study participation: Use of other investigational agent or device prior to screening through to randomization (Day 1).

NOTE: at screening, this exclusion applies to use of the investigational agent within 30 days or within five half-lives (whichever is longer).

Section 5.5. Permanent Discontinuation of Randomized Treatment. Removed the word ‘chronic’ from use of prohibited medication

Revised Text:

Need for ~~chronic~~ (more than 14 days) use of a prohibited medication (Section 6.9.2)

Section 5.5. Permanent Discontinuation of Randomized Treatment. Added wording regarding re-starting randomized treatment

Subjects may be re-approached about restarting randomized treatment in certain circumstances if the Sponsor and the investigator agree

Section 5.5.1. Procedures for Subject Follow-up; deleted second sentence in first bullet to clarify

Revised Text:

- Early Treatment Discontinuation visit: This visit should occur within 2 weeks of stopping randomized treatment. ~~This visit supersedes the scheduled study visit if the Early Treatment Discontinuation visit falls on the same date as a scheduled study visit.~~

Section 5.5.1. Procedures for Subject Follow-up; deleted 2 from 2-4 weeks in the second sub-bullet as this was an error

Revised Text:

- Follow-up: Study visit 2 to 4 weeks after Week 52.

Section 5.7 Subject and Study Completion; included wording in second sentence to clarify

Revised Text:

- A completed subject is one who has completed all periods of the study through the End of Treatment visit **with the following exception: subjects who die while on study are also considered as having completed the study.**

Section 6.1. Investigational Product and Other Randomized Treatment. Added the following wording to the end of the first paragraph to clarify:

Revised Text:

Randomized treatment will be provided by GSK.

Section 6.1. Investigational Product and Other Randomized Treatment. Added wording under Table 1 to provide direction if supply of randomized treatment is interrupted and added wording for clarification of darbepoetin alfa doses.

GSK will supply rhEPO (darbepoetin alfa) for the control group. Darbepoetin alfa as prefilled syringes (PFS) for SC/IV injection. **If the supply to the site is interrupted due to unexpected circumstances (e.g., natural disaster), local standard of care for anemia management may be considered during that time period, without the need to withdraw the subject from the study or to permanently discontinue randomized treatment.**

Darbepoetin alfa doses from 20 µg to 400 µg will be administered using the strengths in Table 2. **See also Appendix 3, Section 12.3.1 for darbepoetin alfa dose steps and dosing frequency. Additional details to deliver the total dose are also captured in the SRM.**

Section 6.1. Investigational Product and Other Randomized Treatment. Updated Table 2 to add additional dose strengths of darbepoetin alfa

Revised Text:

Table 2 Description of Darbepoetin Alfa PFS

PFS Strengths	PFS Volume
20 µg*	0.5 mL
30 µg*	0.3 mL
40 µg	0.4 mL
60 µg	0.3 mL
80 µg*	0.4 mL
100 µg	0.5 mL
150 µg	0.3 mL

* Not available in all countries.

Section 6.2.2. rhEPO Dosing Information. Corrected error to remove 'total weekly' wording in first paragraph.

Revised Text:

For subjects starting HD or PD, the SC/IV darbepoetin alfa ~~total weekly~~ dose will be 0.75 1.0 µg/kg rounded to the nearest available dose.

Section 6.2.2. rhEPO Dosing Information, Darbepoetin alfa dose steps: IRT term expanded as appears in document for the first time

Revised Text

Dose adjustments will be made programmatically by the **Interactive Response Technology (IRT)** system

Section 6.2.3. Daprodustat and rhEPO Dose Adjustment Algorithm. Removed the full word Interactive Response Technology as previously stated as full phrase and added wording for adjustments to the algorithm in this section to allow for adjustments by the Sponsor to the dosing algorithm.

Revised Text:

Dose adjustments will be made programmatically by ~~the Interactive Response Technology (IRT)~~ system to maintain Hgb concentrations within the range of 10-11 g/dL based on the Hgb value measured every 2 to 4 weeks by the HemoCue value disclosed to the IRT system by the investigator.

In order to mitigate subjects remaining below the Hgb target range for an extended period of time, adjustments to the algorithm may be implemented by the Sponsor as outlined in Appendix 3 based on the review of aggregate blinded instream Hgb data.

Section 6.6.1. Randomized Treatment Extended Interruption; new section. Added direction regarding randomized treatment and study continuation for subjects who will be away from the research site for an extended period of time.

Revised Text:

6.6.1. Randomized Treatment Extended Interruption

Every effort must be made to continue randomized treatment and to complete study visits, where able; however, sites should contact their PPD study team member if a subject cannot return to the research site on a temporary basis for any one of the following situations:

- **Subjects who are hospitalized for any duration.**
- **Subjects who cannot return to the site for a period >5 weeks.**

In exceptional circumstances, standard of care for anemia management during this time period may be considered based on consultation with the PPD medical monitor. If non-study ESAs are administered, doses should be recorded on the Prior/Concomitant Medications – ESA eCRF page

Section 6.9.2. Prohibited Medications; new text added for clarification that no other investigational agents or devices are permitted during the study.

Revised Text:

Except for study randomized treatment, no other investigational agents or devices are permitted from study entry through completion of the study.

Section 6.10. Iron Management Criteria; paragraph 1. Added clarification for when the criteria start and stop.

Revised Text:

The investigator will follow the iron management criteria from randomization (Day 1) through the end of the study treatment period for subjects receiving randomized treatment

Section 6.11. Anemia rescue therapy; paragraph 2. Minor clarification in wording.

Revised Text:

This rescue algorithm does not apply to subjects with a ~~decrease in~~ **low** Hgb as a result of an acute or subacute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or vascular access).

Section 6.11. Anemia rescue therapy; added wording in Table 5 to clarify the rescue applies at scheduled visits only

Revised Text:

HemoCue Hgb remains <9 g/dL **(at a scheduled visit, Week 4 onwards)** despite three¹ consecutive dose increases above the starting dose or post-rescue² (where HemoCue Hgb<9 g/dL prior to each dose increase) OR HemoCue Hgb is <7.5 g/dL despite a dose increase at the prior study visit

Section 7. Study Assessments and Procedures; paragraphs leading up to 1st bullet. Clarified valid study period for study visits.

Revised Text:

~~Study visit days should be scheduled as follows:~~

Designated study visits for subjects in the screening period or study treatment period who have not yet initiated dialysis can occur on any day of the week.

Designated study visits for subjects on dialysis should be scheduled as follows from the screening assessment to the end of the study:

- For subjects on 3X/week HD: The designated study visit must not occur on the first dialysis session of the week. For example, if on a Monday-Wednesday-Friday schedule, the study visit should be on Wednesday or Friday.
- ~~For subjects on PD: study visits can occur on any day of the week.~~
- For subjects on 2X/week HD: The visit should occur during the session that is closest to the previous HD session. For example, if a subject receives dialysis on a Monday and Thursday, the study visit should be on the Thursday (2 days from the previous dialysis session) rather than the Monday (3 days from the previous dialysis session).
- For subjects on PD: study visits can occur on any day of the week.**

Section 7. Study Assessments and Procedures; 1st paragraph after bullets. Inserted new text to state the revised visit window for the Week 2 and 4 visits.

Revised Text:

Post-randomization visits should be referenced back to the Randomization visit (Day 1). **The visit window for those on randomized treatment for the Week 2 and Week 4 visits is ± 3 days.** The visit window specified for those on randomized treatment from **Week 6 ~~12~~ onwards** is ± 1 week.

Section 7.1. Table 6, Time and Events Table for Subjects on Randomized Treatment. Updated visit window text.

Revised Text:

Protocol activity (visits ± 1 week, (Note: all visit timings except Weeks 2 and 4 which are relative to Day 1) ± 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
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Section 7.1. Table 6, Time and Events Table for Subjects on Randomized Treatment. Added Informed Consent activity and associated footnote (#19) as these were missing.

Revised Text:

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							

Section 7.1, Table 6, Time and Events Table for Subjects on Randomized Treatment. Updated IRT system timing to indicate it is not notified at Week 52.

Revised Text:

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
IRT system	X	X	X	X	X	x	X	X

Section 7.1, Table 6, Time and Events Table for Subjects on Randomized Treatment. Added EGG to screening visit and updated corresponding footnote to clarify ECG can be done between screening and before randomization to treatment.

Revised Text:

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
ECG ³	X	X						

³All ECGs assessment must be recorded pre-dialysis for dialysis subjects. ECG may be performed as early as at screening Week -2 and prior to randomization (Day1).

Section 7.1, Table 6, Time and Events Table for Subjects on Randomized Treatment. Removed randomized treatment dispensing at Week 52 and added Healthcare resource utilization (subject reported) for completeness.

Revised Text:

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
Randomized treatment dispensing		X		X	X	X	X	
Healthcare resource utilization (subject reported)	X	X	X	Weeks 4, 8, 12, 16, 20, 24, 28 only		X		X

Section 7.1. Table 6, Time and Events Table for Subjects on Randomized Treatment. Replaced “MACE” wording with “Clinical events” in order to more accurately represent all safety data being collected.

Revised Text:

Non-serious AEs, SAEs, AEs of Special Interest, MACE clinical events	X ¹⁵	X	X	X	X	X	X	X
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Section 7.1. Table 6, Time and Events Table for Subjects on Randomized Treatment. Modified footnote 1 to clarify that 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

Revised Text

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 Section 5.2. ~~HemoCue Hgb~~, 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

Section 7.1. Table 6, Time and Events Table for Subjects on Randomized Treatment. Added footnotes associated with randomized treatment dispensing and compliance (#16); pregnancy testing for Argentina only as required by local law (#17), clarity around Biomarker samples storage (#18) and Informed Consent requirement before any study procedures (#19)

Revised Text:

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 $\nless 12$ 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.

Section 7.1. Table 7 Time and Events Table for subjects that permanently discontinue randomized treatment. Removed Recue Medication, corrected MACE to **Clinical events** and updated footnotes

Revised Text:

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 \pm 2 weeks)	Unscheduled	Follow-up (4 weeks post-study termination \pm 1 week)
IRT SYSTEM call	X	X	X	X
SBP/DBP ¹ , HR ¹	X (triplicate)	X	X	X
Iron therapy, transfusions ²	X			
Rescue medication				
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, MACE , clinical events	X	X	X	X
Review concomitant medications	X	X	X	X
Healthcare resource utilization	X			
CKD Anemia Symptoms Questionnaire (CKD-AQ) questionnaire, PGI-S, PGI-C ^{23,2}	X			
SF-36 ² , EQ-5D-5L ^{23,2}	X			

1. See Section 7.4.8 for details.

2. Record in eCRF, if applicable

4-3. Subjects who are unable to or require assistance to read must not complete the questionnaires

~~3. See details on Rescue in Section 6.11.~~

Section 7.3. Efficacy, corrected third paragraph

Revised Text:

Blood samples (not fingersticks) for measurement of Hgb via HemoCue and also by the central laboratory will be collected ~~and as~~ as specified in the Time and Events Table (Table 6). ~~and the collection will be recorded in the eCRF~~

Section 7.4.1. Events Referred to the Clinical Events Committee; 1st paragraph. Replaced “MACE” wording with “Clinical events”. Added reference to CEC Site Manual for scope of reporting requirements

Revised Text:

Investigators should refer any event suspected to be one the following ~~MACE~~ events **below** to the CEC. The CEC will review and adjudicate the following **MACE clinical events**. See CEC Site Manual for full scope of reporting requirements.

Section 7.4.1. Events Referred to the Clinical Events Committee; 3rd paragraph after bullets. Added clarity where to find description of source documentation required to support adjudication of events.

Revised Text:

Source documentation required to support the adjudication of the events is described in the **SRM-CEC Site Manual**.

*Section 7.4.4. Adverse Events of Special Interest. Corrected **venous thromboembolism** to **thromboembolic events***

Revised Text:

- *Death, myocardial infarction, stroke, heart failure, ~~venous thromboembolism~~ **thromboembolic events**, thrombosis of vascular access*

Section 7.4.4. Adverse Events of Special Interest. Added wording to clarify where Adverse Events of Special Interest should be recorded.

Revised Text

The results of any investigation should be recorded ~~in the relevant sections~~ **on the AE page and in the relevant AE of special interest page** of the subjects' eCRFs

Section 7.4.7. Height and Weight. Added clarity on timing of assessments.

Revised Text:

*For HD subjects, this will be measured pre-and post dialysis **when possible, or at study visits between dialysis sessions**. For PD subjects these assessments will be done **at study visits, as per standard of care.** ~~between treatments.~~*

Section 7.4.8. Blood Pressure and Heart Rate; new text. Added clarity for PD subjects as to the timing of the assessments and for the ordering of the various assessments.

Revised Text:

- ~~Measurements~~ **For HD subjects** ~~Measurements~~ **Measurements** will be taken **pre and post dialysis** with the subject in a semi-supine or seated position in the dialysis chair after at least a 5-minute rest period ~~(pre and post dialysis).~~
- **For PD subjects, this assessment will be done at study visits, as per standard of care.**

~~For HD subjects, SBP, DBP and HR will be performed before collection of blood samples for laboratory testing, where applicable. measured pre and post dialysis. For PD subjects these assessments will be done between treatments. Pre-dialysis measurements will be taken prior to blood sample collection~~

Section 7.4.9. Electrocardiogram (ECG). Added clarity on reading of ECGs

Revised Text:

For the Day 1 ECG ~~At the Day 1 visit when ECGs are performed,~~ two additional ECGs are required if the initial ECG indicates prolonged QTc using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility (Section 5.2, item 14 for detail). Additional details are provided in the SRM.

ECG data will be read locally **by a physician with experience in reading and interpreting ECGs. The over-read of the Day 1 ECG is required to confirm eligibility. Additional details are provided in the SRM.**

Section 7.4.11. Clinical Laboratory Assessments. Clarified timing of laboratory assessments for HD and PD subjects in the first paragraph and made a correction with reference to source notes in the third paragraph.

Revised Text:

All protocol required laboratory assessments, as defined in Table 8, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Table 6). **Laboratory assessments will be done pre-dialysis for in-center HD subjects, in between dialysis sessions and at the study visits and at the study visits for PD subjects, as per standard of care.**

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's **source notes eCRF**.

Section 7.4.11. Clinical Laboratory Assessments. Table 8; Clarified that Iron parameters TSAT and TIBC will be calculated and not actual measurements will be considered

Revised Text:

Iron parameters	Serum iron	Ferritin	UIBC
	Hepcidin	TSAT (calculated)	TIBC (calculated)

Section 7.5 Pharmacokinetics; edited text. Minor change to clarify PK assessment will be performed in all subjects on daprodustat and added wording to clarify PK sampling in relation to subjects on dose hold.

Revised Text:

PK sampling will ~~Only~~ be performed in **all** in-center HD subjects randomized to the daprodustat arm.

The dose taken in the clinic should be from the same bottle(s) the subject has been using prior to the PK visit, **not** from any newly dispensed bottle(s) at the PK visit.

[Note: a subject placed on a dose hold at the previous visit should not have PK samples taken; PK collection should be delayed until the visit after the subject has restarted study treatment.]

Record the date and actual time of the dose taken in the **clinic and three doses prior to the visit**, and the date and actual time of all PK samples collected.

Samples may be collected within ± 20 min of the planned collected time

Section 7.7. Patient Reported Outcomes. Edited wording to change “procedure” to “reference”

Revised Text:

Details on patient reported outcomes are provided in the study **reference procedure** manual.

Section 7.7. Patient Reported Outcomes; new text in 1st paragraph. Clarified healthcare resource utilization data to be collected.

Revised Text:

In addition, healthcare resource utilization will be assessed including out-patient visits

Section 7.7. Patient Reported Outcomes; new text in last paragraph. Added process for exceptional circumstances when Patient Reported Outcomes cannot be conducted.

Revised Text

If there are other exceptional circumstances whereby the Patient Reported Outcomes assessments cannot be conducted, the completion of these assessments will be discussed with the Sponsor on a case-by-case basis.

Section 7.7.4. Health Status (EQ-5D-5L & EQ-VAS). Updated endpoint labels for clarification.

Revised Text:

The EQ VAS records the respondent’s self-rated health on a vertical, visual analogue scale where the endpoints are labeled **‘the best health you can imagine best imaginable health state’** and **‘the worst health you can imagine worst imaginable health state’**. This information is used as a quantitative measure of health outcome as judged by individual subjects.

Section 7.7.5 Psychometric Analysis of the CKD Anemia Symptoms Questionnaire (CKD-AQ), updated study visit for interim data cut.

Revised Text:

In order establish and evaluate the measurement properties of the CKD-AQ, a interim cut of blinded observations of the first 50 subjects who completed the week 28 ~~S2~~-visit will be taken. In order to establish content validity, the data cut will require a

comparison to the following variables: PGI-C, PGI-S, Hgb, SF-36, demographic & baseline clinical characteristics. All data will be abstracted from screening until week 28 ~~S2~~.

Section 9.1. Primary hypothesis; in the third paragraph. Change from two-sided testing at the 5% level to one-sided testing at the 2.5% level and two-sided 95% CI.

Revised Text:

Statistical significance of non-inferiority will be assessed at the ~~two one-sided 2.5%~~ level. An analysis of covariance (ANCOVA) model including randomization stratification factors, baseline hemoglobin and treatment will be used to obtain a point estimate and the **two-sided** 95% CI for the treatment difference (daprodustat-rhEPO) and generate the p-value for the non-inferiority test.

Section 9.2.1 Sample Size Assumptions, in the third paragraph. Added two-sided 95% CI.

Revised Text:

With 300 randomized subjects, it is anticipated that the difference in mean Hgb change from baseline between arms will be estimated with a precision of 0.408 g/dL (half width of the **two-sided** 95% CI)

Section 9.4.1 Primary analysis; first and second paragraph. Added supplementary analyses information.

Revised Text:

It will provide a point estimate and **two-sided** 95% CI for the treatment effect, together with the **one-sided** non-inferiority test p-value.

Sensitivity and **Supplementary** Analyses: Sensitivity analyses for the primary estimand will include a multiple imputation-based “tipping point” analysis where assumptions are adjusted until non-inferiority is lost by imputing data for subjects who did not fully complete the EP. A further **supplementary** analysis will evaluate efficacy in those subjects who adhere to randomized treatment, defined as ITT subjects with at least one on-treatment Hgb during the EP (this approach corresponds to evaluating an efficacy estimand). A similar “tipping point” analysis as that described above for the primary analysis will be performed for this “on-drug” analysis. In addition, a **supplementary** per-protocol ~~sensitivity~~ analysis will estimate the treatment effect in subjects who strongly adhere to the protocol, and sensitivity analyses to explore a shorter EP (Weeks 28 to 36) will be performed for the primary effectiveness estimand and “on-drug” efficacy estimand. Full details of all sensitivity and **supplementary** analyses will be provided in the RAP.

Section 9.4.2.1. Principal Secondary Efficacy Analyses; first and last paragraph. Added one-sided 2.5% and Changed significance levels to p-values.

Revised Text:

Conditional on the primary endpoint achieving non-inferiority at the ~~two~~**one**-sided 2.5% level, statistical testing will progress to the principal secondary endpoint with a focus on superiority using a ~~two~~**one**-sided 2.5% significance level.

All analyses of secondary endpoints are of exploratory nature, summary statistical and nominal ~~two~~**one**-sided 5% significance levels **p-values** will be used for any treatment comparisons.

Section 9.4.3 Multiplicity Strategy. Added one-sided 2.5% wording in both paragraphs.

Revised Text:

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

The additional secondary/exploratory endpoints as listed in Appendix 2, if tested, will not be adjusted for multiplicity. A nominal **one-sided** 2.5% significance level will be applied per test.

Section 9.4.4. Covariates and Subgroups of Interest; paragraph 2. Revised sentence to more complete describe adjustments to statistical model.

Revised Text:

Statistical models will be adjusted for **the covariates used in the original analysis**, baseline, subgroup, treatment and treatment by subgroup interaction. Point estimates and **two-sided** 95% CIs will be estimated (presented on Forest Plots) and the subgroup by treatment interaction p-value calculated.

Section 9.4.4.1. Exploratory Cardiovascular Safety Analysis. Added two-sided for 95% CI

Revised Text:

With fewer than 80 first MACE (defined as all-cause mortality, non-fatal MI, or non-fatal stroke) expected to occur during the trial, incidence rates and **two-sided** 95% CIs will be computed for the following mortality and CV composite or component endpoints: 1) MACE; 2) MACE or a thromboembolic event (vascular access thrombosis, a symptomatic deep vein thrombosis or a symptomatic pulmonary embolism); 3) MACE or hospitalization for heart failure; 4) all cause mortality; 5) CV mortality; 6) MI (fatal and

non-fatal); 7) stroke (fatal and non-fatal); 8) CV mortality or non-fatal MI; 9) all cause hospitalization

Section 9.4.7 Analysis of Patient Reported Outcomes Measures Paragraph 1. Updated study visit for interim data cut.

Revised Text:


In order to establish and evaluate the measurement properties of the CKD-QA, an interim cut of blinded observations of at least 50 subjects who completed the Week ~~S2~~ **28** visit will be taken. The data cut will require the following variables through Week ~~S2~~ **28**: PGI-C, PGI-S, Hgb, SF-36, demographic and baseline clinical characteristics.

Section 12.2. Appendix 2: Exploratory Objectives/ Endpoints; exploratory endpoints. Minor updates to blood transfusion objective and iron parameter, blood transfusion, and dose adjustment endpoints.

Revised Text:

<p>To further compare daprodustat and rhEPO on Hgb variability</p>	<ul style="list-style-type: none"> • 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 and MP • Number (%) of subjects with mean Hgb above, within and below the Hgb analysis range during EP and at the end of treatment • Number (%) of subjects with a Hgb <7.5 g/dL during EP and MP • 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 increase in Hgb within any 4-week period from Week 4 to Week 52 • N (%) of subjects with a Hgb value 12 12 g/dL during EP • Number of times Hgb 12 12 g/dL during the EP • % of time Hgb 12 12 g/dL during the EP
<p>To compare daprodustat to rhEPO on measures of iron parameters</p>	<ul style="list-style-type: none"> • Observed and change from baseline in hepcidin, ferritin, transferrin saturation, total iron, total iron binding capacity (TIBC) across all visits to end of

	<p>treatment</p> <ul style="list-style-type: none"> • Average quarterly TSAT • Average quarterly ferritin • Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria • N (%) of subjects who reduced IV iron supplementation relative to baseline (defined as total iron (mg) over 4 weeks prior to randomization) to EP (defined as average monthly IV iron dose (mg) over Weeks 28-52)
To compare daprodustat to rhEPO on the need for RBC and whole blood transfusions	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Assigned dose by visit and at Day 1, Week 28, Week 52 • Most recent dose prior to Week 28, Week 52, yearly and End of Treatment • Number (%) of patients with 0, 1, 2, or >2 dose adjustments during the following periods: <ul style="list-style-type: none"> ○ Day 1 - < Week 28 ○ Week 28 - < Week 52 ○ Day 1 - < End of Treatment • Number of dose adjustments during the following periods: <ul style="list-style-type: none"> ○ Day 1 - < Week 28 ○ Week 28 - < Week 52 ○ Day 1 - < End of Treatment • Number of dose adjustments during Day 1 - < End of Treatment • Final (mean and median) dose at Week 28, Week 52, and at end of treatment • 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 - Week 52, > Week 28- end of treatment Day 1 - the end of treatment. • Number of dose adjustments during the following periods: Day 1 - < Week 28, Week 28 - Week 52, Day 1 - Week 52, > Week 28- end of

	treatment, Day 1 — the end of treatment <ul style="list-style-type: none"> Time dose held for Hgb  12 g/dl
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*Section 12.3.1. Darbepoetin Alfa Dose Steps. Removed partial dosing as partial doses will no longer be available; clarified “every week” frequency to be “once a week” and added a * and footnote to clarify which 4-weekly starting doses will have ‘booster’ doses where appropriate.*

Revised Text:

Total 4-weekly Dose (µg)	PFS Dose and Frequency (PD/HD)
20 µg	20 µg (0.2 ml of 40 µg) Q4 weeks
30 µg	30 µg (0.3 ml of 40 µg) Q4 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 (0.4 ml of 100 µg) every 2 weeks
200 µg	100 µg every 2 weeks
300 µg	150 µg every 2 weeks
400 µg	100 µg every once a week

*** Subjects starting on these doses at the Randomization (Day1) who have >1 g/dL Hgb decrease or Hgb < 7.5 g/dL at Week 2 or Week 6 from the last visit will receive a “booster” dose of 20 µg in addition to their previous dose.**

Section 12.4. Appendix 4: Risk Assessment. Updates included throughout to align with version 8 of the Investigator's Brochure.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Daprodustat		
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	<p>In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion/inflammation, microthrombi, and tissue ischemia in a number of organs.</p> <p>Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose levels, and dose adjustment scheme to optimize Hgb management.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p> <p>Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose levels, and dose adjustment scheme to optimize Hgb management.</p>	<ul style="list-style-type: none"> • Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 5.1 • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb (including rate of change) is provided in Section 6.2 and Section 6.11 • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Risk of Death, MI, stroke, heart failure, thromboembolic events,	Marketed rhEPO and its analogs have been associated with an increased risk for death and serious cardiovascular events	<ul style="list-style-type: none"> • Specific eligibility criteria related to CV risk are outlined in Section

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)	<p>when used in patients with anemia of CKD.</p> <p>In non-clinical studies conducted to date, not observed at tolerated doses when hemoglobin/hematocrit within normal range for species.</p> <p>The clinical data received to date are insufficient to conclude or refute this risk.</p>	<p>5.2</p> <ul style="list-style-type: none"> Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table (Table 6) Unblinded monitoring of safety data by an IDMC in-stream throughout the study
Esophageal and gastric erosions	<p>In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ ulcers with hemorrhage were observed with daprodustat.</p> <p>In rodents rats stomach erosions were observed with intravenous and oral administration of daprodustat.</p> <p>Stomach erosions/ulcers also reported in rats with some marketed rhEPO and its analogs.</p> <p>Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat).</p> <p>In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported</p>	<ul style="list-style-type: none"> Suspected GI bleeding or significant symptoms consistent with erosions or ulcers should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted. Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>adverse event, however causal association has not been established.</p> <p>Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.</p>	
Cancer-related mortality and tumor progression and recurrence	<p>In clinical trials, use of rhEPO and its analogs in patients with cancer has been associated with increased risk of cancer related morbidity and mortality.</p> <p>Administration of 60mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p> <p>There were no test article-related neoplastic findings in 2-year rat (oral daprodustat) or mouse (daprodustat + subcutaneous injection of the 3 major human metabolites; M2, M3 and M13) carcinogenicity studies.</p> <p>In clinical studies with daprodustat up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations, an angiogenic factor that has been implicated in tumor growth, was observed at doses ranging from 10 to 150 mg. In clinical studies up to 24 weeks duration at doses up to 25mg, changes</p>	<ul style="list-style-type: none"> • Specific eligibility criteria related to personal history of malignancy or subjects with complex kidney cyst are outlined in Section 5.2.. • Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 5.5. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>in VEGF plasma concentrations were variable but similar relative to control.</p> <p>In clinical studies conducted to date, administration of daprodustat has been associated with:</p> <p><u>Once daily administration:</u></p> <ul style="list-style-type: none">• In studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg.• In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentration were variable but similar relative to control.• Systemic EPO concentrations within the physiologic range. <p><u>Three times weekly administration:</u></p> <ul style="list-style-type: none">• In studies up to 4 weeks duration at doses of 10 to 30 mg:<ul style="list-style-type: none">○ Dose dependent increases in plasma VEGF and EPO concentrations were observed.○ Pre-dose concentrations of EPO and VEGF were	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>near or below baseline indicating no accumulation of EPO or VEGF after three times weekly dosing</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	
Pulmonary artery hypertension (PAH)	<p>A role for HIF-regulated pathways in the pathophysiology of PAH has been suggested based on well-established effects of acute and chronic hypoxia in man on the pulmonary vasculature (vasoconstriction), and by findings in patients with naturally occurring mutations that result in decreased HIF degradation [Smith, 2006; Formenti, 2011].</p> <p>There have been no histopathologic findings suggestive of PAH in pre-clinical safety studies with daprodustat up to 13-weeks duration in mice and dogs, up to 26 weeks 2-years in rats and mice, and up to 39-weeks in monkeys.</p> <p><u>Acute hypoxic challenge (rats):</u> Daprodustat produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. However, these hypoxia-induced PRVP changes were within the range of PRVP changes noted among non un-treated rats.</p>	<ul style="list-style-type: none"> Unblinded monitoring of safety data by an IDMC in-stream throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with daprodustat 5mg or 100mg had no clinically significant effect on transthoracic echocardiographically (ECHO) estimates of pulmonary artery systolic pressure (sPASP) under either normoxic or hypoxic conditions.</p> <p>ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in sPASP in subjects not on dialysis for daprodustat. In hemodialysis subjects, mean absolute change from baseline in sPASP was similar for both treatment groups; however, there was a numeric imbalance (daprodustat Total: 8 [7%]; Control 0) in subjects reaching the sPASP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 subjects with resolution of sPASP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study drug; and there was no dose relationship for subjects meeting the sPASP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat.</p> <p>Following review of clinical data received to date, this has not</p>	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	been identified as a safety concern for daprodustat.	
Cardiomyopathy	<p>Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized.</p> <p>Small increases in cardiac troponin in 6 month rat study with daprodustat were consistent with the background finding of spontaneous rodent cardiomyopathy. There were no elevations observed in cardiac troponin in 9 month monkey study with daprodustat.</p> <p>With lifetime exposure to daprodustat in a 2-year rat oral carcinogenicity study, an exacerbation of rat spontaneous, progressive cardiomyopathy (PCM)(focal myofiber degeneration/necrosis with inflammatory infiltrates) was observed at doses of 0.8 mg/kg/day and above, although total incidence and severity distribution within any daprodustat-group were within historical control ranges. This is consistent with an equivocal threshold for exacerbation of spontaneous, progressive cardiomyopathy at 0.8 mg/kg/day which is also the threshold dose for observing increased Hct values in individual rats.</p> <p>Cardiomyopathy has not been associated with naturally</p>	<ul style="list-style-type: none"> Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>occurring mutation in man which results in increased HIF stabilization.</p> <p>ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in LVEF with daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	
Proliferative retinopathy, macular edema, choroidal neovascularization	<p>Increases in local (ocular) VEGF production with retinal neovascularization and macular edema observed in diabetic retinopathy and to choroidal leakage, edema and neovascularization seen in age-related macular degeneration [Campochiaro, 2006].</p> <p>Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.</p> <p>Aside from congestion of retinal vessels and optic disc hyperemia secondary to markedly increased red cell mass, there were no ocular abnormalities observed in non-clinical studies.</p> <p>No ocular abnormalities with daprodustat were seen in non-clinical studies of up to 13 weeks duration in mice and dogs, 26</p>	<ul style="list-style-type: none"> • Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>weeks in rats, and 39-weeks in monkeys.</p> <p>In clinical studies with daprodustat up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg administered once daily and from 10 to 30mg administered three times weekly. In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentrations were variable but similar relative to control.</p> <p>Ophthalmologic assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization for daprodustat.</p> <p>Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.</p>	
Exacerbation of rheumatoid arthritis	<p>In inflamed rheumatic joints, activation of HIF- related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra, 2010; Muz, 2009].</p> <p>No abnormalities were seen in non-clinical studies conducted to date for daprodustat.</p> <p>Following review of clinical data received to date, this has not</p>	<ul style="list-style-type: none"> Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	been identified as a safety concern for daprodustat.	
Drug-drug interactions	<p>Daprodustat is a substrate of CYP2C8: Co-administration of daprodustat with a strong CYP2C8 inhibitor (gemfibrozil) increased the C_{max} and AUC of daprodustat, 4- and 19-fold, respectively, while co-administration of a weak inhibitor (trimethoprim) increased the C_{max} and AUC of daprodustat by 1.3- and 1.5-fold, respectively.</p> <p>Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with a moderate CYP2C8 inhibitor (clopidogrel), leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response.</p> <p>daprodustat is an inhibitor of CYP2C8 <i>in vitro</i>, with an IC₅₀ value of 21 µM.</p> <p>Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with clopidogrel (a moderate CYP2C8 inhibitor) leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution</p> <p>Co-administration of daprodustat with potent BCRP inhibitors</p>	<ul style="list-style-type: none"> Co-administration of daprodustat with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.9.2. Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 6.9.1. Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.9.. Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>has the potential to increase exposure of daprodustat. Use of BCRP inhibitors (mostly weak) was found to result in a small change in metabolite exposure (20% increase in AUC).</p> <p>Daprodustat is an inhibitor of OATP1B1/1B3 <i>in vitro</i>, with IC₅₀ values of 6 µM and 11 µM, respectively. A clinical drug interaction study between 25mg daprodustat with either a CYP2C8 substrate or an OATP1B1/1B3 substrate showed that there is no PK interaction at this dose of daprodustat.</p> <p>Although CYP2C8 induction studies were not performed, co-administration of daprodustat with an inducer of CYP2C8 (e.g., rifampin/rifampicin) may decrease the exposure of daprodustat.</p> <p>Even though co-administration of daprodustat with strong inhibitors and inducers of CYP2C8 is prohibited, inadvertent co-administration may occur. Due to the known time delay in enhancing erythropoiesis by daprodustat, co-administration with strong CYP2C8 inhibitors for up to 14 days is not anticipated to lead to immediate marked increases in hemoglobin levels. Therefore, there is adequate time to change to alternate therapy that does not inhibit CYP2C8.</p> <p>Additionally, as the time for maximum induction of CYP2C8 occurs after approximately 10-14 days of dosing with rifampin (Brodie, 2013 and Ohnhaus, 1989), daprodustat</p>	<p>Table (Table 6)</p> <ul style="list-style-type: none"> • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb is provided in Section 6.2.1 and Appendix 3. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>systemic exposure will decrease over time which will result in a lag period before an effect on Hgb is recognized and is of clinical concern.</p> <p><u>Daprodustat is an inhibitor of CYP2C8:</u> A clinical drug interaction study between 25mg and 100mg daprodustat with a CYP2C8 substrate (pioglitazone) showed that there is no PK interaction at these doses of daprodustat.</p> <p><u>Daprodustat is a substrate of BCRP:</u> Population PK analysis from Phase 2 studies suggested that while BCRP inhibitors were a covariate for daprodustat CL/F (8.6% lower clearance) the predicted change in exposure was not considered to be of clinical relevance.</p> <p><u>Daprodustat is an inhibitor of OATP1B1/1B3:</u> A clinical drug interaction study between 25mg and 100mg daprodustat with an OATP1B1/1B3 substrate (rosuvastatin) showed that there is no PK interaction at these doses of daprodustat</p>	
Other		
rhEPO risks (Control)	<ul style="list-style-type: none"> See risks outlined in table for daprodustat for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia, Death, MI, stroke, thromboembolic events, thrombosis of vascular access, and for Increased cancer-related mortality and tumor progression. 	<ul style="list-style-type: none"> See mitigation strategies outlined in table for daprodustat for Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia, Risk of death, MI, stroke, thromboembolic

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<ul style="list-style-type: none">• Uncontrolled hypertension• Pure red cell aplasia	<p>events, thrombosis of vascular access, and for Increased cancer-related mortality and tumor progression.</p> <ul style="list-style-type: none">• Specific eligibility criteria related to current uncontrolled hypertension are outlined in Section 5.2.• Specific eligibility criteria related to personal history of pure red cell aplasia are outlined in Section 5.2.

Section 12.5. Appendix 5: Female Eligibility Criteria; # 2 under Non-reproductive potential definitions. Removed upper boundary of FSH to confirm menopause, corrected conventional units for FSH and added SI units for FSH.

Rationale for change:

Revised Text:

2. Postmenopausal defined as 12 months of spontaneous amenorrhea. In questionable cases, a blood sample with simultaneous FSH and estradiol consistent with menopause is confirmatory (FSH ~~23.0–116.3~~ **23.0** MIU/mL (**23.0** TU/L) and estradiol :SIO pg/mL (or :S37 pmol/L) is confirmatory).

Section 12.11, Appendix 11 is totally removed. France is not taking part in this study so this Appendix is no longer relevant

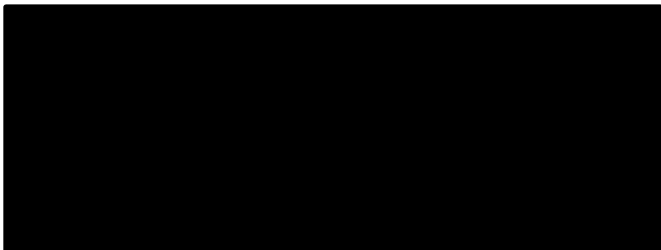
Division	Worldwide Development
Information Type	Reporting and Analysis Plan (RAP)

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	08-APR-2018

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2015N234534_01.

PPD Author's Name and Functional Area:

GSK RAP Team Approvals:

Approver	Date	Approval Method
[REDACTED] SERM Director (Global Clinical Safety & Pharmacovigilance)	04-Apr-2018	Email
[REDACTED] Director, Medicine Delivery Unit (Physician Lead)	04-Apr-2018	Email
[REDACTED] Manager, Clinical Data Management (Data Quality Lead)	04-Apr-2018	Email
[REDACTED] Clinical Development Manager (Operational Science Lead)	08-Apr-2018	Email
[REDACTED] Senior Director Therapeutic Group (Regulatory Affairs)	04-Apr-2018	Email
[REDACTED] Manager, Clinical Pharmacology (Clinical Pharmacology Modelling & Simulation)	04-Apr-2018	Email
[REDACTED] Medical Writing Manager (Medical Writing)	05-Apr-2018	Email
[REDACTED] Statistics Leader (Clinical Statistics)	04-Apr-2018	Email
[REDACTED] Senior Director, Value Evidence Leader, Neurosciences and Cell & Gene Therapy (Value Evidence & Outcomes)	04-Apr-2018	Email
[REDACTED] Clinical Development Director (Clinical Investigation Lead)	04-Apr-2018	Email
[REDACTED] Programming Manager (Lead Programmer)	04-Apr-2018	Email

GSK Clinical Statistics and Clinical Programming Line Approvals:



Approver	Date	Approval Method	Signature
 Senior Director, Statistics & Programming (Clinical Statistics)	04-Apr-2018	Email, Wet-ink signature	NA
 Programming Manager (Clinical Programming)	04-Apr-2018	Email, Wet-ink signature	NA

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	<ul style="list-style-type: none"> This RAP describes the planned analyses and outputs required for the final Clinical Study Report (CSR) for study 201410
Protocol	<ul style="list-style-type: none"> This RAP is based on the first protocol amendment [(Dated: 06OCT2017) of study 201410 (GSK Document No. 2015N234534_01].
Primary Objective	<ul style="list-style-type: none"> To compare daprodustat to rhEPO for hemoglobin (Hgb) efficacy (non-inferiority)
Primary Endpoint	<ul style="list-style-type: none"> The mean change in Hgb between baseline and the evaluation period (EP, mean over Weeks 28-52)
Study Design	<ul style="list-style-type: none"> 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 rhEPO (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 rhEPO, iron management, and anemia rescue therapy.

Overview	Key Elements of the RAP
Planned Analyses	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> The primary Hgb efficacy objective will assess the estimand defined as the comparative treatment effect in mean Hgb change between baseline and EP (i.e., mean over Weeks 28 to 52 inclusive) in all randomized subjects; defined as those who remain in follow-up throughout the period of stabilization and have at least one Hgb assessment during the EP (i.e., Weeks 28 to 52) regardless of adherence to study treatment. The analysis will test whether daprodustat is non-inferior to rhEPO according to the following statistical hypotheses: <ul style="list-style-type: none"> Null: The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-rhEPO), is less than or equal to -0.75 g/dl. Alternative: The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-rhEPO), is greater than -0.75 g/dl.
Primary Analyses	<ul style="list-style-type: none"> 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-rhEPO) and generate the p-value for the non-inferiority test. Non-inferiority will be established if the lower limit of the two-sided 95% CI for the treatment difference is greater than -0.75 g/dl.
Key Secondary Analyses	<p>Principal Secondary Endpoint (adjusted for multiplicity, tested for superiority)</p> <ul style="list-style-type: none"> Average monthly IV iron dose (mg)/subject from baseline to Week 52 <p>Safety Endpoints</p> <ul style="list-style-type: none"> Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including those AEs of special interest 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

There were no changes or deviations to the originally planned statistical analysis specified in the first protocol amendment (Dated 06OCT2017), except that 'Day 1 -< End of Treatment' analysis period is added to the exploratory endpoint of evaluating the dose adjustment schemes. See details in Section 2.2.

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

Objectives	Endpoints
Primary Objectives	Primary Endpoints
<ul style="list-style-type: none"> To compare daprodustat to rhEPO for Hgb efficacy (non-inferiority) 	<ul style="list-style-type: none"> 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)
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the use of intravenous (IV) iron 	<ul style="list-style-type: none"> Average monthly IV iron dose (mg)/subject from baseline to Week 52
Secondary Objectives	Secondary Endpoints (tested for superiority¹, no multiplicity adjustment)
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on BP 	<ul style="list-style-type: none"> Change from baseline in SBP, DBP, and MAP at Week 52 and at end of treatment Number of BP exacerbation events per 100 patient years N (%) with at least one BP exacerbation event during study
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on Hgb variability 	<ul style="list-style-type: none"> Hgb change from baseline to Week 52¹ 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the time to rescue (defined as permanently stopping randomized treatment due to meeting rescue criteria) 	<ul style="list-style-type: none"> Time to stopping randomized treatment due to meeting rescue criteria
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on HRQol and Utility score 	<ul style="list-style-type: none"> Mean change in SF-36 HRQOI 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the symptom severity and change 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To summarize the PK parameters of daprodustat and three major metabolites in dialysis subjects 	<ul style="list-style-type: none"> Plasma daprodustat, M2, M3, and M13 PK parameters pre-dose trough (Ctau) and Cmax

Objectives	Endpoints
Exploratory Objectives	Exploratory Endpoints (Statistical testing not planned)
<ul style="list-style-type: none"> To further compare daprodustat and rhEPO on Hgb variability 	<ul style="list-style-type: none"> 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 \geq 12 g/dl during the EP Number of times Hgb \geq 12 g/dl during the EP % of time Hgb \geq 12 g/dl during the EP
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on measures of iron parameters 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the need for RBC and whole blood transfusions 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To evaluate the dose adjustment schemes 	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Day 1 - < Week 28 Week 28 - < Week 52 Day 1 - < End of Treatment Number of dose adjustments during the following periods: <ul style="list-style-type: none"> Day 1 - < Week 28 Week 28 - < Week 52 Day 1 - < End of Treatment Time dose held for Hgb \geq12 g/dl
<ul style="list-style-type: none"> To further compare daprodustat to rhEPO on BP and BP medication changes 	<ul style="list-style-type: none"> 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

Objectives	Endpoints
	subject by visit <ul style="list-style-type: none"> N (%) of subjects who had no change, an increase or a decrease in the dosage or number of BP medications from baseline by visit
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on lipid parameters 	<ul style="list-style-type: none"> 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)]
<ul style="list-style-type: none"> To further compare daprodustat to rhEPO on the symptom severity and change 	<ul style="list-style-type: none"> 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.
<ul style="list-style-type: none"> To further compare daprodustat to darbepoetin alfa on HRQol and Utility score 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To evaluate graphical relationships between exposure parameters and selected efficacy endpoints 	<ul style="list-style-type: none"> Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP. Scatter plots of average daprodustat dose during EP vs. percent time in range during EP. Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP vs. percent time in range during EP. Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) 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 (C_{tau} and C_{max}) dose normalized to average dose during EP vs. change from baseline of Hgb during EP.
<ul style="list-style-type: none"> To evaluate graphical relationships between daprodustat exposure and MACE and the composite endpoint of MACE + thromboembolic event + hospitalization for heart failure 	<ul style="list-style-type: none"> Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint. Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) 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
<ul style="list-style-type: none"> To compare the safety and tolerability of daprodustat to rhEPO 	<ul style="list-style-type: none"> 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)

- 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	
<p>The flowchart illustrates the study timeline. It begins with a 'Screening 2 weeks*' box. An arrow leads from this box to a 'Randomization' box. From 'Randomization', two arrows branch out to two parallel treatment arms: 'Daprodustat' and 'Darbepoetin alfa'. Each treatment arm is represented by a long horizontal box. Above these treatment boxes, three time periods are defined: 'Stabilization period Day 1 to Week 28', 'Evaluation period Week 28 to Week 52', and 'F/up (Week 56-58)'. Small vertical boxes at the end of the treatment arms align with the 'F/up' period.</p> <p>* Screening period may be extended by an additional 4 weeks for ultrasound examination, IV iron supplementation and/or vitamin B12 treatment as needed.</p>	
Design Features	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 comparative treatment effect in mean Hgb change between baseline and EP (i.e., Weeks 28 to 52 inclusive) in all randomized subjects; defined as those who remain in follow-up throughout the period of stabilization and have at least one Hgb assessment during the EP (i.e., Weeks 28 to 52) regardless of adherence to study treatment. The analysis will test whether daprodustat is non-inferior to rhEPO according to the following statistical hypotheses

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

The non-inferiority margin is pre-defined as -0.75 g/dL; determined based upon a combination of clinical judgment, statistical reasoning and regulatory guidance for designing non-inferiority trials.

Statistical significance of non-inferiority will be assessed at the one-sided 2.5% level. An ANCOVA model including 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 -rhEPO) and generate the p-value for the non-inferiority test. The non-inferiority p-value will show strength of evidence against the null hypothesis. Non-inferiority will be established if the lower limit of the two-sided 95% CI for the treatment difference is greater than -0.75 g/dL.

3. PLANNED ANALYSES

3.1. Interim Analyses

The IDMC will periodically receive unblinded safety reports containing, at a minimum, clinical endpoints (whether adjudicated or pending adjudication) and SAEs, from an independent Statistical Data Analysis Center (SDAC) while the study is ongoing. The IDMC may recommend stopping the study for safety at any time. 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	<ul style="list-style-type: none"> All screened subjects. 	<ul style="list-style-type: none"> Study Population Safety
Intent-To-Treat (ITT)	<ul style="list-style-type: none"> All randomized subjects. Subjects will be analyzed according to the treatment to which they were randomized. 	<ul style="list-style-type: none"> Study Population Efficacy Safety
Enrolled	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Study Population
Per-Protocol (PP)	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Efficacy
Safety	<ul style="list-style-type: none"> All randomized subjects who receive at least one dose of randomized treatment. Subjects will be analyzed according to the treatment received.¹ 	<ul style="list-style-type: none"> Safety
Pharmacokinetic (PK)	<ul style="list-style-type: none"> Subjects for whom a PK sample was obtained and analyzed 	<ul style="list-style-type: none"> PK

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

4.1. Protocol Deviations and Study Population Exclusions

- Significant protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) 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 Significant Protocol Deviations Plan and Study Deviation Rules Document.
 - Data will be reviewed prior to unblinding the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
 - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 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 2](#) provides an overview of the planned study population analyses.

Tab e 2 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
Exclusions from Study Population	ITT	y		y
Subject Disposition				
Subject Status and Reasons for Study Withdrawal	ITT	y	y	y
Subject Status and Reasons for Study Withdrawal by Region	ITT	y		
Subject Status and Reasons for Study Withdrawal by Country	ITT	y		
Treatment Status and Reasons for Discontinuation of Randomized Treatment	ITT	y	y	y
Treatment Status and Reasons for Discontinuation of Randomized Treatment by Region	ITT	y		
Treatment Status and Reasons for Discontinuation of Randomized Treatment by Country	ITT	y		
Subject Disposition at Each Study Epoch	Screened	y		
Number of Subjects by Region, Country and Site ID	Enrolled	y		
Type of Subject Contact at Wk52	ITT	y		
Subject Completion Status	ITT	y		
Subject Survival Status	ITT	y		
Planned and Actual Treatments	ITT			y
Protocol Deviations				
Significant Protocol Deviations	ITT	y		y
Subjects with Inclusion/Exclusion Criteria Deviations	ITT	y		y
Demographic & Baseline Characteristics				
Demographic & Baseline Characteristics	ITT & Safety	y		y
Demographic & Baseline Characteristics by Baseline Dialysis Type	ITT	y		
Demographic & Baseline Characteristics by Baseline Dialysis Start Manner	ITT	y		

Parameter	Analysis Population	Data Displays Generated		
		Table	Figure	listing
Age Ranges	Enrolled	y		
Race and Racial Combinations	ITT	y		y
Substance Use	ITT	y		
Medical Conditions	ITT	y		
Dialysis Modality and Frequency	ITT	y		
Dialysis Modality Changes	ITT	y		
Prior and Concomitant Medications				
Pre-Treatment Medications	ITT	y		
On-Treatment Medications	ITT	y		y
Post-Treatment Medications	ITT	y		
Non-randomized ESA Use During Treatment Period	ITT	y		y
Treatment Compliance				
Extent of Exposure to Randomized Treatment	ITT	y		y
Randomized Treatment Compliance Categories	ITT	y		
Randomized Treatment Compliance	ITT	y		
IRT and eCRF Dose and Frequency Discrepancies	ITT	y		

NOTES :

- y = yes display generated.

6.2. Display Details

6.2.1. Populations Analyzed

The number of randomized 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 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.

The summary of subject status and reasons for study withdrawal will be repeated by region and by country.

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.

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.

The summary of treatment status and reasons for discontinuation of randomized treatment will be repeated by region and by country.

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. The first plot will include all subjects who

discontinued randomized treatment, the second plot will only include subjects who discontinued randomized treatment but did not die while on randomized treatment.

A box and whisker plot of time to permanent discontinuation of randomized treatment due to an Adverse Event by treatment group will be produced.

The number and percentage of subjects who entered, withdrew from and completed each epoch of the study will be summarized by treatment group and overall.

The number and percentage of subjects by region, country, site ID and investigator name will be summarized by treatment group and overall for the enrolled population.

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

A summary of the subject completion status, including the number and percentage of subjects included in the primary Hgb analysis, and by vital status (known and unknown at the end of study) will be provided by treatment group and overall.

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

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

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, including the number of subjects who required B12 supplementation to be

eligible for randomization. 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, partial date 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 substance use 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 baseline, Week 28 and Week 52 will be provided by treatment group and overall. This summary will include the number and percentage of subjects who have temporarily or permanently stopped dialysis at these time points, as well as summary statistics for total residual urine volume 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 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 any discrepancy and the number of discrepancies between the IRT-assigned dose/frequency and the dose/frequency 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).

7. PRIMARY STATISTICAL ANALYSES

7.1. Primary Hgb Efficacy Analysis

7.1.1. Overview of Planned Primary Hgb Efficacy, Sensitivity and Supplementary Analyses

Table 3 provides an overview of the planned primary Hgb efficacy, sensitivity and supplementary analyses.

Table 3 Overview of Planned Primary Hgb Efficacy, Sensitivity and Supplementary Analyses

Endpoint	Analysis Population	Absolute				Change from Baseline							
		Summary		Individual		Stats Analysis			Summary		Individual		
		T	F	F	I	T	F	I	T	F	F	I	
Mean Change in Hgb between Baseline and EP													
Primary Analysis	ITT [treatment) Hgb values]	y	y			y	y		y	y			y
Supplementary Analysis On-Drug	ITT [evaluable Hgb values]	y	y			y	y		y	y			
Supplementary Analysis PP	PP [evaluable Hgb values]	y	y			y	y		y	y			
Sensitivity & Supplementary Tipping Point Analyses ¹	ITT					y	y						
Sensitivity & Supplementary Analyses Alternative EP ¹	ITT	y				y	y		y				
By Subgroup ¹	ITT					y	y		y				

NOTES :

- T = Table, F = Figure, I = listing, y = yes display generated.
- Stats Analysis = Represents TFI related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFI related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FI related to any displays of individual subject observed raw data.

^[1] Analysis will be performed using all available (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

Primary Hgb Efficacy Statistical Analyses	
Endpoint(s)	
<ul style="list-style-type: none"> Mean change in Hgb between baseline and EP 	
Model Specification	
<ul style="list-style-type: none"> Hgb during the EP will be defined as the mean of all available 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: <ul style="list-style-type: none"> Treatment Baseline Hgb (see Section 10.5.2) Dialysis type (as randomized, see Section 10.10.2) Dialysis start manner (whether dialysis start is planned or unplanned; as randomized) 	
Model Checking & Diagnostics	
<ul style="list-style-type: none"> Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses. 	
Model Results Presentation	
<ul style="list-style-type: none"> All available Hgb values (on and off-treatment) will be summarized using mean, standard deviation, minimum, P25, median, P75 and maximum at each visit by treatment group. In addition to scheduled visits, the baseline value and mean EP values will be included (see Section 10.6.3). All available Hgb change from baseline values (on and off-treatment) will also be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each post-baseline visit, including mean EP values (see Section 10.6.3). The number and percentage of subjects with missing data in the primary Hgb analysis will be provided by treatment group. Subjects will be classified as either not included or included in the analysis. Subjects will not be included in the analysis if they are missing a baseline Hgb value, if they are missing all EP Hgb values, or if they are missing a baseline Hgb value and all EP Hgb values. The number and percentage of subjects by reason for the monotone missing EP Hgb values will be provided. Reasons include: death before Week 28, death during Week 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 who are included in the analysis will be further classified as either having all 7 scheduled EP Hgb values, having partial scheduled EP Hgb values, or having no scheduled EP Hgb values with at least one unscheduled EP Hgb value. For subjects with partial scheduled EP Hgb values, both the pattern of missing data (intermittent, monotone) and the amount of missing data (1 - 6 scheduled Hgb values missing) will be summarized. For subjects with partial scheduled EP Hgb values and a monotone missing data pattern, the reason for the monotone missing scheduled EP Hgb values will be provided. Reasons include: death during Week 28-52, lost to follow-up during Week 28 - 52, consent withdrawn during Week 28 - 52, and other monotone missing Hgb values. And for summaries of the amount of missing scheduled EP Hgb values, the presence or absence of additional unscheduled EP Hgb values will be summarized. The least square (LS) mean estimates and standard errors by treatment group, LS mean difference, two-sided 95% CI and one-sided non-inferiority p-value for the difference in the primary Hgb endpoint between the daprodustat and rhEPO arms from the ANCOVA model will be presented. The number of subjects contributing to the analysis and the associated mean 	

Primary Hgb Efficacy Statistical Analyses
<p>and standard deviation of the baseline and EP Hgb values will also be displayed with the results of the ANCOVA model.</p> <ul style="list-style-type: none"> The IS mean difference, associated two-sided 95% CI and one-sided non-inferiority p-value will be displayed on a forest plot together with sensitivity and supplementary analysis results (excluding the Tipping Point Analysis). All available Hgb values (on and off-treatment) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values \pm standard errors by time will include horizontal reference lines to depict the target hemoglobin range (10-11 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) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values \pm standard errors by time will include vertical reference lines to identify the EP (Weeks 28-52), and the number of subjects by treatment group contributing to each mean value. A listing of all hemoglobin values will be provided, including treatment, site ID, unique subject ID, visit, assessment date, select demographic information and central laboratory and HemoCue Hgb values.
Model Results Interpretation
<ul style="list-style-type: none"> 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 and Supplementary Statistical Analyses
On Drug Analysis
<ul style="list-style-type: none"> For this analysis which estimates the effect of daprodustat in subjects who adhere to treatment, the primary Hgb analyses and summaries described above will be performed using evaluable Hgb values (see Section 10.6.3), which are on-treatment Hgb values that exclude any values recorded that occurred within 8 weeks after a red blood cell transfusion or taking non-randomized ESA treatment. The IS mean treatment difference, associated 95% CI and one-sided non-inferiority p-value from this analysis will be included on a forest plot with the primary Hgb analysis results.
PP Population Analysis
<ul style="list-style-type: none"> The primary 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 IS mean treatment difference, associated two-sided 95% CI and one-sided non-inferiority p-value from this analysis will be included on a forest plot with the primary Hgb analysis results.
Tipping Point (Multiple Imputation) Analysis
<ul style="list-style-type: none"> Tipping point 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). Tipping point sensitivity and supplementary analyses will be conducted under a range of missing data assumptions to determine how extreme assumptions need to be for non-inferiority conclusions to change. Assumptions about missing Hgb values on the daprodustat and rhEPO arms will vary independently, and will include scenarios where subjects with missing data on daprodustat have worse outcomes than subjects with missing data on rhEPO. <ul style="list-style-type: none"> Intermittent missing Hgb data in both arms through Week 52 will be imputed with

Sensitivity and Supplementary Statistical Analyses
<p>a longitudinal model assuming missing at random (MAR). The MMRM model will use an unstructured covariance matrix and will include factors for treatment, time, prognostic randomization factors, baseline Hgb and the baseline Hgb by time and treatment by time interactions.</p> <ul style="list-style-type: none"> • Monotone missing data that occurs before Week 52 (i.e., due to permanent stop of randomized treatment, death, withdrawal from the study, etc.) will be imputed across a range of scenarios using multiple imputation. For each treatment arm separately, the imputed 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. Beginning with the first missed visit (which could occur before Week 28), each sequential missed visit will increase the multiple of delta (i.e., 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, utilizing low and high cutoffs at Hgb values of 7 g/dl and 14 g/dl, respectively. Delta scenarios which are known ahead of time to not possibly represent the tipping point may not be explored. • EP Hgb values will be computed for each value of delta and compared across treatment groups using the primary ANCOVA model described above and Rubin's rules [Rubin, 1987] will be used to combine results of the imputed datasets. • Graphics depicting treatment difference and one-sided non-inferiority (NI) p-value surfaces will be produced using an enhanced tipping point approach [liublinska, 2014].
Alternative EP (Week 28-36) Analysis
<ul style="list-style-type: none"> • The primary analysis and summaries (using on- and off-treatment Hgb values) and on-drug analysis and summaries (using evaluable Hgb values) described above (with the exception of the missing data summary) will be repeated using an alternative EP from Week 28-36. • The IS mean treatment difference, associated two-sided 95% CI and one-sided non-inferiority p-value from these analyses will be included on a forest plot with the primary Hgb analysis results.
Subgroup Analysis
<ul style="list-style-type: none"> • Subgroup 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). • 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 4 provides an overview of the planned principal secondary efficacy analyses.

Table 4 Overview of Planned Principal Secondary Efficacy Analyses

Endpoint	Analysis Population	Absolute							
		Stats Analysis			Summary		Individual		
		T	F	I	T	F	F	I	
Iron Use									
Average monthly IV iron dose (mg)/Subject from baseline to Week 52	ITT	y			y	y		y	
Supplementary 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, I = listing, y = yes display generated.
- Stats Analysis = Represents TFI related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFI related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FI 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)	
<ul style="list-style-type: none"> • Average monthly IV iron dose (mg)/subject from baseline to Week 52 	
Model Specification	
<ul style="list-style-type: none"> • Average monthly IV iron dose (mg)/subject from baseline to Week 52 will be determined by calculating the total elemental IV iron dose per subject from Day 1 to Week 52 while the subject was on randomized treatment and dividing by (the number of days the subject was on randomized treatment/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: <ul style="list-style-type: none"> ○ Treatment ○ Baseline monthly IV iron dose (see Section 10.5.2) ○ Dialysis type (as randomized, see Section 10.10.2) ○ Dialysis start manner (whether dialysis start is planned or unplanned; as randomized, see Section 10.10.2). 	

Principal Secondary Efficacy Statistical Analyses: Average Monthly IV Iron Dose	
Model Results Presentation	
<ul style="list-style-type: none"> 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 drug name and treatment. Average monthly IV iron dose at baseline, while on treatment during the EP, and while on treatment to Week 52 will be summarized by treatment group using mean, standard deviation, minimum, P25, median, P75, and maximum. The least square (LS) mean estimates and standard errors by treatment group, LS mean difference, two-sided 95% CI and one-sided superiority p-value for the difference in average monthly IV iron dose/subject to Week 52 between the daprodustat and rhEPO arms from the ANCOVA model will be presented. The number of subjects contributing to the analysis and the associated mean and standard deviation of the baseline and Week 52 values will also be displayed with the results of the ANCOVA model. A listing of average monthly IV iron dose will be provided including treatment, site ID, unique subject ID, time period, and average monthly IV iron dose to Week 52. 	
Model Results Interpretation	
<ul style="list-style-type: none"> See Section 10.11.1. 	

Sensitivity and Supportive Statistical Analyses	
Supplementary Analysis: Average monthly IV iron dose (mg)/subject to Week 52 using on and off treatment IV iron records	
<ul style="list-style-type: none"> 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. The average monthly IV iron dose (mg)/subject to Week 52 for this analysis will be determined by calculating the total elemental IV iron dose per subject from Day 1 to Week 52 and dividing by (earliest of the (Week 52 visit date, study completion/withdrawal date) - Randomization date + 1 day)/30.4375 days. 	
Subgroup Analysis	
<ul style="list-style-type: none"> 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 5](#) provides an overview of the planned additional secondary efficacy analyses.

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Tab e 5 Overv ew of P anned Add t ona Secondary Eff cacy Ana yses

Endpoint	Analysis Population	Absolute								Change from Baseline							
		Stats Analysis			Summary		Individual			Stats Analysis			Summary		Individual		
		T	F	I	T	F	F	I	T	F	I	T	F	F	I		
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, I = listing, y = yes display generated.
- Stats Analysis = Represents TFI related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFI related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FI related to any displays of individual subject observed raw data.

^[1] Analysis will be performed using all available (on and off-treatment) Hgb values.

^[2] Analysis will be performed using evaluable Hgb values only (see Section 10.6.3).

^[3] Subgroup analysis will 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)	
<ul style="list-style-type: none"> 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) 	
Model Specification	
<ul style="list-style-type: none"> For the secondary analysis of Hgb change from baseline to Week 52, a mixed model repeated measures (MMRM) approach will be used with an unstructured covariance matrix to compare the difference in means between arms. The model will be fitted to Hgb data collected after baseline up to Week 52, excluding values collected during the stabilization period (Day 1 to Week 28). The model will include factors for treatment, time, prognostic randomization stratification factors (as randomized, see Section 10.10.2), baseline Hgb and the baseline Hgb by time and treatment by time interaction terms. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors. This analysis will be performed using all available Hgb values (on and off-treatment) and separately using evaluable Hgb values only (see Section 10.6.3). In the analysis using all available Hgb values, subjects who withdraw from the study before Week 52 are considered to be missing at random and in the analysis using evaluable Hgb values, subjects who permanently discontinue randomized treatment before Week 52 are assumed to be missing at random. For the Hgb responder analysis, mean Hgb during the EP will be defined as in the on-drug supplementary analysis (Section 10.6.3). Responders will be subjects with a mean Hgb during the EP that falls within the Hgb analysis range of 10-11.5 g/dl. A Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment and the prognostic randomization stratification factors (as randomized, see Section 10.10.2), will be used to compare the number and % of responders between the treatment groups. For the analysis of % time in range, the method by Rosendaal [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 10.10.2). This analysis will be performed using evaluable Hgb values only. 	
Model Results Presentation	
<ul style="list-style-type: none"> For the MMRM analysis of change from baseline in Hgb, an LSMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - rhEPO) at Week 52. The one-sided non-inferiority p-value for this test will be calculated. For the responder analysis, the number and percentage of subjects with mean EP Hgb above, within and below the Hgb analysis range will be summarized by treatment group. For the responder analysis, the number and % of responders by treatment group, relative response rate (daprodustat vs. rhEPO) and two-sided 95% CI will be provided along with the 	

Additional Secondary Efficacy Statistical Analyses: Hgb Variability
<p>one-sided CMH p-value for the treatment group comparison.</p> <ul style="list-style-type: none"> 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 - rhEPO) and associated two-sided 95% CI [Kawaguchi, 2011] will be presented in addition to the one-sided superiority p-value from the van Elteren test.
Model Results Interpretation
<ul style="list-style-type: none"> 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 is above -0.15. If the non-inferiority test is successful, nominal superiority will be achieved if the lower limit of the two-sided 95% CI is above 0 and the one-sided p-value is < 0.025.

Sensitivity and Supportive Statistical Analyses
Subgroup Analysis
<ul style="list-style-type: none"> Subgroup analyses will be performed for all Hgb variability endpoints, using the stratification factor subgroups only (described in Section 10.10.2).

Time to Rescue

Additional Secondary Efficacy Statistical Analyses: Time to Rescue
Endpoint(s)
<ul style="list-style-type: none"> Time to stopping randomized treatment due to meeting rescue criteria
Model Specification
<ul style="list-style-type: none"> The Cox Proportional Hazards model will adjust for the following baseline categorical values: <ul style="list-style-type: none"> Treatment Dialysis type (as randomized, see Section 10.10.2) Dialysis start manner (whether dialysis start is planned or unplanned; as randomized, see Section 10.10.2) 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.

Additional Secondary Efficacy Statistical Analyses: Time to Rescue									
Model Results Presentation									
<ul style="list-style-type: none"> Summaries will include the number and percentage of subjects evaluated for rescue by reason in addition to the number and percentage of subjects qualifying for each step in the rescue algorithm. 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. rhEPO 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									
<ul style="list-style-type: none"> 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 6 provides an overview of the planned exploratory efficacy analyses.

Table 6 Overview of Planned Exploratory Efficacy Analyses

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	I	T	F	F	I
Hgb Variability									
Hgb observed and change from baseline (CFB) cross all visits to end of treatment	ITT	Included with Hgb primary & sensitivity & supplementary 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)							
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,	ITT	y							

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	I	T	F	F	I
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									
N(%) of subjects with a Hgb value \blacklozenge 12 g/dl during the EP ¹	ITT	y							
Number of times Hgb \blacklozenge 12 g/dl during the EP ¹	ITT	y							
% of time Hgb \blacklozenge 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 transfusions per 100 patient years	ITT	y							
Number of RBC and whole blood units per 100 patient years	ITT	y							
Dose Adjustment Scheme Evaluation									
Assigned dose by visit	ITT	y	y						
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 \blacklozenge 12 g/dl	ITT	y							

NOTES :

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- Individual = Represents FI 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 < 7.5 g/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 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 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 number and percentage of subjects with a >1 g/dL decrease in Hgb over 2 weeks (assessed at Week 2, Week 4, Week 6, and Week 8) or 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 and separately 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 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 percentage of time Hgb is ≥ 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 and TSAT 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.

Ferritin, total iron, 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 and TSAT on-treatment values will be 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.

Change from baseline in ferritin, total iron 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 and average quarterly ferritin while on treatment will be summarized by presenting average TSAT and ferritin 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.

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 (see Section 10.6.3). Assessment of meeting iron management thresholds will be made based on central laboratory data values. Further, the subjects who met the threshold requiring iron administration will be grouped by the type of iron therapy that was started (i.e., oral, IV or none) according to concomitant medication records and the subjects who met the threshold requiring the stopping of iron administration will be further classified to identify the number subjects that did stop iron administration according to concomitant medication records.

REC and Whole Blood Transfusions

The number and percentage of subjects who receive at least one RBC and at least one whole blood transfusion by Week 52, and the associated number of RBC and whole blood transfusions and number of RBC and whole blood units will be summarized by treatment group.

The number of RBC and whole blood transfusions per 100 patient years will be summarized by treatment group (see Section 10.6.3).

The number of RBC and whole blood units per 100 patient years will be summarized by treatment group (see Section 10.6.3).

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 at Day 1, and Week 28 will also be summarized by treatment group using the number and percentage of subjects assigned to each dose level.

The most recent dose prior to each scheduled visit will be summarized by treatment group using mean, standard deviation, minimum, P25, median, P75, and maximum.

The most recent dose prior to Week 28, Week 52, and end of treatment will also be summarized by the number and percentage of subjects at each dose level.

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, or >2 dose adjustments will be summarized by treatment group. Summaries will be presented for the following categories of time Day 1 - < Week 28, Week 28 - <Week 52, and Day 1 - < end of treatment.

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

The time (in days) that study treatment was withheld for Hgb values ≥ 12 g/dL per subject will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. Summaries will be presented for the following categories of time Day 1 - < Week 28, Week 28 - <Week 52, and Day 1 - < end of treatment.

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

- Region
- Race group
- Dialysis type at randomization
- Dialysis start manner
- Baseline weight quartiles

The mean assigned dose by treatment and visit will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean assigned dose \pm standard errors by time will include vertical reference lines to identify the EP as well as the number of subjects by treatment group contributing to each mean value. This plot will also be overlaid on a graph of corresponding 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 7 provides an overview of the planned secondary safety analyses.

Table 7 Overview of Planned Secondary Safety Analyses

Endpoint	Analysis Population	Absolute								Change from Baseline							
		Stats Analysis			Summary		Individual			Stats Analysis			Summary		Individual		
		T	F	■	T	F	F	■	T	F	■	T	F	F	■		
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 :

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- Stats Analysis = Represents TFI related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFI related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FI 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)
<ul style="list-style-type: none"> • Change from baseline in SBP, DBP and MAP at Week 52 and at end of treatment • Number of BP exacerbation events per 100 patient years • N (%) of subjects with at least one BP exacerbation event during study
Model Specification
<ul style="list-style-type: none"> • 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 four times: <ul style="list-style-type: none"> ○ On-treatment BP values only, excluding values collected during the stabilization period (post-baseline to Week 28). ○ On-treatment BP values only, including values collected during the stabilization period. ○ On- and off-treatment BP values, excluding values collected during the stabilization period. ○ On- and off-treatment BP values, including values collected during the stabilization period. <p>The models will include factors for treatment, time, prognostic randomization stratification factors (see Section 10.10.2), baseline BP parameter and the baseline BP parameter by time and treatment by time interaction terms. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors. For analyses using on- and off-treatment values, subjects who withdraw from the study before Week 52 are considered to be missing at random and in the analysis using on-treatment values only, subjects who permanently discontinue randomized treatment before Week 52 are assumed to be missing at random.</p> • The difference in change from baseline in BP (SBP, DBP, and MAP) at the derived end of treatment (see Section 10.6.4) will be analyzed with an ANCOVA model including terms for treatment, prognostic randomization stratification factors (see Section 10.10.2) and the corresponding baseline BP parameter. This analysis will be performed using on-treatment BP values only and separately using on- and off-treatment BP values. • 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, the two-sided 95% confidence interval will be obtained using an exact Poisson method. For differences in rates between treatments, the two-sided 95% confidence interval will be constructed with a Normal approximation using Wald's method [Liu, 2006]. A one-sided p-value for the treatment group comparison will be generated using a negative binomial approach. • The number and percentage of subjects with at least one on-treatment BP exacerbation event during the study will be analyzed with a CMH chi-squared test, adjusting for treatment and the prognostic randomization stratification factors (see Section 10.10.2).
Model Results Presentation
<ul style="list-style-type: none"> • 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 derived mean EP and end of treatment values will be summarized (see Section 10.6.4). Summaries of on-treatment BP

Secondary Safety Statistical Analyses: Blood Pressure

- values only and on- and off-treatment BP values together will be produced. Additionally, for subjects who undergo dialysis in-clinic, pre-dialysis BP values will be summarized separately. On-treatment BP parameter values will be plotted by visit using a line plot.
- BP parameter change from baseline values (SBP, DBP, and MAP) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each post-baseline visit by treatment group. In addition to scheduled visits, the derived mean EP 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. Additionally, for subjects who undergo dialysis in-clinic, pre-dialysis BP values will also be summarized separately. On-treatment BP parameter change from baseline values will be plotted by visit using a line plot.
 - For the MMRM analyses of change from baseline in BP parameters to Week 52, an ISMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - rhEPO) and a one-sided superiority p-value for this test.
 - For the ANCOVA analyses of change from baseline in BP parameters to the derived end of treatment, the 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 BP parameter between the daprodustat and rhEPO arms from the ANCOVA model will be presented. The number of subjects contributing to the analysis and the associated mean and standard deviation of the baseline and end of treatment values will also be displayed with the results of the ANCOVA model.
 - The number and percentage of subjects experiencing an on-treatment BP exacerbation event, the number of events and the relative response rate (daprodustat vs. rhEPO) and two-sided 95% CI will be provided along with the one-sided CMH p-value for the treatment group comparison of the number and percentage of subjects experiencing an on-treatment BP exacerbation event. The number of on-treatment BP exacerbation events per 100 person-years will be summarized by treatment group, along with the two-sided 95% confidence intervals for the within-group rates. The treatment difference in rates and the two-sided 95% confidence interval for the difference in rates will also be provided, along with the one-sided negative binomial p-value for the treatment group comparison.
 - Additionally, for subjects who undergo dialysis in-clinic, the number and percentage of subjects experiencing an on-treatment BP exacerbation event based on a pre-dialysis BP value and the number of events will be summarized separately.

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 8 provides an overview of the planned exploratory safety analyses.

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Table 8 Overview of Planned Exploratory Safety Analyses

Endpoint	Analysis Population	Absolute				Change from Baseline			
		Summary		Individual		Summary		Individual	
		T	F	F	I	T	F	F	I
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 medications¹	ITT					y			
Number of BP medications per subject by visit¹	ITT	y							
CFB in number of BP medications per subject by visit¹	ITT					y			
Number (%) of subjects who had no change, an increase or a decrease in dosage or number of BP medications from baseline by visit¹	ITT	y							
Lipid Parameters									
lipid parameters by visit (TC, LDL-C, HDL-C)	ITT	y	y			y	y		

NOTES:

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- Individual = Represents FI 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.

Number of BP medications per subject while the subject was on treatment overall and by class will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group.

Change from baseline in the number of BP medications per subject while the subject was on treatment overall and by class will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group.

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 overall and by class will be summarized for each scheduled post-baseline visit by treatment group (see Section 10.6.4 for details of classifying BP medication changes).

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 values will be summarized using geometric mean, CV, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided.

Total cholesterol, LDL-C (direct), and HDL-C percent change from baseline values will be summarized using percent change geometric mean, CV, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided.

8.2.2.3. Overview of Exploratory Cardiovascular Safety Analysis

Table 9 provides an overview of exploratory cardiovascular safety analyses.

Table 9 Overview of Exploratory Cardiovascular Safety Analyses

Endpoint ¹	Analysis Population	Absolute						
		Stats Analysis			Summary		Individual	
		T	F	I	T	F	F	I
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			
CV mortality or non-fatal MI	ITT	y			y			
All-cause hospitalization	ITT	y			y			

NOTES :

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- Stats Analysis = Represents TFI related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFI related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FI 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:	
<ul style="list-style-type: none"> • 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) • Stroke (fatal and non-fatal) • CV mortality or non-fatal MI • All-cause hospitalization 	
Model Specification	
<ul style="list-style-type: none"> • For all exploratory CV endpoints except all-cause hospitalization, 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 all-cause hospitalization, treatment groups will be compared in terms of the rate of all-cause hospitalization over the study using a negative binomial model, adjusting for treatment 	

Exploratory CV Safety Analyses

and the prognostic randomization strata. A summary of the unadjusted hospitalization rate will be provided, in addition to the incidence rate ratio, standard error, and two-sided 95% CI for the treatment comparison from the negative binomial model.

- 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

- 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, ECT 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 and percentage 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), difference in rates between treatments (along with two-sided 95% CI), and hazard ratios (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 treatment group.
- Time from Randomization to first occurrence of adjudicated MACE event or end of trial will be evaluated using Kaplan-Meier (KM) methodology and displayed graphically for the comparison of daprodustat vs. rhEPO.

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.

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

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

8.2.3.1. Overview of Planned Adverse Event Analyses

Table 10 provides an overview of the planned adverse event safety analyses.

Table 10 Overview of Planned Adverse Event Safety Analyses

Parameter	Absolute			
	Summary		Individual	
	T	F	F	I
AESIs				
Summary of AESIs	y	y		
Adverse Events				
All AEs by System Organ Class (SOC) and Preferred Term	y			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 SOC, Preferred Term & Verbatim Text				y
Pregnancy Data				y
Serious and Other Significant Adverse Events				
SAEs by SOC and Preferred Term (subjects and occurrences)	y			
Reasons for Considering as a SAE				y
Drug-Related SAEs by SOC and Preferred Term (subjects and occurrences)	y			

Parameter	Absolute			
	Summary		Individual	
	T	F	F	I
Fatal SAEs by SOC and Preferred Term (subjects and occurrences)	y			y
Non-Fatal SAEs by SOC and Preferred Term (subjects and occurrences)	y			y
Drug-Related Fatal SAEs by SOC and Preferred Term (subjects and occurrences)	y			
AEs leading to Permanent Discontinuation of Randomized Treatment by SOC and Preferred Term	y			y
BP Exacerbation Events	y			
BP Exacerbation SAEs	y			
Other Significant AEs				y
Other CV Events				
Other CV Events ²				y

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- Individual = Represents FI related to any displays of individual subject observed raw data.

[1]: Plot of common AEs and relative risk will be generated.

[2]: Electronically generated patient profiles will be produced as listings and used in the preparation of SAE summaries as a part of the study report.

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, the duration of first, second, and third occurrence of the AE, 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
- Duration of the occurrence (days) AE resolution date - AE onset date/AE worsening date + 1 for the occurrence

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 and/or duration of the first, second, and third occurrence will be left missing for the subject. These summaries of special interest AEs will be provided for those AEs classified as treatment emergent, follow-up and post-randomization.

Kaplan-Meier plots may be produced for each special interest AE summarizing the time to first occurrence of the special interest AE by treatment group.

Dot plots displaying the incidence of the event beside the hazard ratio and two-sided 95% CI may be provided for AESIs by treatment group. The censoring time period for the calculation of the hazard ratio will use the treatment emergent last contact date as described in Section 10.6.4.

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, post-randomization, treatment emergent and follow-up AEs will be summarized separately.

Summaries of all treatment emergent AEs will be produced for the age group, gender, race group, baseline dialysis type subgroups, and baseline dialysis start manner subgroups. Summaries of treatment emergent AEs by subgroup will be produced twice by system organ class and preferred term and separately by overall frequency.

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

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

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

Additionally, the most common treatment emergent AEs will be summarized graphically by preferred term and treatment group. The incidence rate in each treatment group and corresponding two-sided 95% confidence interval for the appropriate comparator estimate (e.g. relative risk / odds ratio) of the daprodustat group compared to the rhEPO group will be provided. Displays will be sorted by magnitude of risk, from largest to smallest. AE displays may include various types of estimates for comparison of treatment

groups, which may include risk differences, odds ratios, risk ratios, and hazard ratios, as appropriate.

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

A listing of reasons for considering as a SAE will be produced for all 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 or led to an intervention, dose reduction, or significant additional concomitant therapy). For this study, other significant AEs will be defined as non-fatal non-serious AEs resulting in an action taken with study treatment of '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

Individual electronically generated patient profiles will be produced as listings if a subject reports one of the events above.

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](#)) and include the following tests

Clinical Chemistry	Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)	Bilirubin (total and direct/indirect)
	Potassium (serum)	Urea (serum)	Albumin (serum)
	Calcium (total and albumin-adjusted)	Inorganic phosphate	Creatinine (eGFR CKD-EPI)
Hematology	Platelet count	<i>RBC n ces:</i>	<i>White cell WBC) count with Differential</i>
	RBC count	Mean corpuscular volume (MCV)	Neutrophils
	Reticulocyte count	Mean corpuscular hemoglobin (MCH)	lymphocytes
	Hgb	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
	Hematocrit	Red cell distribution width (RDW)	Eosinophils
			Basophils
Other Laboratory Tests	Serum hCG pregnancy test	Follicle-stimulating hormone (FSH)	Estradiol
	HemoCue Hgb	High-sensitivity C-reactive protein (hsCRP)	Intact parathyroid hormone (iPTH)
	Stored sample (blood)	Vitamin B12	Folate

Summaries of central laboratory Hgb values, HemoCue Hgb values, iron parameter values (serum iron, ferritin, UIBC, 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 hemoglobin, MCHC, total calcium, albumin-adjusted calcium, inorganic phosphate, albumin, urea, total cholesterol, LDL-C, and HDL-C. Conversions from SI units to conventional units are included in Section 10.6.4.

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 11 provides an overview of the planned clinical laboratory safety analyses.

Table 11 Overview of Planned Clinical Laboratory Safety Analyses

Parameter	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	I	T	F	F	I
Clinical Chemistry								
Chemistry Values by Visit	y				y			
Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	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 Relative to Normal Range Post-Baseline Relative to Baseline	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 Relative to Normal Range Post-Baseline Relative to Baseline	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 AIT		y						
Scatter Plot of Maximum AIT vs. Maximum Total Bilirubin		y						
All Laboratory								
All laboratory Data for Subjects with Any Value of PCI				y				
laboratory Data with Character Results				y				

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- Individual = Represents FI 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. Graphical summaries may be provided.

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. Graphical summaries may be provided.

The number and percentage of subjects with on-treatment worst case laboratory results relative to the normal range which are post-baseline relative to baseline will be summarized by laboratory test, category and treatment group. See Section 10.6.4 for additional information on worst case values and normal range categories.

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

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. For reporting purposes, iron parameters will be included in other laboratory tests for PCI displays.

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) hsCRP values will be summarized using geometric mean, coefficient of variation, 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 laboratory data with character results will be provided.

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 12 provides an overview of the planned vital signs analyses.

Table 12 Overview of Planned Vital Signs Analyses

Parameter	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	I	T	F	F	I
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				

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- Individual = Represents FI related to any displays of individual subject observed raw data.

8.2.5.2. Panned 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. Separate summaries of pre-dialysis vital signs for subjects who have dialysis in clinic will be provided. Graphical summaries may be provided.

Vital sign change from baseline values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit and for end of treatment by treatment group. Separate summaries of pre-dialysis vital signs change from baseline for subjects who have dialysis in clinic will be provided. Graphical summaries may be provided.

The number and percentage of subjects with on-treatment or post- treatment worst case vital sign results relative to PCI criteria (see Section 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.

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.

8.3. Pharmacokinetic Analyses**8.3.1. Overview of Planned Pharmacokinetic Analyses**

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

Overview of Planned Pharmacokinetic Analyses for GSK1278863, and/or GSK2391220, GSK2531403 and GSK2531401

Table 13 provides an overview of the planned analyses.

Tab e 13 Overview of Planned Pharmacokinetic Analyses

Parameter	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	I	T	F	F	I	T	F	I	T	F	F	I
GSK1278863, GSK2391220, GSK2531403 and GSK2531401														
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														
Average GSK1278863 Dose EP TIR (mg)				y			y							
GSK1278863 Special Parameter ³ Data by Treatment				y			y				y			y
GSK1278863 Special Parameter ³ Data				y							y			

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 - Summary = Represents TFI related to any summaries (i.e. descriptive statistics) of the observed raw data.
 - Individual = Represents FI related to any displays of individual subject observed raw data.
1. Mean and median plots will be generated
 2. C_{max}, T_{max}, C_{tau}
 3. C_{tau}/1mg Dose, C_{tau}/avg Dose EP TIR, C_{tau}/ Dose at safety event, C_{max}/1mg Dose, C_{max}/avg Dose EP TIR, C_{max}/ Dose at safety event

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), GSK2531403 (M3), and GSK2531401 (M13)) will be

calculated by standard non-compartmental analysis according to current working practices and using Phoenix.

- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in [Table 14](#) will be determined from the plasma concentration-time data, as data permits.

Table 14 Derived Pharmacokinetic Parameters for GSK1278863, and/or GSK2391220, GSK2531403 and GSK2531401

Parameter	Parameter Description
GSK1278863, GSK2391220, GSK2531403 and GSK2531401	
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 in target Hgb range during the evaluation period (EP) Weeks 28-52 (see Section 10.6.3.1).
Ctau/1mg Dose	Ctau normalized to 1mg dose: Observed Ctau divided by dose administered on the PK day
Ctau/avg Dose EP TIR	Ctau normalized to average dose during EP TIR: Observed Ctau divided by the average daily GSK1278863 dose when the subject is in target Hgb range during Weeks 28-52 (see Section 10.6.3.1)
Ctau/Dose at safety event	Ctau normalized to dose at MACE, combined safety endpoint, or end of treatment if no endpoint: Observed Ctau divided by dose patient is taking during MACE, combined safety endpoint or end of treatment if no safety endpoint.
Cmax/1mg Dose	Cmax normalized to 1mg dose: Observed Cmax divided by dose administered on the PK day
Cmax/avg Dose EP TIR	Cmax normalized to average dose during EP TIR: Observed Cmax divided by the average daily GSK1278863 dose when the subject is in target Hgb range during Weeks 28-52 (see Section 10.6.3.1)
Cmax/Dose at safety event	Cmax normalized to dose at MACE, combined safety endpoint, or end of treatment if no endpoint: Observed Cmax divided by dose patient is taking during MACE, combined safety endpoint or end of treatment if no safety endpoint.

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-normalized to the dose administered during the PK collection period. Any changes to the proposed analyses would be described in the CSR.

Tab e 15 Overview of Planned Pharmacokinetic / Pharmacodynamic Analyses for GSK1278863

Parameter	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	I	T	F	F	I	T	F	I	T	F	F	I
GSK1278863														
Scatter plot of % Time in Range during EP vs. Avg GSK1278863 Dose during EP TIR						y								
Scatter plot of Change from Baseline Hgb during EP vs. Avg GSK1278863 Dose during EP TIR						y								
Scatter plot of % Time in Range during EP vs. GSK1278863 Ctau/1mg Dose						y								
Scatter plot of % Time in Range during EP vs. GSK1278863 Ctau/Avg Dose during EP TIR						y								
Scatter plot of Change from Baseline Hgb during EP vs. GSK1278863 Ctau/1mg Dose						y								
Scatter plot of Change from Baseline Hgb during EP vs. GSK1278863 Ctau/Average Dose during EP TIR						y								
Boxplot of Ctau/1mg Dose by Subjects with or without Safety Endpoint						y								
Boxplot of Ctau/Dose at Safety Event by Subjects with or without Safety Endpoint						y								
Scatter plot of % Time in Range during EP vs. GSK1278863 Cmax/1mg						y								

Parameter	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	I	T	F	F	I	T	F	I	T	F	F	I
Dose														
Scatter plot of % Time in Range during EP vs. GSK1278863 Cmax/Avg Dose during EP TIR						y								
Scatter plot of Change from Baseline Hgb during EP vs. GSK1278863 Cmax/1mg Dose						y								
Scatter plot of Change from Baseline Hgb during EP vs. GSK1278863 Cmax/Avg Dose during EP TIR						y								
Boxplot of Cmax/1mg Dose by Subjects with or without Safety Endpoint						y								
Boxplot of Cmax/Dose at Safety Event by Subjects with or without Safety Endpoint						y								

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- Individual = Represents FI 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](#).

8.5.1. Overview of Planned Patient Reported Outcomes Analyses

Table 16 provides an overview of the planned patient reported outcomes analyses.

Table 16 Overview of Planned Patient Reported Outcomes Analyses

Endpoint	Analysis Population	Absolute								Change from Baseline							
		Stats Analysis			Summary		Individual			Stats Analysis			Summary		Individual		
		T	F	I	T	F	F	I		T	F	I	T	F	F	I	
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 overall scores	ITT				y					y	y		y				
CKD-AQ item scores	ITT				y								y				

NOTES :

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- Summary = Represents TFI related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FI 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)	
<ul style="list-style-type: none"> 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)	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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. Stacked bar graphs displaying mean baseline and at visit values 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. Stacked 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 ISMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - rhEPO) and a one-sided superiority p-value for this test at Weeks 8, 12, 28, and 	

Patient Reported Outcomes Statistical Analyses: HRQoL and Utility Score
52 for the SF-36 component scores and domains, and at Week 52 for the EQ-5D-5l and EQ VAS.
Model Results Interpretation
<ul style="list-style-type: none"> 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.

8.5.2.2. Symptom Severity & Change

Patient Reported Outcomes Statistical Analyses: Symptom Severity & Change
Secondary Endpoint(s)
<ul style="list-style-type: none"> 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
Exploratory Endpoint(s)
<ul style="list-style-type: none"> Change from baseline at Weeks 8, 12, 28, 52 by item on the CKD-AQ 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
<ul style="list-style-type: none"> Scoring for the PGI-S and PGI-C parameters is outlined in Section 10.6.5. The mean change from baseline in PGI-S score, CKD-AQ domain, and CKD-AQ overall symptom score will be analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in means between arms. The models will be fitted to data collected after baseline up to Week 52. The model will include factors for treatment, time, prognostic randomization stratification factors, 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
<ul style="list-style-type: none"> PGI-S scores, CKD-AQ domain, CKD-AQ overall symptom, and CKD-AQ 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, CKD-AQ overall symptom, and CKD-AQ item score values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. Stacked bar graphs displaying mean baseline and at visit values for the Week 8, 12, 28, and 52 visits for the CKD-AQ domain and overall symptom scores will be provided by treatment group. For the MMRM analyses of change from baseline in PGI-S, CKD-AQ domain, and CKD-AQ overall symptom score, an ISMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - rhEPO) and a one-sided superiority p-value for this test at Weeks 8, 12, 28, and 52. Additionally, shift tables by treatment group will be generated that display the number and percentage of subjects in each PGI-S category at baseline and the resulting PGI-S category at

Patient Reported Outcomes Statistical Analyses: Symptom Severity & Change
<p>each scheduled visit.</p> <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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

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10. APPENDICES

Section	Appendix
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Section 10.13	Appendix 13 : Abbreviations & Trade Marks

10.1. Append x 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/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 Hgb value ¹ outside of Randomization (Day 1) Hgb entry criteria range
02	less than 5 out of 7 scheduled evaluable ² Hgb values ¹ from the EP
03	Non-compliance with 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 :: 100 ng/ml on two consecutive visits or TSAT :: 20% on two consecutive visits
05	Subject received prohibited medication ³ for more than two weeks during EP

NOTES:

1. Based on central laboratory Hgb values. If central laboratory Hgb value is missing, a non-missing HemoCue Hgb value will be used.
2. See Section [10.6.3](#).
3. Prohibited medications include strong inhibitors of CYP2C8 (e.g., gemfibrozil) and strong inducers of CYP2C8 (e.g., rifampin/rifampicin).

10.2. Append x 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 \pm 1 week, except Weeks 2 and 4 which are \pm 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 \pm 1 week, except Weeks 2 and 4 which are \pm 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		
KtV _{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 taken 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.,

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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 8. 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 \pm 2 weeks)	Unscheduled	Follow-up (4 weeks post-study termination \pm 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, Transfusion and PRO Data

Treatment Phase	Definition
Pre-Treatment	Date \leq Treatment Start Date
On-Treatment	Treatment Start Date < Date \leq Treatment Stop Date + 1 day
Post-Treatment	Date > Treatment Stop Date + 1 day

NOTES:

If the treatment stop date is missing and the treatment start date is non-missing, 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 \leq Date \leq last Non-Zero Dose Date + 28 days
Post-Treatment	Date > last Non-Zero Dose Date + 28 days

NOTES:

- If the treatment stop date is missing and the treatment start date is non-missing, 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, L p d Parameters, Clinical Chemistry, Hematology, Other Laboratory Tests, Hepatobiliary (Liver) and Vital Signs Data

Treatment State	Definition
Pre-Treatment	Date \leq Treatment Start Date
On-Treatment	Treatment Start Date < Date \leq last Non-Zero Dose Date + 1 day
Post-Treatment	Date > last Non-Zero Dose Date + 1 day

NOTES:

- If the treatment stop date is missing and the treatment start date is non-missing, 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.

Treatment State	Definition
Pre-Treatment	<ul style="list-style-type: none"> 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
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
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
Onset /Worsening Time Since 1 st 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 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 treatment stop 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

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.

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
(a)	x—x	Randomized Treatment Start Date		Last Non-zero Dose Date + 1 Day	Last Non-zero Dose Date + 2 Days	y	N	N
(b)	x—		—x			y	y	N
(c)	x—		—			y	y	y
(d)			x—x			N	y	N
(e)			x—			N	y	y
(f)						N	N	y
(g)	?—x					y	N	N
(h)	?—		—x			y*	y	N
(i)	?—		—			y*	y*	y
(j)	x—		—			y	y**	y**
(k)			x—			N	y	y**
(l)						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:

- Order represents treatments being presented in TFI, 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	Day 1
Monthly IV iron ¹		X	Day 1
Iron parameters		X	Day 1
Safety			
Subjects who have in-clinic HD: pre-dialysis BP parameters, HR and weight		X	Day 1
Subjects who have in-clinic HD: post-dialysis BP parameters, HR, weight, and dry weight ²	X		Week -2
Subjects who do not have in-clinic HD: BP parameters, HR, weight, and dry weight		X	Day 1
lipid parameters, clinical		X	Day 1

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening Week - 2	Day 1 (Pre-Dose)	
chemistry, hematology, other laboratory and hepatobiliary (liver) tests			
PRO			
SF-36 domain and component scores		X	Day 1
EQ-5D-5l & VAS		X	Day 1
PGI-S		X	Day 1
CKD-AQ		X	Day 1

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 4 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-Dose 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 the log-transformed data
4. Exponentiate the mean, (if required, the mean - SE, the mean + SE) and the endpoints of the confidence interval, back to the original scale and then subtract 1, then multiply everything by 100% in order to express the geometric mean, (the geometric mean - SE, the geometric mean + SE) and the confidence interval (CI) as the percent change from baseline.

So, geometric mean for percent change from baseline =

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

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

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

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

So, minimum percent change from baseline =

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

Where i = subject.

Unless otherwise specified, the baseline definitions specified in Section 10.5.2 will be used for derivations for endpoints/parameters and indicated on summaries and listings. Unless otherwise specified, if baseline data is missing, no derivation will be performed and the % change from baseline value will be set to missing. The baseline definition will be footnoted on all change from baseline displays.

10.5.3. Reporting Process & Standards

Reporting Process
Software
<ul style="list-style-type: none"> The currently supported versions of SAS software, Version 9.2 (or higher) will be used for all analyses unless otherwise specified. Additionally, R Version 3.1.0 or higher may be used for analysis and the production of graphics.
Analysis Datasets
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Rich text format (RTF) files will be generated.









Reporting Standards
General
<ul style="list-style-type: none"> The current GSK Integrated Data Standards library (IDSI) will be applied for reporting, unless otherwise stated: <ul style="list-style-type: none"> 4.03 to 4.23: General Principles 5.01 to 5.08: Principles Related to Data listings 6.01 to 6.11: Principles Related to Summary Tables 7.01 to 7.13: Principles Related to Graphics
Formats
<ul style="list-style-type: none"> GSK IDSI 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 IDSI statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
<ul style="list-style-type: none"> Reporting for tables, figures and formal statistical analyses : <ul style="list-style-type: none"> 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. Reporting for Data listings: <ul style="list-style-type: none"> Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSI Statistical Principle 5.05.1). Unscheduled or unplanned readings will be presented within the subject's listings.

Reporting Standards	
<ul style="list-style-type: none"> Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings 	
Unscheduled Visits	
<ul style="list-style-type: none"> Unscheduled visits will not be included in summary tables, with the following exceptions: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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. 	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSI Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
<ul style="list-style-type: none"> Refer to IDSI Statistical Principals 7.01 to 7.13. 	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> • Date subject was randomized
Treatment Start Date
<ul style="list-style-type: none"> • First randomized treatment start date
Last Non-Zero Dose Date
<ul style="list-style-type: none"> • Date of last actual dose of randomized study treatment from IP Discontinuation eCRF form. <ul style="list-style-type: none"> ○ 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 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 the following conventions will be applied in order to impute a last non-zero dose date: <ul style="list-style-type: none"> ○ Missing day: <ul style="list-style-type: none"> ■ 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; <ul style="list-style-type: none"> ■ '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: <ul style="list-style-type: none"> ■ Treatment stop date will be used only for subjects who have a non-missing treatment start date.

Treatment Stop Date
<ul style="list-style-type: none"> Calculated as the latest randomized treatment dose stop 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: <ul style="list-style-type: none"> Missing day: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> '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: <ul style="list-style-type: none"> The study completion or withdrawal date will be used only for subjects who have a non-missing treatment start date.
End of Treatment Value
<ul style="list-style-type: none"> 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, or if the treatment stop date is missing, the study completion date for subjects who have a non-missing treatment start date. Blood pressure, central laboratory, and vital signs parameters: the latest value on or before the last non-zero dose date + 1 day, or if the last non-zero dose date is missing, the study completion date for subjects who have a non-missing treatment start date.
Study Completion/Withdrawal Date
<ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> Note: Subjects who die while on study are considered as having completed the study
Study Day
<ul style="list-style-type: none"> Calculated as the number of days from randomization date : <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Calculated as the number of days from treatment start date: <ul style="list-style-type: none"> 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

First Study Contact Date
<ul style="list-style-type: none"> First study contact with the subject while on the study
Last Study Contact Date
<ul style="list-style-type: none"> last study contact with subject (clinic, telephone, or other contact with subject) with the subject while on the study
Time Definitions (per GSK standard principles)
<ul style="list-style-type: none"> 1 week = 7 days 1 month = 30.4375 days 1 year = 365.25 days
Production of Two-Sided p-values
<ul style="list-style-type: none"> The majority of the efficacy and safety analyses in this study will use one-sided 2.5% p-values assess statistical significance. Should two-sided p-values be required for publication purposes after the study is complete, the corresponding two-sided p-values will be produced at that time.

10.6.2. Study Population

10.6.2.1. Demographics

Demographics
Age
<ul style="list-style-type: none"> GSK standard IDSI algorithms will be used for calculating age where birth date will be imputed as follows: <ul style="list-style-type: none"> 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'. Birth date will be presented in listings as 'yyyy'.
Body Mass Index (BMI)
<ul style="list-style-type: none"> Calculated as $\text{Weight (kg)} / [\text{Height (m)}]^2$
Race Groups
<ul style="list-style-type: none"> Geographic ancestry data will be combined into categories as provided by the United States (US) Food and Drug Administration (FDA) and summarized as FDA race group: <ul style="list-style-type: none"> American Indian or Alaskan Native Asian (Asian-East Asian Heritage, Asian-Japanese Heritage, Asian-Central/South Asian Heritage, Asian-South East Asian Heritage, Asian-Mixed Race) Black (African American/African Heritage) Native Hawaiian or Other Pacific Islander White (White-Arabic/North African Heritage, White-White/Caucasian/European Heritage, White - Mixed Race) Mixed Race (Multiple races are selected, but excludes Asian - Mixed Race and White - Mixed Race) <p>Note: Asian - Mixed Race includes subjects who have more than one Asian category selected, but no other categories. White - Mixed Race includes subjects who have more than one White category selected, but no other categories.</p>

10.6.2.2. Randomized Treatment Discontinuation and Study Withdrawal

Randomized Treatment Discontinuation and Study Withdrawal
Randomized Treatment Discontinuation
<ul style="list-style-type: none"> Randomized Treatment Discontinuation Censored Time (days) = Treatment stop date - Randomization date +1 <p>Note: In the case where a subject on randomized treatment is lost to follow-up, a final treatment stop date is presumed, though unobserved. In this case, the last point of contact of the patient is used for both the treatment stop date and withdrawal date.</p> <p>In the case where a subject on randomized treatment dies and has a missing treatment stop date, the date of death or imputed date of death (see Section 10.6.4) will be used for the treatment stop date.</p>
<ul style="list-style-type: none"> Time to Randomized Treatment Discontinuation (days) = Treatment stop date - Randomization date +1
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Randomized Treatment Discontinuation Incidence Rate (per 100 person years) = $100 * \text{Number of subjects who discontinued randomized treatment} / \text{randomized treatment person years}$
Study Withdrawal
<ul style="list-style-type: none"> Study Censored Time (days) = Study completion date - Randomization date +1
<ul style="list-style-type: none"> Time to Study Withdrawal (days) = Study withdrawal date - Randomization date +1
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Study Withdrawal Incidence Rate (per 100 person years) = $(100 * \text{Number of subjects who have withdrawn from study}) / 365.25$

10.6.2.3. Prior and Concomitant Medications

Prior and Concomitant Medications
Non-randomized ESA use during treatment period
<ul style="list-style-type: none"> Subjects will be considered to have non-randomized ESA use during the treatment period if they have any ESA concomitant medication records where the reason for medication = "Additional non-randomized treatment during treatment period"
Duration of non-randomized ESA use during treatment period
<ul style="list-style-type: none"> If there is only one ESA concomitant medication record where the reason for medication = "Additional non-randomized treatment during treatment period", then: <ul style="list-style-type: none"> Duration (days) = concomitant medication record end date - concomitant medication start date + 1 day If there are multiple ESA concomitant medication records where the reason for medication = "Additional non-randomized treatment during treatment period", then the duration of non-

Prior and Concomitant Medications

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 \geq 80% and \leq 120%	Compliance for the exposure record > 120%

Where compliance for the exposure record is calculated as 100% *

$$[\# \text{ dispensed} - (\# \text{ returned} + \# \text{ lost})] / \# \text{ tablets per day} / (\text{dose stop date} - \text{dose start date} + 1)$$

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

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

Exposure and Compliance

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

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

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

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

- 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 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
<ul style="list-style-type: none"> When source of Hgb measurement is not specified: <ul style="list-style-type: none"> 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. Multiple HemoCue Hgb values at a single visit: <ul style="list-style-type: none"> The dose adjustment algorithm will require sites to obtain two HemoCue Hgb values at some visits. In the case where two HemoCue Hgb values are obtained at a visit, the average of the two measurements should be used as the HemoCue Hgb value for that visit.
Evaluable Hemoglobin Values
<ul style="list-style-type: none"> 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.
Evaluation Period (EP) Hemoglobin Value for Primary Hgb Analysis
<ul style="list-style-type: none"> For each subject, the mean of all available (on and off treatment) Hgb values between Weeks 28 and 52, inclusive, including any unscheduled Hgb values that were taken during this time period.
Evaluation Period (EP) Hemoglobin Value for On-drug Hgb Supplementary Analysis
<ul style="list-style-type: none"> For each subject, the mean of all evaluable Hgb values between Weeks 28 and 52, inclusive, including any unscheduled Hgb values that were taken during this time period.
Evaluation Period (EP) Hemoglobin Value for Alternative EP Sensitivity & Supplementary Analysis
<ul style="list-style-type: none"> For each subject, the mean of all Hgb values between Weeks 28 and 36, inclusive, including any 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.

Time In Range
Time in Range During the EP
<ul style="list-style-type: none"> Number of days that a subject's evaluable Hgb is within the analysis range of 10-11.5 g/dl inclusive between Weeks 28 and 52 inclusive, including any unscheduled evaluable Hgb values that were taken during this time period. linear interpolation is used to estimate Hgb between visits, accounting for any intermittent missing values (Rosendaal, 1993).
Percent Time in Range During the EP
<ul style="list-style-type: none"> Time in Range During the EP / [Earlier of (Treatment Stop Date, Week 52 visit date) - Week 28 visit date + 1]

Time In Range

- Note: Percent time in range during the EP is only defined for subjects with a Treatment Stop Date that is after their Week 28 visit date. For subjects who have Week 28 visit date < Treatment Stop date, yet have no evaluable Hgb values during the EP, their percent time in range will be 0.

10.6.3.2. Iron Endpoints**Iron Endpoints****IV iron medications**

- During the study, subjects may be receiving IV iron in multiple ways, including: Iron saccharate, iron sucrose (Venofer), iron dextran low molecular weight, ferric carboxymaltose (Ferinject), Ferumoxytol (Feraheme), Iron pyrophosphate (Triferic), Sodium ferric gluconate (Ferrlecit).

Baseline average monthly IV iron

- 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 the Screening Week -2 visit to the day before the Randomization date.
- IV iron therapy concomitant medication records that occur or are ongoing during the period from the subject's Screening Week -2 visit date to the Randomization date will be selected and ordered by start and end date.
- The standardization will be carried out with the following formula:
 - Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency

Note: Frequency and Gap Factors defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)	Gap Factor
2 times per week	2	2.5 days
3 times per week	3	1.33 days
4 times per week	4	0.75 day
5 times per week	5	0.4 day
BID	14	0 days
Once daily	7	0 days
One time dose	see below	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.

Iron Endpoints

- If the concomitant medication record end date + gap factor < Screening Week -2 visit date, the duration of the record is 0.
- If the concomitant medication record end date + gap factor \geq Screening Week -2 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 Screening Week -2 visit date).
 - 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 Randomization date \geq concomitant medication record start date, then duration of the record is 0.
 - If Screening Week -2 visit date \geq concomitant medication record start date < Randomization date, then:
 - Frequency (for standardization formula) = 1
 - Duration = 7 days
 - If concomitant medication record start date < Screening Week -2 visit date, then:
 - Frequency (for standardization formula) = $7 / [\text{earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before randomization)} - \text{start date of record} + 1 \text{ day}]$.
 - If the earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before randomization) < Screening Week -2 visit date, the duration of the record is 0.
 - If the earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before randomization) \geq Screening Week -2 visit date, the duration of the record is calculated as Stop Date - Start Date + 1, where:
 - Start date will be the Screening Week -2 visit date.
 - Stop date will be the earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before randomization)
 - The total dose for each IV iron record will be: Standardized dose * duration / 7 days
 - A weighted mean will then be used to obtain the baseline monthly IV iron dose:
 - Mean baseline monthly IV iron dose = $[(\text{IV iron total dose}_{\text{Record 1}}) + \dots + (\text{IV iron total dose}_{\text{Record n}})] / [(\text{Randomization Date} - \text{Screening Week -2 Visit Date}) / 30.4375 \text{ days}]$.

Average monthly IV iron 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 day before the Week 52 visit while the subject is on treatment.
 - Note: Subjects who are randomized but never treated will not have a value for average monthly IV iron from Randomization to Week 52.
- IV iron therapy concomitant medication records that occur or are ongoing during the period

Iron Endpoints

from the subject's Screening Week -2 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	see below	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 \diamond earliest of (treatment stop date 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 \diamond Randomization date or the record is ongoing, the duration of the record will be calculated as Stop Date - Start Date +1 day where:
 - Start date will be the latest of (concomitant medication record start date, randomization date, treatment start date).
 - Stop date will be the earliest of (concomitant medication record stop date + gap factor, treatment stop date, and the day before the Week 52 visit).
- If the frequency of the record is 'one time dose', then:
 - If earliest of (treatment stop date and Week 52 visit date) :: concomitant medication record start date, then duration of the record is 0.
 - If latest of (Randomization date, treatment start date) :: concomitant medication record start date < earliest of (treatment stop date and Week 52 visit date), then:
 - Frequency (for standardization formula) = 1
 - Duration = 7 days
 - If concomitant medication record start date < treatment start date, then:
 - Frequency (for standardization formula)=7/[earliest of (the day before the next

Iron Endpoints

- sequential IV iron concomitant medication record start date and the day before the Week 52 visit date) – start date of record + 1 day].
- If the earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before the Week 52 visit date) < treatment start date, the duration of the record is 0.
 - If the earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before the Week 52 visit date) \geq treatment start date, the duration of the record is calculated as Stop Date – Start Date + 1, where:
 - Start date will be the treatment start date.
 - Stop date will be the earliest of (the day before the next sequential IV iron concomitant medication record start date, treatment stop date, and the day before the Week 52 visit date)
- 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 =
$$[(\text{IV iron total dose}_{\text{Record 1}}) + \dots + (\text{IV iron total dose}_{\text{Record n}})] / \{[\text{earliest of (treatment stop date, Week 52 Visit Date)} - \text{treatment start date}] / 30.4375 \text{ days}\}.$$

Average monthly IV iron from Week 28 to Week 52 (EP average monthly IV iron)

- 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 day before the Week 52 visit while the subject is on treatment.
 - Note: Subjects who are randomized but never treated 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	see below	n/a
Every 12 Hours	14	0 days

Iron Endpoints

Frequency (from eCRF)	Frequency (for standardization formula)	Gap Factor
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 \diamond earliest of (treatment stop date 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 \diamond Week 28 visit date or the record is ongoing, the duration of the record will be calculated as Stop Date - Start Date + 1 day where:
 - Start date will be the latest of (concomitant medication record start date, and the Week 28 visit date).
 - Stop date will be the earliest of (concomitant medication record stop date + gap factor, treatment stop date, and the day before the Week 52 visit).
- If the frequency of the record is 'one time dose', then:
 - If earliest of (treatment stop date and Week 52 visit date) :: concomitant medication record start date, then duration of the record is 0.
 - If Week 28 visit date :: concomitant medication record start date < earliest of (treatment stop date and Week 52 visit date), then:
 - Frequency (for standardization formula) = 1
 - Duration = 7 days
 - If concomitant medication record start date < Week 28 visit date, then:
 - Frequency (for standardization formula) = $7 / [\text{earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before the Week 52 visit date)} - \text{start date of record} + 1 \text{ day}]$.
 - If the earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before the Week 52 visit date) < Week 28 visit date, the duration of the record is 0.
 - If the earliest of (the day before the next sequential IV iron concomitant medication record start date and the day before the Week 52 visit date) \diamond Week 28 visit date, the duration of the record is calculated as Stop Date - Start Date + 1, where:
 - Start date will be the Week 28 visit date.
 - Stop date will be the earliest of (the day before the next sequential IV iron concomitant medication record start date, treatment stop date, and the day before the Week 52 visit date)
- 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

Iron Endpoints
<p>52:</p> <p>Mean monthly IV iron dose from Week 28 to Week 52 while on treatment = $[(\text{IV iron total dose}_{\text{Record 1}}) + \dots + (\text{IV iron total dose}_{\text{Record n}})] / \{[\text{earliest of (treatment stop date, Week 52 Visit Date)} - \text{Week 28 Visit Date}]/30.4375 \text{ days}\}.$</p>
TIBC
<ul style="list-style-type: none"> TIBC will be calculated automatically by the central laboratory using: <ul style="list-style-type: none"> TIBC = UIBC + total iron
TSAT
<ul style="list-style-type: none"> TSAT will be calculated automatically by the central laboratory using: <ul style="list-style-type: none"> TSAT = $100 * (\text{Serum Iron}/\text{TIBC})$
Average quarterly IV iron dose/subject
<ul style="list-style-type: none"> The average monthly IV iron dose/subject will be summarized by quarters, where quarters will be defined using study visits as follows: <ul style="list-style-type: none"> Quarter 1 = [Day 1 - Week 12) <ul style="list-style-type: none"> Follow derivation for average monthly IV iron from Randomization to Week 52, replacing Week 52 with Week 12. Quarter 2 = [Week 12 - Week 24) <ul style="list-style-type: none"> Follow derivation for average monthly IV iron from Week 28 to Week 52, replacing Week 28 with Week 12 and Week 28 with Week 24. Quarter 3 = [Week 24 - Week 36) <ul style="list-style-type: none"> Follow derivation for average monthly IV iron from Week 28 to Week 52, replacing Week 28 with Week 24 and Week 28 with Week 36. Etc.
Meeting Iron Management Criteria
<p>Iron therapy will be administered if at any visit:</p> <ul style="list-style-type: none"> Ferritin :: 100 ng/ml and/or TSAT :: 20% <p>All iron must be stopped if at any visit:</p> <ul style="list-style-type: none"> Ferritin > 800 ng/ml and TSAT >20%, or TSAT > 40%

10.6.3.3. Time to Rescue

Time to Stopping Randomized Treatment Due to Meeting Rescue Criteria
Event Date
<ul style="list-style-type: none"> Treatment stop date when the primary reason and subreason for randomized treatment stop are: <ul style="list-style-type: none"> Primary reason: Subject reached protocol-defined stopping criteria Subreason: Rescue
General Definitions
<ul style="list-style-type: none"> Time to event (days) = date of event - randomization date +1 Censored time (days) = censoring date - randomization date + 1

Time to Stopping Randomized Treatment Due to Meeting Rescue Criteria
<ul style="list-style-type: none"> Rescue person years = (cumulative total time to stopping randomized treatment for subjects who stopped randomized treatment due to meeting rescue criteria + cumulative total of censoring time for subjects who did not stop randomized treatment due to meeting rescue criteria) / 365.25 Rescue incidence rate (per 100 person years) = (100 * number of subjects who stopped randomized treatment due to meeting rescue criteria) / rescue person years Rescue absolute rate difference (per 100 person years) = daprodustat rescue incidence rate (per 100 person years) - rhEPO rescue incidence rate (per 100 person years)
Time Period for Treatment Discontinuation
<p>The period for treatment discontinuation begins at randomization. The end of this time period is defined as follows:</p> <ul style="list-style-type: none"> 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 <p>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.</p>

10.6.3.4. Transfusion Endpoints

Transfusion Endpoints
General
<ul style="list-style-type: none"> Time to event (days) = date of event - randomization date + 1 Censored time (days) = censoring date - randomization date + 1
<ul style="list-style-type: none"> Transfusion person years = (cumulative total of censoring time for all subjects) / 365.25 Transfusion incidence rate (per 100 person years) = (100 * number of transfusions) / transfusion person years Blood products unit incidence rate (per 100 person years) = (100 * number of units) / transfusion person years
Time Period for Transfusions
<ul style="list-style-type: none"> Transfusions will be evaluated during the Time Period for Treatment Discontinuation (see Section 10.6.3).

10.6.3.5. Dose Adjustment Scheme Endpoints

Dose Adjustment Scheme Endpoints
General
<ul style="list-style-type: none"> 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

Dose Adjustment Scheme Endpoints

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

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 based on new IRT instruction received at that visit. 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.
 - oFor 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.

Dose Adjustment Scheme Endpoints
Most Recent Dose Prior to A Scheduled Visit / End of Treatment
<ul style="list-style-type: none"> The most recent dose prior to a particular visit refers to the dose the subject received in the period directly preceding the visit. The most recent dose prior to Visit X is the dose from the latest exposure record with a start date that is on or after the Visit X-1 date and before the Visit X date. <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Death: event date reported by CEC Myocardial infarction: event date reported by CEC <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> Fatal heart failure/cardiogenic shock events only identified through a primary

CV Safety Endpoints

cause of death, without a corresponding heart failure event: death event date reported by CEC

- Thromboembolic event (DVT, PE, VAT): event date reported by CEC
 - Fatal PE events only identified through a primary cause of death, without a corresponding positively adjudicated PE event: death event date reported by CEC

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

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

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

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

CV Safety Endpoints


mortality, the death date will be used.

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

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

Missing or Partial Endpoint Dates

- 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

CV Safety Endpoints
<p>last known to be alive then impute the missing day of death as equal to this date instead. For example:</p> <ul style="list-style-type: none"> ■ 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. <p>○ 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:</p> <ul style="list-style-type: none"> ■ If ----- is given as the death date and the latest date is a non-fatal MI on 08FEB2016 then the imputed date of death would be 08FEB2016 rather than 01JAN2016 such that the death is not before the non-fatal MI. ■ If ----- 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. <p>○ For deaths that occur after subjects have prematurely withdrawn from the study, missing or partial dates will be imputed as specified above except if the imputation places the death prior to or on the premature withdrawal date. In this case the death date will be imputed as the premature withdrawal date + 1 day.</p>
Order of CV Safety Endpoint Events
<ul style="list-style-type: none"> • 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: <ol style="list-style-type: none"> 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
<ul style="list-style-type: none"> • 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.
Investigator-reported Endpoint Events for Concordance
<ul style="list-style-type: none"> • For purposes of concordance tables, events with an investigator-reported event date  randomization date that meet the following final diagnosis criteria will be considered to be investigator-reported endpoint events:

CV Safety Endpoints	
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	<p>Systolic heart failure, Diastolic heart failure, Heart failure - unspecified type</p> <p>Additional criteria: <i>If missing/ schedule times are missing, test the following must be true 1-3):</i> 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 <i>Or missing/ schedule times are missing, then test the following must be true 4-6):</i> 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</p>
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
Undetermined (sub-category of All-cause mortality)	Any Undetermined primary cause of death
All-cause Hospitalization	
<ul style="list-style-type: none"> All-cause hospitalization events are defined to be hospital admissions recorded on the Hospitalization eCRF form with a hospitalization duration ≥ 24 hours. Hospitalization rate (per year) across the study = number of all-cause hospitalization events / [follow-up time (days) / 365.25]. 	
General Definitions	
<ul style="list-style-type: none"> Time to event (days) = date of event - randomization date + 1 Censored time (days) = censoring date - randomization date + 1 	
<ul style="list-style-type: none"> 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 	

CV Safety Endpoints

- First event absolute rate difference (per 100 person years) = daprodustat incidence rate (per 100 person years) - rhEPO incidence rate (per 100 person years)

10.6.4.2. Blood Pressure Endpoints

Blood Pressure Endpoints
Pre- and Post- Dialysis BP
<ul style="list-style-type: none"> For subjects undergoing dialysis in-clinic, both pre- and post- dialysis BP values will be measured. Unless otherwise specified, for summaries and analyses of BP values, the post-dialysis BP values for subjects undergoing dialysis in-clinic will be used.
End of Treatment BP Value
<ul style="list-style-type: none"> See Section 10.6.1.
Mean Arterial Pressure (MAP)
<ul style="list-style-type: none"> $MAP = [(2 \times DBP) + SBP] / 3$
Blood Pressure Exacerbations
<ul style="list-style-type: none"> BP exacerbations will be defined as follows: <ul style="list-style-type: none"> SBP: ≥ 25 mmHg increase from baseline or a SBP ≥ 180 mmHg DBP: ≥ 15 mmHg increase from baseline or a DBP ≥ 110 mmHg <p>Notes:</p> <ul style="list-style-type: none"> 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.
Blood Pressure Exacerbation Event Date
<ul style="list-style-type: none"> Date of BP exacerbation
On-Treatment BP Medication
<ul style="list-style-type: none"> See Section 10.4.1 for treatment states for concomitant medications.
General
<ul style="list-style-type: none"> Time to event (days) = date of event - randomization date + 1 Censored time (days) = censoring date - randomization date + 1
<ul style="list-style-type: none"> BP exacerbation person years = (cumulative total of censoring time for all subjects) / 365.25 BP exacerbation event incidence rate (per 100 person years) = (100 * number of BP exacerbations) / BP exacerbation person years
Time Period for Blood Pressure Exacerbations
<p>The time period for capturing BP exacerbations begins at the treatment start date. The end of this time period is defined as follows:</p> <ul style="list-style-type: none"> For subjects whose last randomized treatment stop date is missing and who took

Blood Pressure Endpoints
<p>randomized treatment, use date of study withdrawal/completion</p> <ul style="list-style-type: none"> For subjects continuing on study past the last non-zero dose date + 1 day, use (last non-zero dose date + 1 day) For subjects whose study withdrawal/completion date is on or before (last non-zero dose date + 1), use date of study withdrawal/completion <p>Any events that occurred before the start of this time period are considered to be prior to the time period for BP exacerbations, and any events that occurred after the end of this time period are considered to be post the time period for BP exacerbations.</p>
Changes in Blood Pressure Medications
<ul style="list-style-type: none"> No change: no new anti-hypertensive records since Day 1 and no change to anti-hypertensive records since Day 1. Increase: addition of new anti-hypertensive records without a change or a change with a reason of 'increased due to.' Decrease: discontinuation of an anti-hypertensive record without a change or a change with a reason of 'Decreased due to.' Switch = change with a reason of 'switched to another agent...'

10.6.4.3. Adverse Events

Adverse Events
AEs of Special Interest
<p>Adverse events of special interest are classified as follows:</p> <ul style="list-style-type: none"> 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
<p>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:</p> <ul style="list-style-type: none"> Any Hgb value \geq 13 g/dl (measured pre-dialysis) Hgb increase > 2 g/dl over 2 weeks Hgb increase > 4 g/dl over 4 weeks <p>Note: Scheduled central laboratory Hgb values will be used, unless a scheduled central laboratory Hgb value is missing, in which case, a corresponding non-missing scheduled HemoCue Hgb value will be used. Unscheduled Hgb values will also be used in the assessment of secondary to excessive erythropoiesis as follows:</p>

Adverse Events
<ul style="list-style-type: none"> If an unscheduled central laboratory Hgb value and an unscheduled HemoCue Hgb value are on the same date, only the central laboratory Hgb value will be used. If there is only one unscheduled Hgb value available on an individual date, then that value will be used regardless of the data source (i.e., either central laboratory or HemoCue). <p>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.</p> <p>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 above 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.</p>
Blood Pressure Events
<p>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.</p> <p>In addition, subjects that experience BP values that meet the following criteria at any visit will also be considered to have a BP event and be required to complete the Blood Pressure Exacerbation eCRF page:</p> <ul style="list-style-type: none"> SBP: an increase from baseline of ≥ 25 mmHg or SBP ≥ 180 mmHg DBP: an increase from baseline of ≥ 15 mmHg or DBP ≥ 110 mmHg <p>BP-related SAEs are those SAEs that have been identified via the BP Exacerbation eCRF page.</p>
General Definitions
<ul style="list-style-type: none"> Post-Randomization last contact date for censoring (subjects not having AE) will be defined as the study completion date.
<ul style="list-style-type: none"> Treatment emergent last contact date for censoring (subjects not having AE) will be defined as follows: <ul style="list-style-type: none"> 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) last non-zero dose date for all other subjects
<ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> For treatment emergent AEs, the start date of the patient year value for each subject

Adverse Events
<p>should be the treatment start date.</p> <ul style="list-style-type: none"> ○ For post-randomization AEs, the start date of the patient year value for each subject should be the randomization date. ○ For follow-up AEs, the start date of the patient year value for each subject should be 28 days after the last non-zero dose date (last non-zero dose date + 28). ○ If the AE onset/worsening date is completely missing, then the randomization date will be used for calculations of patient years.
<ul style="list-style-type: none"> • Incidence Rate (per 100 patient years): $(100 * \text{Number of subjects with at least 1 AE}) / \text{AE person years}$
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ Example 1: 2 Significant Digits = '< x' becomes $x - 0.01$ ○ Example 2: 1 Significant Digit = '> x' becomes $x + 0.1$ ○ Example 3: 0 Significant Digits = '< x' becomes $x - 1$
<ul style="list-style-type: none"> • 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' is present, then the corresponding numeric value will be set equal to x.
<ul style="list-style-type: none"> • 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.
<ul style="list-style-type: none"> • The following will be used to convert laboratory values from SI units to conventional units [Iverson, 2007]: <ul style="list-style-type: none"> • Hemoglobin, MCHC and Albumin: Divide the g/l value by 10 to get the g/dl value. • Total calcium and Albumin-adjusted calcium: Divide the mmol/l value by 0.25 to get the mg/dl value. • Inorganic phosphate: Divide the mmol/l value by 0.323 to get the mg/dl value. • Urea: Divide the mmol/l value by 0.357 to get the mg/dl value • Total cholesterol, IDI-C and HDI-C: Divide the mmol/l value by 0.0259 to get the mg/dl value.

Laboratory Parameters
Normal Range Categories, PCI Criteria Categories and Worst Case Values
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ■ 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
<ul style="list-style-type: none"> • 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.

10.6.5. Patient Reported Outcomes

SF-36
General Information & Scoring
<ul style="list-style-type: none"> • 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 QualityMetric's scoring software version 5.0 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 QualityMetric software.

EQ-5D-5L
General
<ul style="list-style-type: none"> 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 dimension 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 full health and 0 is the worst health. 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 country specific value sets for the health states are currently developed by EuroQol Group. Should the country specific value sets not be available for all countries requiring them at the time of final reporting of the study, the crosswalk value sets will be used. If neither a country specific value set, nor a crosswalk value set is available for a country, the United Kingdom (UK) value set will be used.

EQ-VAS
General
<ul style="list-style-type: none"> The EQ-VAS is a self-assessment visual analogue scale, ranging from 0=worst imaginable - 100=best.

PGI-S
General
<ul style="list-style-type: none"> 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 0-4 as follows: <ul style="list-style-type: none"> o Absent = 0 o Mild = 1 o Moderate = 2 o Severe = 3 o Very severe = 4

PGI-C
General
<ul style="list-style-type: none"> 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

PGI-C
General
<p>worse).</p> <ul style="list-style-type: none"> • Scores range from 1 to 7 as follows: <ul style="list-style-type: none"> ○ Very much improved = 1 ○ Moderately improved = 2 ○ Minimally improved = 3 ○ No change = 4 ○ Minimally worse = 5 ○ Moderately worse = 6 ○ Very much worse = 7

CKD-AQ
General
<ul style="list-style-type: none"> • The CKD-AQ is a self-reported anemia of CKD-specific questionnaire designed to capture the frequency and severity of symptoms and relevance concepts of subjects with anemia associated with CKD. It will measure both the frequency and/or severity concepts of: Weakness, Energy, Tiredness, Shortness of Breath, Exertion, Chest Pain, Memory, Concentration, Standing, Sleep and Distress in anemia associated with CKD. • An interim cut of blinded observations from the first 50 subjects who completed the week 28 visit will be taken to establish the scoring algorithm for potential instrument domains and to evaluate the reliability, validity and responsiveness of the instrument without regard to treatment group.

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

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> The eCRF allows for the possibility of partial dates (i.e., only month and year or only year) to be recorded for AE start/worsening and end dates. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:

Element	Reporting Detail
	<ul style="list-style-type: none"> • Imputing a Start/Worsening Date from a Partial Start/Worsening Date: <ul style="list-style-type: none"> ○ If an imputed worsening date is before the start date, then the start date will be used as the imputed worsening date. ○ <u>Completely missing stop date:</u> <ul style="list-style-type: none"> ▶ 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. <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> • 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. ○ <u>Partial or non-missing stop date is before treatment start date:</u> <ul style="list-style-type: none"> ▶ 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. ○ <u>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:</u> <ul style="list-style-type: none"> ▶ 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: <ul style="list-style-type: none"> ○ <u>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:</u> <ul style="list-style-type: none"> ▶ 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

Element	Reporting Detail
	<p>case the treatment stop date will be used at the stop date.</p> <ul style="list-style-type: none"> ▶ 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. o <u>latest of (start date and latest worsening date) is partial or non-missing and is after treatment stop date:</u> <ul style="list-style-type: none"> ▶ 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 (serum)	g/l	< 30 g/l	>55 g/l
Aspartate Aminotransferase (AST)	IU/l		⚡ 3x UIRR
Alanine Aminotransferase (ALT)	IU/l		⚡ 3x UIRR
Bilirubin (total)	μmol/l		⚡ 2x UIRR
Calcium (albumin-adjusted)	mmol/l	< 1.87 mmol/l	> 2.56 mmol/l
Inorganic phosphate	mmol/l	< 0.81 mmol/l	1.77 mmol/l
Potassium (serum)	mmol/l	> 0.5 mmol/l below IIRR	> 1.0 mmol/l above UIRR

Hematology			
Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag	High Flag
Platelet Count	GI/l	< 80 GI/l	> 500 GI/l
WBC Count with Differential	GI/l	< IIRR	> 5x UIRR
Neutrophils	GI/l	< 0.5x IIRR	
Lymphocytes	GI/l	< 0.5x IIRR	

Iron Parameters			
Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag	High Flag
Ferritin	ng/ml	< 100 ng/ml	> 1200 ng/ml
TSAT	%	<15%	> 40%

Other PCI Values			
Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag	High Flag
iPTH	ng/l		> 9x UIRR

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: <ul style="list-style-type: none"> 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
US	USA
EU	France, Germany, Italy, Spain, United Kingdom, Poland, Russia, South Africa
RoW	Australia, Argentina, Brazil, Canada, India, Malaysia, Mexico, South Korea

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

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

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

10.10.1. Handling of Covariates, Subgroups & Other Strata

- The following is a non-exhaustive list of covariates that may be used in summaries of demographics, descriptive summaries and statistical analyses.
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.
- 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 [10.10.2](#)).
- 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
Key Covariates/Subgroups of Regulatory/Clinical Interest or Potential Biological Plausibility for Different Subgroup Effects	
Age at randomization (Grouping 1)	<65 years, 65-<75 years, ≥75 years
Age at randomization (Grouping 2)	18-64 years, 65-84 years, ≥85 years
Gender	Female, Male
Ethnicity	Hispanic, Non-Hispanic
Race group	American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race
Region	US, EU, RoW (repeat using US, Non-US)
Dialysis type at randomization ¹	HD, PD (repeat using HD, HDF/HF, PD)
Dialysis start manner	Planned, unplanned (urgent) start
Dialysis status at randomization	Dialysis not initiated, On dialysis ≤ 90 days
Baseline Hgb	Continuous covariate for Hgb primary analysis; <9 g/dl, 9- <10g/dl, 10-11g/dl, >11 g/dl
Baseline BMI	<30 kg/m ² , ≥30 kg/m ²
Baseline Weight	<75 kg, ≥75 kg
Baseline Weight Quartiles	Quartile 1: xx kg, Quartile 2: xx kg, Quartile 3: xx kg, Quartile 4: xx kg
Baseline hsCRP	≤3 mg/l, >3 mg/l
Required B12 Supplementation to be Eligible for Randomization	No, yes
Other Exploratory Covariates/Subgroups where Biological Plausibility for Heterogeneous Effects Are Not Known or Anticipated	
History of diabetes	No, yes
History of stroke or MI	No, yes
History of cancer	No, yes
History of HF	No, yes
History of thromboembolic events	No, yes
Hospitalization within 6 months prior to screening	No, yes
Transfusion within 6 months prior to screening	No, yes
Additional Covariates/Subgroups Used in Analysis Models	
Baseline IV Iron dose (mg)	Continuous covariate for monthly IV iron dose analysis
Baseline SBP (mmHg)	Continuous covariate for change from baseline in SBP analysis
Baseline DBP (mmHg)	Continuous covariate for change from baseline in DBP analysis
Baseline MAP (mmHg)	Continuous covariate for change from baseline in MAP analysis

NOTES:

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

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 form

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)	<ul style="list-style-type: none">• Hgb Change from Baseline to the EP
Analysis	<ul style="list-style-type: none">• ANCOVA
<ul style="list-style-type: none">• 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.	

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

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SAS
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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
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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.



RAP Author(s):

(Method: E-mail)

Author	Date
Lead [REDACTED]	20-Nov-2020
Statistician (Specialty Biostatistics)	
Co-Authors [REDACTED]	20-Nov-2020
Director Clinical Statistics (Specialty Biostatistics)	
[REDACTED] Statistics Leader (Specialty Biostatistics)	20-Nov-2020
[REDACTED] Principal Statistician (Specialty Biostatistics)	20-Nov-2020
[REDACTED] Director Clinical Pharmacology Modelling and Simulation (Clinical Pharmacology and Experimental Medicine)	20-Nov-2020

RAP Team Reviews:**RAP Team Review Confirmations**

(Method: E-mail)

Reviewer	Date
 Sr. Director Clinical Development Lead (Clinical Sciences Respiratory and Specialty)	20-Nov-2020
 Principal Programmer/Analyst (Specialty Biostatistics)	20-Nov-2020

Clinical Statistics and Clinical Programming Line Approvals:**Clinical Statistics & Clinical Programming Line Approvals**

(Method: Pharma TMF eSignature)



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

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	<ul style="list-style-type: none"> This RAP describes the planned analyses and outputs required for the final Clinical Study Report (CSR) for study 201410
Protocol	<ul style="list-style-type: none"> This RAP is based on the first protocol amendment [(Dated: 06OCT2017) of study 201410 (GSK Document Number. 2015N234534_01)].
Primary Objective	<ul style="list-style-type: none"> To compare daprodustat to darbepoetin alfa for hemoglobin (Hgb) efficacy (non-inferiority)
Primary Endpoint	<ul style="list-style-type: none"> The mean change in Hgb between baseline and the evaluation period (EP, mean over Weeks 28-52)
Study Design	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<p>Principal Secondary Endpoint (adjusted for multiplicity, tested for superiority)</p> <ul style="list-style-type: none"> Average monthly IV iron dose (mg)/subject from baseline to Week 52
Safety Endpoints	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> New displays related to COVID-19 pandemic have been added 	<ul style="list-style-type: none"> Assessing the impact of the COVID-19 pandemic
<ul style="list-style-type: none"> Only include randomized subjects who have both baseline and at least one Hgb assessment during the EP in the primary Hgb analysis 	<ul style="list-style-type: none"> All randomized subjects will be included in the primary Hgb analysis by imputing missing post-baseline Hgb data using pre-specified multiple imputation approach 	<ul style="list-style-type: none"> Addressing the feedback from FDA
<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Worsening of Hypertension has been added to the list of AESI is included in the summary and analysis of AESI 	<ul style="list-style-type: none"> Worsening of Hypertension has been added to the list of AESI based on Safety Review Team update on AESI
<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Number of RBC whole blood and transfusion event is included in the exploratory efficacy analysis of RBC and Whole Blood Transfusions 	<ul style="list-style-type: none"> Number of RBC whole blood and transfusion event has been defined and included in the exploratory endpoints
<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Time to first RBC and whole blood transfusion is included in the exploratory efficacy analysis of RBC and Whole Blood Transfusions 	<ul style="list-style-type: none"> Time to first RBC and whole blood transfusion has been included in the exploratory endpoints
<ul style="list-style-type: none"> PK exploratory endpoints described as dose normalized 	<ul style="list-style-type: none"> PK exploratory endpoints described as dose extrapolated 	<ul style="list-style-type: none"> Terminology clarification following discussion with regulatory agencies.
PK exploratory endpoints include: <ul style="list-style-type: none"> Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. 	PK exploratory endpoints modified as follows: <ul style="list-style-type: none"> <i>Endpoints removed:</i> Scatter plots of daprodustat PK 	<ul style="list-style-type: none"> 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
<p>percent time in range during EP.</p> <ul style="list-style-type: none"> 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 (C_{tau} and C_{max}) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint 	<p>parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP.</p> <ul style="list-style-type: none"> 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. <i>Endpoints removed:</i> Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. change from baseline of Hgb during EP. <i>Endpoints removed:</i> Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint 	<p>what will be available from remaining endpoints.</p>

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

Objectives	Endpoints
Primary Objectives	Primary Endpoints
<ul style="list-style-type: none"> To compare daprodustat to rhEPO for Hgb efficacy (non-inferiority) 	<ul style="list-style-type: none"> 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)
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the use of intravenous (IV) iron 	<ul style="list-style-type: none"> Average monthly IV iron dose (mg)/subject from baseline to Week 52
Secondary Objectives	Secondary Endpoints (tested for superiority ¹ , no multiplicity adjustment)
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on BP 	<ul style="list-style-type: none"> Change from baseline in SBP, DBP, and MAP at Week 52 and at end of treatment

Objectives	Endpoints
	<ul style="list-style-type: none"> Number of BP exacerbation events per 100 patient years N (%) with at least one BP exacerbation event during study
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on Hgb variability 	<ul style="list-style-type: none"> Hgb change from baseline to Week 52¹ 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the time to rescue (defined as permanently stopping randomized treatment due to meeting rescue criteria) 	<ul style="list-style-type: none"> Time to stopping randomized treatment due to meeting rescue criteria
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on HRQoL and Utility score 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the symptom severity and change 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To summarize the PK parameters of daprodustat and three major metabolites in dialysis subjects 	<ul style="list-style-type: none"> Plasma daprodustat, M2, M3, and M13 PK parameters pre-dose trough (C_{tau}) and C_{max}
Exploratory Objectives	Exploratory Endpoints (Statistical testing not planned)
<ul style="list-style-type: none"> To further compare daprodustat and rhEPO on Hgb variability 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on measures of iron parameters 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on the need for RBC and whole blood transfusions 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To evaluate the dose adjustment schemes 	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Day 1 - < Week 28 Week 28 - < Week 52 Day 1 - < Week 52 Number of dose adjustments during the following periods: <ul style="list-style-type: none"> Day 1 - < Week 28 Week 28 - < Week 52 Day 1 - < Week 52 Time dose held for Hgb ≥ 12 g/dL
<ul style="list-style-type: none"> To further compare daprodustat to rhEPO on BP and BP medication changes 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To compare daprodustat to rhEPO on lipid parameters 	<ul style="list-style-type: none"> 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)]
<ul style="list-style-type: none"> To further compare daprodustat to rhEPO on the symptom severity and change 	<ul style="list-style-type: none"> 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.
<ul style="list-style-type: none"> To further compare daprodustat to darbepoetin alfa on HRQoL and Utility score 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To evaluate graphical relationships between exposure parameters and selected efficacy endpoints 	<ul style="list-style-type: none"> Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP.

Objectives	Endpoints
	<ul style="list-style-type: none"> 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.
<ul style="list-style-type: none"> To evaluate graphical relationships between daprodustat exposure and MACE and the composite endpoint of MACE + thromboembolic event + hospitalization for heart failure 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To compare the safety and tolerability of daprodustat to rhEPO 	<ul style="list-style-type: none"> 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	
<p>The flowchart illustrates the study design timeline. It begins with a 'Screening 2 weeks*' box. An arrow leads from screening to a 'Randomization' box. From randomization, two parallel paths emerge: one for 'Daprodustat' and one for 'Darbepoetin alfa'. Both treatment paths lead to a final 'F/up (Week 56-58)' box. Above the treatment paths, two periods are defined: 'Stabilization period Day 1 to Week 28' and 'Evaluation period Week 28 to Week 52'.</p> <p>* Screening period may be extended by an additional 4 weeks for ultrasound examination, IV iron supplementation and/or vitamin B12 treatment as needed.</p>	
Design Features	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> All screened subjects. 	<ul style="list-style-type: none"> Study Population Safety
Intent-To-Treat (ITT)	<ul style="list-style-type: none"> All randomized subjects. Subjects will be analyzed according to the treatment to which they were randomized. 	<ul style="list-style-type: none"> Study Population Efficacy Safety
Enrolled	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Study Population
Per-Protocol (PP)	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Efficacy
Safety	<ul style="list-style-type: none"> All randomized subjects who receive at least one dose of randomized treatment. Subjects will be analyzed according to the treatment received.¹ 	<ul style="list-style-type: none"> Safety
Pharmacokinetic (PK)	<ul style="list-style-type: none"> Subjects for whom a PK sample was obtained and analyzed 	<ul style="list-style-type: none"> 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 deviations are captured and categorised on the protocol deviations dataset.
 - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the 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)
<ul style="list-style-type: none"> • Mean change in Hgb between baseline and EP
Model Specification
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> • 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). <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> • Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
<ul style="list-style-type: none"> • 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 \pm 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 \pm 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> The following analyses will be repeated using an alternative EP from Week 28-36: <ul style="list-style-type: none"> The primary analysis and summaries (using on- and off-treatment, observed and imputed Hgb values (see Section 10.6.3))

Supportive Statistical Analyses	
<ul style="list-style-type: none"> ○ 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	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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)	
<ul style="list-style-type: none"> • Average monthly IV iron dose (mg)/subject from baseline to Week 52 	
Model Specification	
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ 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	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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

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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)	
<ul style="list-style-type: none"> 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) (<i>non-inferiority analysis that will use a margin of 15 percentage points less time in range</i>) 	
Model Specification	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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)	
<ul style="list-style-type: none"> Time to stopping randomized treatment due to meeting rescue criteria 	
Model Specification	
<ul style="list-style-type: none"> The Cox Proportional Hazards model will adjust for the following baseline categorical values: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Summaries will include (see Section 10.6.3): <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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)	
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> On-treatment BP values only, excluding values collected during the stabilization period (Randomization date + 1 day to <Week 28). On-treatment BP values only, including values collected during the stabilization period. <p>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.</p> 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
<ul style="list-style-type: none"> BP parameter values (SBP, DBP, and MAP) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each visit by treatment group. In addition to scheduled visits, the derived baseline value and end of treatment values will be summarized (see Section 10.6.4). Summaries of on-treatment BP values only and on- and off-treatment BP values together will be produced. A summary of on-treatment BP values by baseline dialysis type will be produced. On-treatment BP parameter values will be plotted by visit using a line plot. BP parameter change from baseline values (SBP, DBP, and MAP) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each post-baseline visit by treatment group. In addition to scheduled visits, the derived end of treatment values will be summarized (see Section 10.6.4). Summaries of on-treatment BP values only and on- and off-treatment BP values together will be produced. A summary of change from baseline in on-treatment BP parameter values by baseline dialysis type will be produced. On-treatment BP parameter change from baseline values will be plotted by visit using a line plot.

Secondary Safety Statistical Analyses: Blood Pressure
<ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> The BP exacerbation summary above will be repeated for the following groups and BP values: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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.

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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 medications¹	ITT					Y			
Number of BP medications per subject by visit¹	ITT	Y							
CFB in number of BP medications per subject by visit¹	ITT					Y			
Number (%) of subjects who had no change, an increase or a decrease in dosage or number of BP medications from baseline by visit¹	ITT	Y							
Lipid Parameters									
Lipid parameters by visit (TC, LDL-C, HDL-C)	ITT	Y	Y			Y			

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- 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 :

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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] Adjudicated events used where available.

8.2.2.4. Planned Exploratory Cardiovascular Safety Analysis Details

Exploratory CV Safety Analyses	
Endpoint(s)¹:	
<ul style="list-style-type: none"> • 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) • Stroke (fatal and non-fatal) • CV mortality or non-fatal MI • All-cause hospitalization 	
Model Specification	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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				
<ul style="list-style-type: none"> 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 SOC, 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 SOC, 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	<i>RBC indices:</i>	<i>Leukocyte (white blood cell) count with Differential</i>
	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 :

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- 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. See Section 10.6.4 for additional information on worst case values and PCI categories.

Hematology

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

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. See 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				

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- 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			

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- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Mean and median plots will be generated
2. C_{max}, T_{max}, C_{tau}
3. C_{tau}/1mg Dose, C_{tau}/avg Dose EP TIR, C_{tau}/avg Dose EP, C_{tau}/ Dose at MACE, C_{tau}/ Final Dose for subjects without MACE, C_{tau}/ Dose at MACE++, C_{tau}/ Final Dose for subjects without MACE++, C_{max}/1mg Dose, C_{max}/avg Dose EP TIR, C_{max}/avg Dose EP, C_{max}/ Dose at MACE, C_{max}/ Final Dose for subjects without MACE, C_{max}/ Dose at MACE++, C_{max}/ 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									

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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			

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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.

8.5.2. 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)	
<ul style="list-style-type: none"> 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)	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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)
<ul style="list-style-type: none"> 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)
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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

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10. APPENDICES

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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 \pm 1 week, except Weeks 2 and 4 which are \pm 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 \pm 1 week, except Weeks 2 and 4 which are \pm 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		
KtV _{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

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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 taken 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	Early Treatment Discontinuation Visit (within 2 weeks of the last dose of randomized treatment)	Day 1 – Week 52 (every 12 weeks \pm 2 weeks)	Unscheduled	Follow-up (4 weeks post-study termination \pm 1 week)
Dialysis: In-clinic assessments done pre-dialysis.				
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	<ul style="list-style-type: none"> 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	<p>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.</p> <p>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.</p>
Treatment emergent	<p>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 <u>randomized</u> treatment start date.</p> <p>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 <u>randomized</u> treatment start date.</p>
Follow-up	<p>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 <u>randomized</u> treatment start date.</p> <p>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 <u>randomized</u> treatment start date.</p>
Onset /Worsening Time Since 1 st Dose (Days)	<p>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.</p>
Onset /Worsening Time Since Last Dose (Days)	<p>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</p>

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

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

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

To calculate a 95% CI of the geometric mean for the ratio of a specific timepoint to baseline (expressed as a percent change from baseline), the following steps are used:

1. Log-transform the data at both the baseline and the specified timepoint
2. For each subject, calculate a change from baseline using the log-transformed data
3. Calculate the mean and standard error (SE) of change from baseline using the log-transformed data
4. Calculate the lower and upper limits of the 95% CI of change from baseline using the log-transformed data assuming a normal distribution: Mean $\pm z(1 - \alpha/2) \times \text{SE}$ (z for $\alpha=0.05$ is obtained through PROBIT function in SAS that is specified as PROBIT(0.975))
5. Exponentiate the lower and upper limits of the 95% CI, back to the original scale and then subtract 1, then multiply everything by 100% in order to express the confidence interval (CI) as the percent change from baseline.

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

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

So, minimum percent change from baseline =

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

Where i = subject.

Unless otherwise specified, the baseline definitions specified in Section 10.5.2 will be used for derivations for endpoints/parameters and indicated on summaries and listings. Unless otherwise specified, if baseline data is missing, no derivation will be performed and the % change from baseline value will be set to missing. The baseline definition will be footnoted on all change from baseline displays.

10.5.3. Reporting Process & Standards

Reporting Process
Software
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Rich text format (RTF) files will be generated.
Reporting Standards
General
<ul style="list-style-type: none"> The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Reporting for tables, figures and formal statistical analyses : <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Unscheduled visits will not be included in summary tables, with the following exceptions: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none">Refer to IDSL Statistical Principals 7.01 to 7.13.	
Adjusted Means	
<ul style="list-style-type: none">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
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> • Date subject was randomized
Treatment Start Date
<ul style="list-style-type: none"> • First randomized treatment start date
Last Non-Zero Dose Date
<ul style="list-style-type: none"> • Date of last actual dose of randomized study treatment from IP Discontinuation eCRF form. <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ Missing day: <ul style="list-style-type: none"> ■ 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; <ul style="list-style-type: none"> ■ ‘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: <ul style="list-style-type: none"> ■ Treatment stop date will be used only for subjects who have a non-missing treatment start date.

Treatment Stop Date
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ Missing day: <ul style="list-style-type: none"> ■ 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: <ul style="list-style-type: none"> ■ '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: <ul style="list-style-type: none"> ■ The study completion or withdrawal date will be used only for subjects who have a non-missing treatment start date.
End of Treatment Value
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ Missing day: <ul style="list-style-type: none"> ■ 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.

<ul style="list-style-type: none"> ○ Missing day and month: <ul style="list-style-type: none"> ■ '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: <ul style="list-style-type: none"> ■ The last study contact date will be used.
Planned/Actual Visit Dates
<ul style="list-style-type: none"> • Planned/actual visit dates will be defined as follows: <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> • Defined as the period between and including the Randomization date + 1 day - <Week 28 visit, using planned/actual dates.
Alternative Evaluation Period (Alt. EP)
<ul style="list-style-type: none"> • Defined as the period between and including Week 28 visit – Week 36 visit, using planned/actual dates.
Evaluation Period (EP)
<ul style="list-style-type: none"> • Defined as the period between and including Week 28 visit – Week 52 visit, using planned/actual dates.
Study Day
<ul style="list-style-type: none"> • Calculated as the number of days from randomization date : <ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Calculated as the number of days from treatment start date: <ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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)
<ul style="list-style-type: none"> • 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days

Production of Two-Sided p-values
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized. <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Was this subject a screen failure? = Yes Reason for screen failure = Missing
Randomized Treatment Discontinuation
<ul style="list-style-type: none"> Any randomized subject with a non-missing treatment start date that is missing an IP Discontinuation eCRF will have the following values imputed: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Any randomized subject that is missing Study Conclusion eCRF will have the following values imputed: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Birth date will be presented in listings as 'YYYY'.
High Level Race
<ul style="list-style-type: none"> Geographic ancestry data will be combined into the following high level race categories: <ul style="list-style-type: none"> 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) <p>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.</p>
Race Detail
<ul style="list-style-type: none"> Geographic ancestry data will be combined into race detail categories: <ul style="list-style-type: none"> 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) <p>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.</p>
Dialysis Type at Randomization
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Planned start Unplanned (urgent) start
Dialysis Status at Randomization
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Dialysis not initiated On dialysis
Baseline Body Mass Index (BMI)
<ul style="list-style-type: none"> Calculated as baseline weight (kg) / [height (m)]² <p>Note: For subjects with in-clinic dialysis, baseline post-dialysis weight is used.</p>
B12 Supplementation Required to Be Eligible for Randomization
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> See Section 10.6.3.
Dialysis Access Type Used at Randomization
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Phosphate binder use at randomization will be summarized as follows: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Concomitant medication records on the day of randomization will be used to determine the following classifications of concomitant medication use at randomization: <ul style="list-style-type: none"> ACEI/ARB Vitamin D Beta blockers

Demographic & Baseline Characteristics	
	<ul style="list-style-type: none"> ○ 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	
<ul style="list-style-type: none"> • Randomized Treatment Discontinuation Censored Time (days) = Treatment stop date – Treatment start date +1 <p>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.</p>	
<ul style="list-style-type: none"> • Time to Randomized Treatment Discontinuation (days) = Treatment stop date – Treatment start date +1 	
<ul style="list-style-type: none"> • 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 	
<ul style="list-style-type: none"> • Randomized Treatment Discontinuation Incidence Rate (per 100 person years) = 100* Number of subjects who discontinued randomized treatment / randomized treatment person years 	
Study Withdrawal	
<ul style="list-style-type: none"> • Study Censored Time (days) = Study completion date – Randomization date +1 	
<ul style="list-style-type: none"> • Time to Study Withdrawal (days) = Study withdrawal date – Randomization date +1 	
<ul style="list-style-type: none"> • 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 	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> If there is only one concomitant medication record of non-randomized ESA use during the treatment period, then: <ul style="list-style-type: none"> 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			
<ul style="list-style-type: none">Exposure (days) = Treatment stop date – treatment start date + 1 day			
Compliance			
<ul style="list-style-type: none">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.<ul style="list-style-type: none">Daprodustat Doses			
Under Compliant		Compliant	
Compliance for the exposure record < 80%		Compliance for the exposure record 80% and ∴ 120%	
Over Compliant			
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			
<ul style="list-style-type: none">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	
15 – 42 days		1 dose	
43 – 70 days		1 or 2 doses	
< 2 doses		> 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.			
<ul style="list-style-type: none"> 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.			
<ul style="list-style-type: none"> 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.			
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> When source of Hgb measurement is not specified: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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					
<ul style="list-style-type: none"> 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					
<ul style="list-style-type: none"> 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					
<ul style="list-style-type: none"> 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					
<ul style="list-style-type: none"> 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					
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> During the study, subjects may be receiving iron in multiple routes, including: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> The number and percentage of subjects in the following iron use categories at baseline will be summarized: <ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> ○ 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	
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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)	
<ul style="list-style-type: none"> • 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		
<ul style="list-style-type: none"> Mean baseline monthly IV iron dose = $[(\text{IV iron total dose}_{\text{Record 1}}) + \dots + (\text{IV iron total dose}_{\text{Record n}})] / [(\text{Randomization Date} - \text{Screening Week -2 Visit Date}) / 30.4375 \text{ days}]$. 		
Standardized IV Iron Dose (mg/month) from Randomization to Week 52		
<ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> If the frequency of the record is not 'one time dose', then duration is calculated as follows: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Start date will be the latest of (concomitant medication record start date, randomization date, treatment start date). 		

Iron Endpoints		
<ul style="list-style-type: none"> ■ 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: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ■ 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 = $\frac{[(IV \text{ iron total dose}_{Record 1}) + \dots + (IV \text{ iron total dose}_{Record n})] / \{[\text{earliest of (treatment stop date + 1, Week 52 Visit Date)} - \text{treatment start date} + 1] / 30.4375 \text{ days}\}}{}$ 		
Standardized Monthly IV Iron Dose (mg/month) from Week 28 to Week 52 (EP Average Monthly IV Iron Dose)		
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency <p>Note: Frequency and Gap Factors defined as follows:</p>		
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 =
$$\frac{[(\text{IV iron total dose}_{\text{Record 1}}) + \dots + (\text{IV iron total dose}_{\text{Record n}})]}{\{[\text{earliest of (treatment stop date + 1, Week 52 Visit Date)} - \text{Week 28 Visit Date} + 1]/30.4375 \text{ days}\}}$$

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
<ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> • The standardized IV iron (mg/month) dose will be summarized by quarters, where quarters will be defined using study visits as follows: <ul style="list-style-type: none"> ○ Baseline ○ For summaries of on & off treatment IV iron dose: <ul style="list-style-type: none"> ■ Quarter 1 = [Randomization date – Week 12) ○ For summaries of on-treatment IV iron dose: <ul style="list-style-type: none"> ■ 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: <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> • TIBC will be calculated automatically by the central laboratory using: <ul style="list-style-type: none"> ○ $TIBC = UIBC + \text{total iron}$
TSAT
<ul style="list-style-type: none"> • TSAT will be calculated automatically by the central laboratory using: <ul style="list-style-type: none"> ○ $TSAT = 100 * (\text{Serum Iron} / TIBC)$
Average Quarterly TSAT and Ferritin
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ 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
<p>Iron therapy will be administered if at any visit:</p> <ul style="list-style-type: none"> Ferritin \leq 100 ng/mL and/or TSAT \leq 20% <p>All iron must be stopped if at any visit:</p> <ul style="list-style-type: none"> Ferritin > 800 ng/mL and TSAT >20%, or TSAT > 40% <p>Subjects meeting iron management criteria requiring starting and stopping of iron administration on the same day:</p> <ul style="list-style-type: none"> Ferritin \leq 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Treatment stop date when the primary reason and subreason for randomized treatment stop are: <ul style="list-style-type: none"> Primary reason: Subject reached protocol-defined stopping criteria Subreason: Rescue
General Definitions
<ul style="list-style-type: none"> Time to event (days) = date of event – randomization date +1 Censored time (days) = censoring date – randomization date + 1
<ul style="list-style-type: none"> 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) – darbapoetin alfa rescue incidence rate (per 100 person years)

Time to Stopping Randomized Treatment Due to Meeting Rescue Criteria
Time Period for Treatment Discontinuation
<p>The period for treatment discontinuation begins at randomization. The end of this time period is defined as follows:</p> <ul style="list-style-type: none"> • 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 <p>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.</p>

10.6.3.4. RBC and Whole Blood Transfusion Endpoints

Number of RBC and Whole Blood Transfusions	
<ul style="list-style-type: none"> • 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						
<ul style="list-style-type: none">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	
<ul style="list-style-type: none">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:
 $(450 \times 0.0025) = 1.125$ (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

<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • The period for capturing on-treatment transfusions begins on the treatment start date + 1 day. The end of this time period is defined as follows: <ul style="list-style-type: none"> ○ For subjects continuing on study past the (treatment stop date + 1 day), use (treatment stop date + 1 day) ○ For subjects whose study withdrawal/completion date is on or before (treatment stop date + 1 day), use date of study withdrawal/completion

Model Specification
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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																				
<ul style="list-style-type: none">• 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:																				
<table><tr><th>Total Daily Dose</th><th>How Administered</th></tr><tr><td>1 mg</td><td>single 1 mg tablet</td></tr><tr><td>2 mg</td><td>single 2 mg tablet</td></tr><tr><td>4 mg</td><td>single 4 mg tablet</td></tr><tr><td>6 mg</td><td>single 6 mg tablet</td></tr><tr><td>8 mg</td><td>single 8 mg tablet</td></tr><tr><td>10 mg</td><td>single 10 mg tablet</td></tr><tr><td>12 mg</td><td>two 6 mg tablets</td></tr><tr><td>16 mg</td><td>two 8 mg tablets</td></tr><tr><td>24 mg</td><td>three 8 mg tablets</td></tr></table>	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
Total Daily Dose	How Administered																			
1 mg	single 1 mg tablet																			
2 mg	single 2 mg tablet																			
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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																							
<p>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:</p>																							
	<table> <tr> <th>Total 4-Weekly Dose</th><th>Pre-filled Syringe Dose and Frequency</th></tr> <tr> <td>20 µg</td><td>20 µg every 4 weeks</td></tr> <tr> <td>30 µg</td><td>30 µg every 4 weeks</td></tr> <tr> <td>40 µg</td><td>40 µg every 4 weeks</td></tr> <tr> <td>60 µg</td><td>60 µg every 4 weeks</td></tr> <tr> <td>80 µg</td><td>40 µg every 2 weeks</td></tr> <tr> <td>120 µg</td><td>60 µg every 2 weeks</td></tr> <tr> <td>160 µg</td><td>80 µg every 2 weeks</td></tr> <tr> <td>200 µg</td><td>100 µg every 2 weeks</td></tr> <tr> <td>300 µg</td><td>150 µg every 2 weeks</td></tr> <tr> <td>400 µg</td><td>100 µg once a week</td></tr> </table>	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
Total 4-Weekly Dose	Pre-filled Syringe Dose and Frequency																						
20 µg	20 µg every 4 weeks																						
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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																							
<ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> 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																							
<ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> 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																							
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Death: event date reported by CEC • Myocardial infarction: event date reported by CEC <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ Fatal PE events only identified through a primary cause of death, without a corresponding positively adjudicated PE event: death event date reported by CEC
<p>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.</p>
<p>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</p>

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
<p><i>Missing of Partial Event (Start) Dates</i></p> <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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. <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ■ 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: <ul style="list-style-type: none"> ■ 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
<ul style="list-style-type: none"> ■ 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.
<p><i>Missing or Partial Hospitalization End Dates</i></p> <ul style="list-style-type: none"> ● 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. <ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> ● 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: <ol style="list-style-type: none"> 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
<ul style="list-style-type: none"> ● 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
<ul style="list-style-type: none"> ● 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	
<ul style="list-style-type: none"> ○ 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	
<ul style="list-style-type: none"> • 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	<p>Systolic heart failure, Diastolic heart failure, Heart failure - unspecified type</p> <p>Additional criteria: <i>If admission/discharge times are non-missing, at least one of the following must be true (1-3):</i> 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 <i>Or if admission/discharge times are missing, then at least one of the following must be true (4-6):</i> 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</p>
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	
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> Time to event (days) = date of event – randomization date +1 Censored time (days) = censoring date – randomization date + 1
<ul style="list-style-type: none"> 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
<p>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.</p> <p>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.</p>
Time Period for Vital Status
<p>The period for capturing vital status begins at the date of randomization. The end of this time period is defined as follows:</p> <ul style="list-style-type: none"> 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, <i>and are known to have not died</i> – use the latest date last known to be alive. If vital status has not been ascertained following study withdrawal, use the study withdrawal date. <p>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.</p>

10.6.4.2. Blood Pressure Endpoints

Blood Pressure Endpoints
Pre- and Post- Dialysis BP
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> See Section 10.6.1.
Mean Arterial Pressure (MAP)
<ul style="list-style-type: none"> $MAP = [(2 \times DBP) + SBP] / 3$
Blood Pressure Exacerbations
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> BP exacerbations <ul style="list-style-type: none"> SBP exacerbations <ul style="list-style-type: none"> ≥ 25 mmHg increase from baseline or SBP ≥ 180 mmHg <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> ≥ 15 mmHg increase from baseline or DBP ≥ 110 mmHg <ul style="list-style-type: none"> DBP ≥ 110 mmHg and baseline DBP < 110 mmHg (including subjects with a missing baseline DBP) DBP ≥ 110 mmHg and baseline DBP ≥ 110 mmHg
Notes:
<ul style="list-style-type: none"> 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 the total BP exacerbation type.
Blood Pressure Exacerbation Event Date
<ul style="list-style-type: none"> Date of BP exacerbation
On-Treatment BP Medication
<ul style="list-style-type: none"> See Section 10.4.1 for treatment states for concomitant medications.
General
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> BP exacerbation event incidence rate (per 100 person years) = (100 * number of BP exacerbations) / BP exacerbation person years
Changes in Blood Pressure Medications
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<p>Adverse events of special interest are classified as follows:</p> <ul style="list-style-type: none"> 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
<p>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.</p> <p>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.</p>
<p>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:</p> <ul style="list-style-type: none"> • Any Hgb value 13 g/dL (measured pre-dialysis) • Hgb increase > 2 g/dL over 2 weeks (+1 week) <ul style="list-style-type: none"> ○ 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) <ul style="list-style-type: none"> ○ 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 <p>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.</p> <p>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:</p> <ul style="list-style-type: none"> • 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. <p>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.</p>
<p>Pre-defined Lists of AE Preferred Terms Corresponding with Each AESI</p> <p><u>Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis</u></p> <ul style="list-style-type: none"> • 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-ischaemic 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

Death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access

- 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

Cardiomyopathy

- Narrow SMQ: Cardiomyopathy

Pulmonary artery hypertension

- High Level Term: Pulmonary hypertension
- Additional Preferred Terms:

○ Right ventricular dilatation	○ Right ventricular enlargement
○ Right ventricular dysfunction	○ Right ventricular failure
○ Right ventricular ejection fraction decreased	○ Right ventricular hypertrophy

Cancer-related mortality and tumor progression and recurrence

- Narrow SMQs:

○ Biliary malignant tumours	○ Myelodysplastic syndrome
○ Biliary tumours of unspecified malignancy	○ Oropharyngeal neoplasms
○ Breast malignant tumours	○ Ovarian malignant tumours
○ Breast tumours of unspecified malignancy	○ Ovarian tumours of unspecified malignancy
○ Liver malignant tumours	○ Prostate malignant tumours
○ Liver tumours of unspecified malignancy	○ Prostate tumours of unspecified malignancy
○ Malignancy related conditions	○ Tumour lysis syndrome
○ Haematological malignant tumours	○ Skin malignant tumours
○ Non-haematological malignant tumours	○ Skin tumours of unspecified malignancy

Adverse Events	
<ul style="list-style-type: none"> ○ Haematological tumours of unspecified malignancy ○ Non-haematological tumours of unspecified malignancy ○ Malignant lymphomas 	<ul style="list-style-type: none"> ○ Uterine and fallopian tube malignant tumours ○ Uterine and fallopian tube tumours of unspecified malignancy
<ul style="list-style-type: none"> • Additional Preferred Terms: <ul style="list-style-type: none"> ○ Aplastic anaemia ○ Cytopenia 	<ul style="list-style-type: none"> ○ Pancytopenia ○ Aplasia pure red cell
<u>Esophageal and gastric erosions</u>	
<ul style="list-style-type: none"> • High Level Terms: <ul style="list-style-type: none"> ○ Duodenal ulcers and perforation ○ Gastric ulcers and perforation ○ Gastrointestinal ulcers and perforation, site unspecified • Additional Preferred Terms: <ul style="list-style-type: none"> ○ Haematemesis ○ Gastrointestinal haemorrhage ○ Upper gastrointestinal haemorrhage 	<ul style="list-style-type: none"> ○ Oesophageal ulcers and perforation ○ Peptic ulcers and perforation ○ Helicobacter duodenitis ○ Helicobacter gastritis ○ Melaena
<u>Proliferative retinopathy, macular edema, choroidal neovascularization</u>	
<ul style="list-style-type: none"> • Broad SMQ: Retinal disorders 	
<u>Exacerbation of rheumatoid arthritis</u>	
<ul style="list-style-type: none"> • High Level Term: Rheumatoid arthropathies • Additional Preferred Terms: <ul style="list-style-type: none"> ○ Rheumatoid factor increased ○ Rheumatoid factor positive 	<ul style="list-style-type: none"> ○ Rheumatoid factor quantitative increased
<u>Worsening of hypertension</u>	
<ul style="list-style-type: none"> • Narrow SMQ: Hypertension 	
Blood Pressure Events	
<p>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.</p> <p>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</p>	

Adverse Events
<p>Exacerbation eCRF page:</p> <ul style="list-style-type: none"> • SBP: an increase from baseline of 25 mmHg or SBP 180 mmHg • DBP: an increase from baseline of 15 mmHg or DBP 110 mmHg
<p>BP-related SAEs are those SAEs that have been identified via the BP Exacerbation eCRF page.</p>
General Definitions
<ul style="list-style-type: none"> • Post-Randomization last contact date for censoring (subjects not having AE) will be defined as the study completion date.
<ul style="list-style-type: none"> • Treatment emergent last contact date for censoring (subjects not having AE) will be defined as follows: <ul style="list-style-type: none"> ○ 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) ○ Last non-zero dose date for all other subjects
<ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> ○ For treatment emergent AEs, the start date of the patient year value for each subject should be the treatment start date. ○ For post-randomization AEs, the start date of the patient year value for each subject should be the randomization date. ○ 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).
<ul style="list-style-type: none"> • Incidence Rate (per 100 patient years): (100 * Number of subjects with at least 1 AE) / AE person years
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ Example 1: 2 Significant Digits = '< x ' becomes x – 0.01

Laboratory Parameters
<ul style="list-style-type: none"> ○ Example 2: 1 Significant Digit = '> x' becomes $x + 0.1$ ○ Example 3: 0 Significant Digits = '< x' becomes $x - 1$
<ul style="list-style-type: none"> ● 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.
<ul style="list-style-type: none"> ● For purposes of flagging worst-case post baseline laboratory values: <ul style="list-style-type: none"> ○ 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.
<ul style="list-style-type: none"> ● The following will be used to convert laboratory values from SI units to conventional units [Iverson, 2007]: <ul style="list-style-type: none"> ● 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/1.73m² value by 60 to get the mL/min/1.73m² 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
<ul style="list-style-type: none"> ● 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. <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ■ 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
<ul style="list-style-type: none"> 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.
<ul style="list-style-type: none"> 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.
<ul style="list-style-type: none"> For purposes of flagging worst-case post baseline vital sign values: <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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 full health and 0 is the worst health. 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
<ul style="list-style-type: none"> The EQ-VAS is a self-assessment visual analogue scale, ranging from 0=worst imaginable – 100=best.
PGI-S
General
<ul style="list-style-type: none"> 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 0-4 as follows: <ul style="list-style-type: none"> Absent = 0 Mild = 1 Moderate = 2

PGI-S
General
<ul style="list-style-type: none"> ○ Severe = 3 ○ Very severe = 4

PGI-C
General
<ul style="list-style-type: none"> • 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 1 to 7 as follows: <ul style="list-style-type: none"> ○ Very much improved = 1 ○ Moderately improved = 2 ○ Minimally improved = 3 ○ No change = 4 ○ Minimally worse = 5 ○ Moderately worse = 6 ○ Very much worse = 7

CKD-AQ
General
<ul style="list-style-type: none"> • 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 1 (time tired or exhausted), 2 (time having low or no energy), 3 (time feeling weak), 9 (severity of feeling tired), 10 (severity of low or no energy), 11 (severity of feeling week), 19 (time not wanting to do anything because you are tired), 20 (time you needed to take a break because you are tired), 21 (time you needed to lie down because you were tired), and 22 (time you were distressed about being tired).; (2) a Chest Pain/Shortness of Breath scale consisting of four items – Items 4 (time having chest pain), 5 (time with shortness of breath while doing an activity), 12 (severity of chest pain), and 13 (severity of shortness of breath while doing an activity. This factor was labeled Chest Pain/Shortness of Breath.); and (3) a Cognitive scale consisting of three item – Items 7 (time forgetting things or difficulty remembering), 8 (time having difficulty concentrating), and 15 (severity of difficulty concentrating. The four CKD-AQ single items are: Items 6 (time with shortness of breath while not doing an activity), 14

CKD-AQ
General
<p>(severity of shortness of breath while sitting or resting), 17 (difficulty standing for long periods of time), and 18 (difficulty sleeping), 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 the worst possible and 100 the best possible score.</p> <ul style="list-style-type: none"> • Scoring instruction: <ul style="list-style-type: none"> ○ Step 1: For items 1-8, 17-23, recode from 5-pt scale (1-None of the time, 5 All of the time) to 0-100 (0 – worst, 100 – best) scale by using $(5\text{-raw score}) \times 25$; for items 9-16, recode from 11-pt scale (0 – absent/did not have, 10 – worst imaginable) to 0-100 scale (0 – worst, 100 – best) by using $(10\text{-raw score}) \times 10$. ○ Step 2: calculate the domain and single item scores as follows: (items 16 and 23 were NOT used currently based on the psychometric report.) <ul style="list-style-type: none"> ■ Tired/Low Energy/Weak domain: average items 1,2,3,9,10,11,19,20,21,22 (0-100 scale) ■ Chest Pain/Shortness of Breath domain: average items 4,5,12,13 (0-100 scale) ■ Cognitive domain: average items 7,8,15 (0-100 scale) ■ Time with shortness of breath while not doing an activity: item 6 (0-100 scale) ■ Severity of shortness of breath while sitting or resting: item 14 (0-100 scale) ■ Difficulty standing for long periods of time: item 17 (0-100 scale) ■ Difficulty sleeping: item 18 (0-100 scale)

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

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Imputing a Start/Worsening Date from a Partial Start/Worsening Date:

Element	Reporting Detail
	<ul style="list-style-type: none"> ○ If an imputed worsening date is before the start date, then the start date will be used as the imputed worsening date. ○ <u>Completely missing stop date:</u> <ul style="list-style-type: none"> ▶ 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. <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> • 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. ○ <u>Partial or non-missing stop date is before treatment start date:</u> <ul style="list-style-type: none"> ▶ 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. ○ <u>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:</u> <ul style="list-style-type: none"> ▶ 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: <ul style="list-style-type: none"> ○ <u>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:</u>

Element	Reporting Detail
	<ul style="list-style-type: none"> ▶ 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. ○ <u>Latest of (start date and latest worsening date) is partial or non-missing and is after treatment stop date:</u> <ul style="list-style-type: none"> ▶ 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: <ul style="list-style-type: none"> 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: \geq 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: \geq 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)	<ul style="list-style-type: none"> Hgb Change from Baseline to the EP
Analysis	<ul style="list-style-type: none"> ANCOVA
<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Multiple Imputation/Tipping Point Analysis
<ul style="list-style-type: none"> Intermittent missing data imputation: <ul style="list-style-type: none"> 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. If convergence issue still occurs, the convergence precision may be set to 1E-3. Monotone missing data imputation: <ul style="list-style-type: none"> 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

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