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:	**A**nemia **S**tudies in **C**KD: **E**rythropoiesis via a **N**ovel PHI **D**aprodustat-in Incident **D**ialysis **(ASCEND-ID)**

Compound Number: GSK1278863

Development Phase: III

Effective Date: 06-OCT-2017

Protocol Amendment Number: 01

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N234534_00	2016-OCT-18	Original
2015N234534_01	2017-OCT-06	Amendment No. 1

Amendment 1 applies to all countries

- 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 ≥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

PPD

October 6, 2017

Alexander R Cobitz, M.D., Ph.D. Date
Executive Director Clinical Development
Metabolic Pathways & Cardiovascular Unit
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PPD

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
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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, CCI

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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	• 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 p*rima*ry 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.

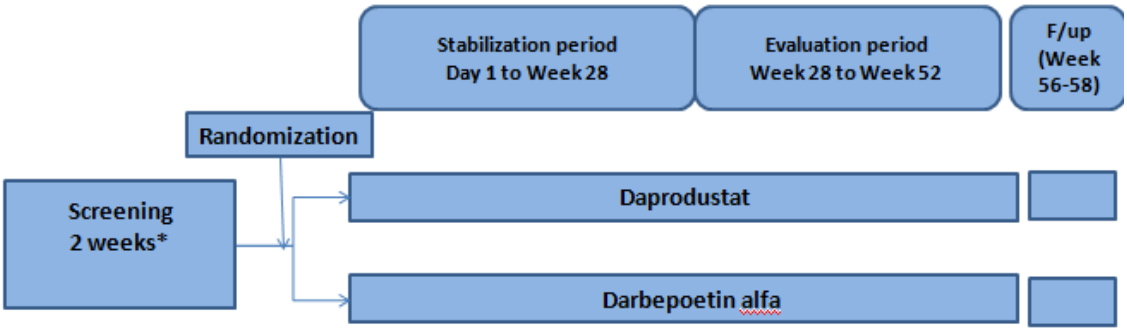
- Subjects will be stratified by dialysis type (hemodialysis [HD] or peritoneal dialysis [PD]) and by whether their dialysis start is planned or unplanned (urgent).

- 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



* 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 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 [Szczech, 2008];CCI

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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: ≥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 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 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**: ≤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 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 ≥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 ± 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

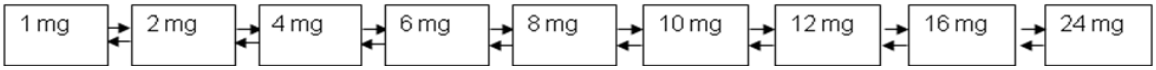
The starting dose of daprodustat will be assigned based on the HemoCue Hgb concentration at randomization (Day 1) (Table 3).

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, deferasirox) 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 ≤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: - 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,** - HemoCue Hgb remains <9 g/dL despite initial intervention based on the average of two HemoCue Hgb values[3] ***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 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 take 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 ≥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 Dialysis: In-clinic assessments done pre-dialysis.	**Early Treatment Discontinuation Visit (within 2 weeks of the last dose of randomized treatment)**	**Day 1 – Week 52 (every 12 weeks ± 2 weeks)**	**Unscheduled**	**Follow-up (4 weeks post-study termination ± 1 week)**
IRT SYSTEM	X			
SBP/DBP[1], HR[1]	X (triplicate)	X	X	X
Iron therapy, transfusions[2]	X			
Serum pregnancy test (FRP only)	X			
HemoCue Hgb	X	X	X	
Hematology	Hgb only	X		X
Clinical chemistry	X			
Ferritin, serum iron, UIBC, hepcidin, lipids	X			
Hospitalization[2] / kidney transplant[2]	X	X	X	X
Non-serious AEs, AEs of Special Interest, SAEs, clinical events	X	X	X	X
Review concomitant medications	X	X	X	X
Healthcare resource utilization (subject reporting)	X			
CKD Anemia Symptoms Questionnaire (CKD-AQ) questionnaire, PGI-S, PGI-C[3]	X			
SF-36[3], EQ-5D-5L[3]	X			

1. See 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	*RBC indices:*	*WBC count with Differential*
	RBC count	MCV	Neutrophils
	Reticulocyte count	MCH	Lymphocytes
	Hgb	MCHC	Monocytes
	Hematocrit	RDW	Eosinophils
			Basophils
Clinical Chemistry[1]	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

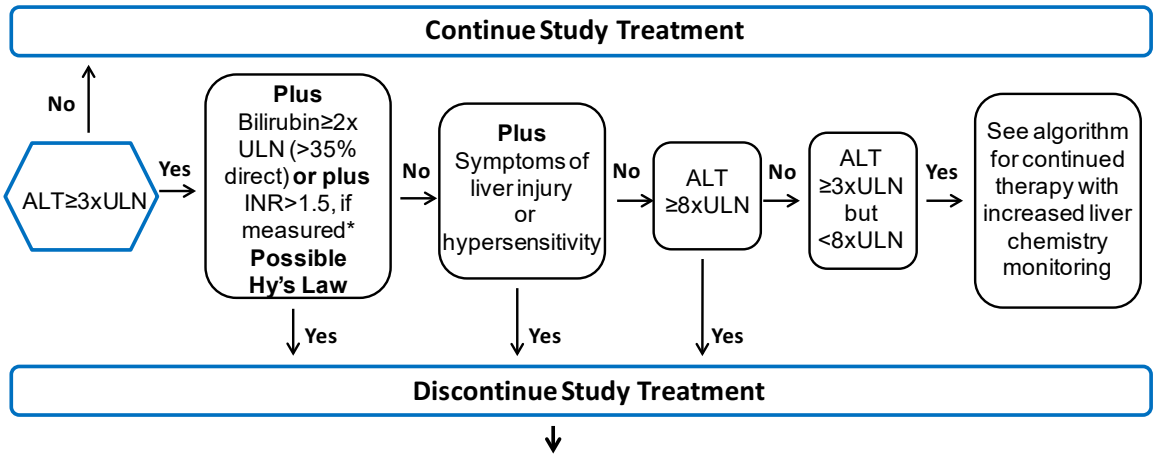
1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Appendix 6.
2. For females of reproductive potential only.
3. Screening only. As needed in postmenopausal women where their menopausal status is in doubt (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

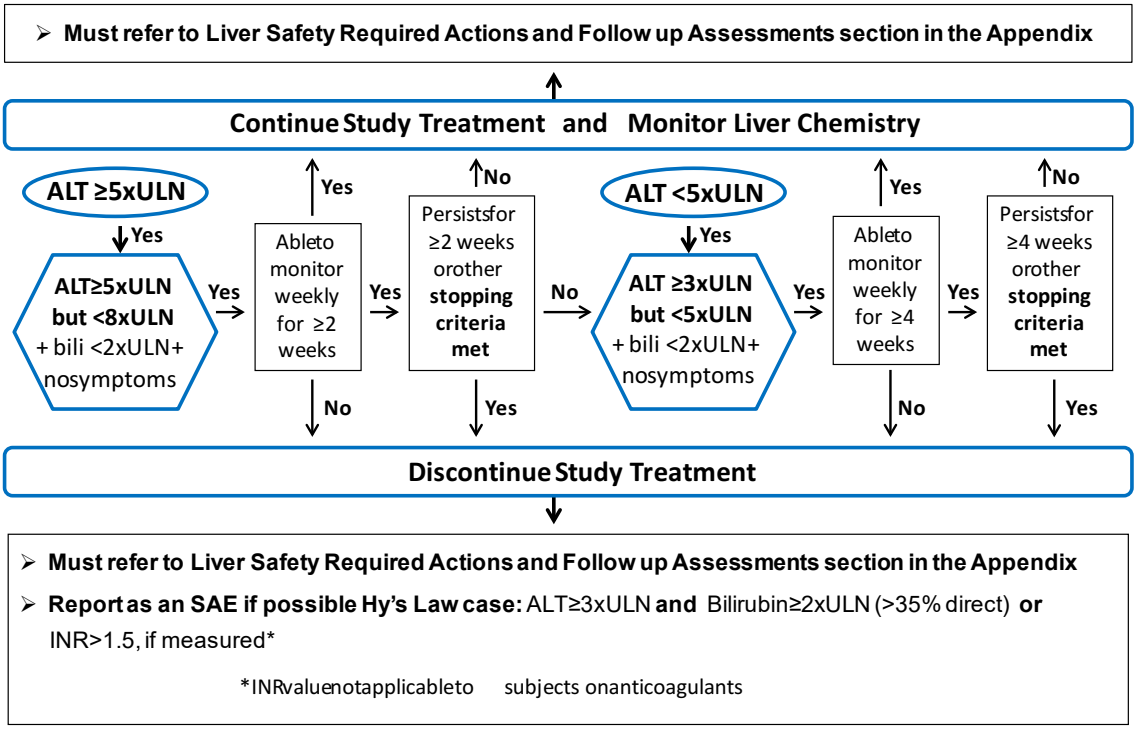


- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

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 ≥3xULN but <8xULN



- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

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 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% (n=120)	25% (n=113)	30% (n=105)	35% (n=98)	40% (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	≤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: Ctau (pre-dose) and Cmax.

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 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 Publically 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
Cmax	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

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	• 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	• Hgb change from baseline to Week 52[1] • N (%) responders, defined as mean Hgb within the Hgb analysis range 10-11.5 g/dL during the EP (Weeks 28 to 52) • % time Hgb in analysis range 10-11.5 g/d during the EP *(non-inferiority analysis that will use a margin of 15% less time in range)*[1]
To compare daprodustat to rhEPO on the time to rescue (defined as permanently stopping randomized treatment due to meeting rescue criteria)	• Time to stopping randomized treatment due to meeting rescue criteria
To compare daprodustat to rhEPO on HRQoL and Utility score	• Mean change in SF-36 HRQOL scores (PCS, MCS and 8 health domains) between baseline and Weeks 8, 12, 28, 52, of particular interest are the changes from baseline in the vitality and physical functioning domains at Weeks 28 and 52 • Change from baseline in Health Utility (EQ-5D-5L) score at Week 52 • Change from baseline in EQVAS at Week 52
To compare daprodustat to rhEPO on the symptom severity and change	• Change from Baseline at Wk 52 by domain and overall symptom score on the CKD-AQ • Change from Baseline at Wk 8,12, 28, 52 in PGI-S
To summarize the PK parameters of daprodustat and three major metabolites in dialysis subjects	• Plasma daprodustat, M2, M3, and M13 PK parameters pre-dose trough (Ctau) and Cmax
Exploratory Objectives	**Exploratory Endpoints (statistical testing not planned)**
To further compare daprodustat and rhEPO on Hgb variability	• Hgb observed and change from baseline across all visits to end of treatment • % of time Hgb is above, within and below the analysis range (10-11.5 g/dL) during EP • Number (%) of subjects with mean Hgb above, within

Objectives	Endpoints
	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 >1g/dL decrease in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL decrease in Hgb within any 4-week period from Week 4 to Week 52 • N (%) of subjects with a Hgb value ≥ 12 g/dL during the EP • Number of times Hgb ≥ 12 g/dL during the EP • % of time Hgb ≥ 12 g/dL during the EP
To compare daprodustat to rhEPO on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, transferrin saturation, total iron, total iron binding capacity (TIBC) across all visits to end of treatment • Average quarterly TSAT • Average quarterly ferritin • Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria
To compare daprodustat to rhEPO on the need for RBC and whole blood transfusions	• Number (%) of subjects who receive at least one RBC or whole blood transfusion by Week 52 • Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years
To evaluate the dose adjustment schemes	• Assigned dose by visit and at Day 1, Week 28, Week 52 • Most recent dose prior to Week 28 and Week 52 • Number (%) of patients with 0, 1, 2, or >2 dose adjustments during the following periods: o Day 1 - <Week 28 o Week 28 - <Week 52 • Number of dose adjustments during the following periods: o Day 1 - <Week 28 o Week 28 - <Week 52 • Time dose held for Hgb ≥12 g/dL
To further compare daprodustat to rhEPO on BP	• Observed and change from baseline in SBP, DBP

Objectives	Endpoints
and BP medication changes	and MAP by visit • Number of BP medications per subject by visit • Change from baseline in the number of BP medications per subject by visit • N (%) of subjects who had no change, an increase or a decrease in the dosage or number of BP medications from baseline by visit
To compare daprodustat to rhEPO on lipid parameters	• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)]
To further compare daprodustat to rhEPO on the symptom severity and change	• Change from Baseline at Wk 8,12, 28, & 52, by item on the CKD-AQ • Shift tables (Baseline to 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	• Change from baseline in Health Utility (EQ-5D-5L) score at Weeks 8,12, &28 • Change from baseline in EQ VAS at Weeks 8, 12, & 28
To evaluate graphical relationships between exposure parameters and selected efficacy endpoints	• Scatter plots of daprodustat PK parameters (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	• 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.

- 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	In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion/inflammation, microthrombi, and tissue ischemia in a number of organs. 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. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• 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)	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. In non-clinical studies conducted to date, not observed at tolerated doses when hemoglobin/hematocrit within normal range for species. The clinical data received to date are insufficient to conclude or refute this risk.	• 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	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. In rats stomach erosions were observed with intravenous and oral administration of daprodustat. Stomach erosions/ulcers also reported in rats with some marketed rhEPO and	• 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
	its analogs . 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. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	
Cancer-related mortality and tumor progression and recurrence	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. Administration of 60mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. 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. In clinical studies conducted to date, administration of daprodustat has been associated with: <u>Once daily administration:</u> • 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. <u>Three times weekly administration:</u> • In studies up to 4 weeks duration at doses of 10 to 30 mg: ○ Dose dependent increases in plasma VEGF and EPO	• 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
	concentrations were observed. o Pre-dose concentrations of EPO and VEGF were near or below baseline indicating no accumulation of EPO or VEGF after three times weekly dosing Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pulmonary artery hypertension (PAH)	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]. 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. Acute hypoxic challenge (rats): 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. 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. 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	• 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
	daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Cardiomyopathy	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. 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. Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization. ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in LVEF with daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Proliferative retinopathy, macular edema, choroidal neovascularization	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]. Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed.	• 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
	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. 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. 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. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Exacerbation of rheumatoid arthritis	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]. No abnormalities were seen in non-clinical studies conducted to date for daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Drug-drug interactions	Daprodustat is a substrate of CYP2C8: 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. 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. 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.	• 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
	Daprodustat is an inhibitor of CYP2C8: 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. Daprodustat is a substrate of BCRP: 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. Daprodustat is an inhibitor of OATP1B1/1B3: 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	
Other		
rhEPO risks (Control)	• 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	•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:

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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 ≥23MIU/mL (≥23.0 IU/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 ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 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**
• 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 SAE[2] • 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	• Viral hepatitis serology[4] • 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 antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hr after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or

study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • 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 **<u>For All other criteria:</u>** • 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	hypersensitivity, on the AE report form • 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 **<u>For bilirubin or INR criteria:</u>** • 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.

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 ≥ 3xULN **and** bilirubin ≥ 2xULN.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 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**
ALT ≥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. OR ALT ≥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.	• 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 ≥5xULN and <8xULN to ≥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. *Hepatol*. 2010;52:2216-2222.

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12.7. Appendix 7: Study Specific Equipment

Study specific equipment required:

- Refrigerator
- Freezer (-20^{o}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 <u>meeting</u> 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 <u>NOT</u> 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: • 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: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** 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.

12.8.3. Recording of AEs and SAEs

AEs and SAE Recording:
• 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

Thisisanamendmenttotheoriginalprotocoldated18 -Oct-2016

Thisamendmentappliestoallcountries.

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 ≥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:

> ~~Approximately600-subjectsareexpectedtobescreenedinordertorandomize approximately300subjects,or150subjectspertreatmentgroup~~
>
> 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 appropraite.

Revised Text:

- Planned:Subjectswhoareplanningtostartdialysis(HD**o** rPD)withinthenext**2** ~~-4~~ **6** weeks(fromthedayofscreening).

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:

~~Basedonanassumedscreenfailurerateof50%,approximately600 subjectsare expectedtobescreenedinordertorandomizeapproximately300subjects,or150 subjectspertreatmentgroup.~~

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 [Szczech, 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:Planningtostartchronicdialysiswithinthenext ~~4~~ **6** weeks(fromthedateof thescreeningvisit)ORhavestartedandreceiveddialysis(asspecifiedbelow)forend -stagerenaldiseaseforamaximumof ≤90daysimmediatelypriortorandomizatio nand isnotexpectedtostopdialysisduringthedurationofthetrial

Section 5.1. Inclusion Criteria; inclusion #2: Updated frequency of dialysis descriptions.

Revised Text:

~~Daily PD (Including continuous and automated PD)~~: PD ≥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. Informedconsent **(at screening)**:capableofgivingsignedinformedconsent whichincludescompliancewiththerequirementsandrestrictionslistedinthe consentformandinthisprotocol

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:Thecountry specificrequirementsfor France-ONLYfortheinformedconsent processisprovidedin Appendix11 (seeSection12.11.1,Item3fordetails)~~

5. ~~**Other study eligibility criteria considerations**~~: ~~Thecountr y-specificrequirementsfor France-ONLYfortheeligibilityforinclusioninthisstudyisprovidedin Appendix11 (see Section12.11.1,Item1fordetails)~~

.

Section 5.2. Exclusion Criteria; exclusion #1. Added or living-unrelated to clarify.

Revised Text:

1. **Kidney transplant:** Plannedliving -related **or living-unrelated ~~donor~~** kidneytransplant within52weeksafterstudystart(Day1).

Section 5.2. Exclusion Criteria; exclusion #7. Added Untreated to clarify.

Revised Text:

7. **Other causes of anemia: Untreated** perniciousanemia,thalassemiamajor,sicklecell diseaseormyelodysplasticsyndrome.

Section 5.2. Exclusion Criteria; exclusion #14. Clarified QTcB exclusion criteria

Revised Text:

14. QTcB(Day1):QTcB>500msec,orQTcB>530msecinsubjectswi thbundle branchblock.ThereisnoQTcexclusionforsubjectswithapredominantly **ventricular** pacedrhythm

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.

GSKwillsupplyrhEPO(darbepoetinalfa)forthecontrolgroup ~~.Darbepoetinalfa~~ as prefilledsyringes(PFS)forSC/IVinjection. **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 usingthestrengthsin 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:

ForsubjectsstartingHDorPD,theSC/IVdarbepoetinalfa**total ~~weekly~~** dosewillbe 0.75 1.0µg/kgroundedtothenearestavailabledose.

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:

Doseadjustmentswillbemadeprogrammaticallyby ~~theInteractiveResponse Technology~~ (IRT~~)~~ systemtomaintainHgbconcentrationswithintherangeof10 -11g/dL basedon the Hgb value measured every 2 to 4 weeks by the HemoCue value disclosed totheIRTsystembytheinvestigator.

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:

> Thisrescuealgorithmdo esnot applytosubjectswithadecreasein **low** Hgb asaresult ofanacuteorsubacuteeventwithanidentifiablecause(e.g.,GIbleed,bloodlossdue tosurgeryorvascularaccess).

Section 6.11. Anemia recue therapy; added wording in Table 5 to clarify the rescue applies at scheduled visits only

Revised Text:

> HemoCueHgbremains<9g/dL**(at a scheduled visit , Week 4 onwards)** despitethree [1] consecutivedoseincreasesabovethestartingdoseorpost- rescue[2] (whereHemoCue Hgb<9g/dLpriortoeachdoseinc rease)ORHemoCueHgbis<7.5g/dLdespiteadose increaseatthepriorstudyvisit

Section 7. Study Assessments and Procedures; paragraphs leading up to 1st bullet. Clarified valid study period for study visits.

Revised Text:

Studyvisitdaysshouldbesc heduledasfollows:

> **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 Day1)~~ **±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

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**						

[3]~~All~~ ECG~~s~~ 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**

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 whorequireIVironsupplementationand/orvitaminB12asoutlinedinSection5.2. ~~HemoCue Hgb~~,Ferritin,TSAT,and/orvitaminB12mustbere -assessed**, where appropriate**, **following iron and/or B12 supplementation** priortorandomizationto meetentrycriteria

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 ≥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 ± 2 weeks)**	**Unscheduled**	**Follow-up (4 weeks post-study termination ± 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:

Bloodsamples(notfingersticks)formeasurementofHgbviaHemoCueandalsobythe centrallaboratorywillbecollectedand~~—~~ **as** specifiedintheTimeandEventsTable(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:

InvestigatorsshouldreferanyeventsuspectedtobeonethefollowingMACE~~———~~ events **below** totheCEC **.** TheCECwillreviewandadjudicatethefollowing**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:

> Sourcedocumentationrequiredtosupporttheadjudi cationoftheeventsisdescribedin 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

> Theresultsofanyinvestigationshouldber ecorded ~~intherelevantsections~~ **on the AE page and in the relevant AE of special interest page** ofthesubjects'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**~~M~~ **m**easurementswillbetaken**pre and post dialysis** withthesubjectinasemi -supineorseatedpositioninthedia lysischairafteratleasta 5-minuterestperiod(~~pre - andpost - dialysis).~~
- **For PD subjects, this assessment will be done at study visits, as per standard of care.**

~~ForHDsubjects,~~ **SBP, DBP and HR will be performed before collection of blood samples for laboratory testing, where applicable.** ~~measuredpreandpost -dialysis.ForPDsubjectsthese assessmentswillbedonebetweentreatments.Pre dialysismeasurementswillbetakenpriorto bloodsamplecollection~~

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:

Detailsonpatientreportedoutcomesareprovidedinthestudy**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:

TheEQVASrecordstherespondent'sself -ratedhealthonavertical,visualanalogue scalewheretheendpointsarelabeled'**the best health you can imagine** be~~stimaginable healthstate~~'and' **the worst health you can imagine** ~~worstimaginablehealthstate~~**'**.This informationisusedasaquantitativemeasureofhealthoutcomeasjudgedbyindividual subjects.

Section 7.7.5 Psychometric Analysis of the CKD Anemia Symptoms Questionnaire (CKD-AQ), updated study visit for interim data cut.

Revised Text:

Inorderestablishandevaluatethemeasurementpropertiesof theCKD -AQ,ainterim cutofblindedobservationsofthefirst50subjectswhocompletedtheweek28**52** ~~—~~visit willbetaken.In ordertoestablishcontentvalidity,thedatacutwillrequirea

comparisontothefollowingvariables:PGI -C,PGI -S,Hgb,SF -36,demographic&baseline clinicalcharacteristics.Alldatawillbeabstractedfromscreeninguntilweek28 ~~52~~.

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:

Statisticalsignificanceofnon -inferioritywillbeassessedatthe**two~~—~~ one-sided 2.5%** level.Ananalysisofcovariance(ANCOVA)modelincludingrandomizationstratification factors,baselinehemoglobinandtreatmentwillbeusedtoobtainapointestimateand the **two-sided** 95%CIforthetreatmentdifference(daprodustat -rhEPO)andgenerate thep- valueforthenon -inferioritytest.

Section 9.2.1 Sample Size Assumptions, in the third paragraph. Added two-sided 95% CI.

Revised Text:

With300randomizedsubjects,itisanticipatedthatthedifferenceinmeanHgbchange frombaselinebetweenarmsw ill be estimated with a precision of 0.408 g/dL (half width ofthe**two -sided** 95%CI)

Section 9.4.1 Primary analysis; first and second paragraph. Added supplementary analyses information.

Revised Text:

Itwillprovideapointestimateand**two -sided** 95%CIforthetreatmenteffect,together withthe**one -sided** non-inferioritytestp -value.

Sensitivityand**Supplementary** Analyses:Sensitivityanalysesfortheprimaryestimand willincludeamultipleimputation -based“tippingpoint”analysiswhereassumptions are adjusteduntilnon- inferiorityislostbyimputingdataforsubjectswhodidnotfully completetheEP.Afurther **supplementary** analysiswillevaluateefficacyinthose subjectswhoadheretorandomizedtreatment,definedasITTsubjectswithatleastone on-treatmentHgbduringtheEP(thisapproachcorrespondstoevaluatinganefficacy estimand).Asimilar“tippingpoint”analysisasthatdescribedaboveforthe primary analysiswillbeperformedforthis“on -drug”analysis.Inaddition,a **supplementary** per-protocol ~~**sensitivity**~~ analysiswillestimatethetreatmenteffectinsubjectswhostrongly adheretotheprotocol,andsensitivityanalysestoexploreashorterEP(Weeks28to36) willbeperformedfortheprimaryeffectivenessestimandand“on -drug”efficacy estimand.Fulldetailsofallsensitivityand **supplementary** analyseswillbeprovidedin theRAP.

*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:

> Conditionalontheprimaryendpointachievingnon -inferiorityatthe**two ~~—~~ one-**sided **2**.5%level,statisticaltestingwillprogresstotheprincipalsecondaryendpointwitha focusonsuperiorityusinga**two ~~—~~ one-**sided **2**.5%significanceleve l.
>
> 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:

> Theprimaryendpointwillbetestedfirstfornon -inferiority,usingthelowerlimitofthe 2-sided95%confidenceinterval.Conditionalonachievingstatisticalsignificance(i.e. passingtheprimarygatebyestablishingnon -inferiority)thesingleprincipalsecondary endpointwillbetestedforsuperiorityusinga ~~**two**~~ **one**-sided **2.**5%significancelevel. Thistwo -stephierarchicalstrategywillpreservethestudy -wiseTypeIerrorrateata ~~**two**~~ **one**-sided **2.**5%level.
>
> Theadditionalsecondary/exploratoryendpointsaslistedin Appendix 2,iftested,will notbeadjustedformultiplicity.Anominal**one -sided 2.**5%significancelevelwillbe appliedpertest.

Section 9.4.4. Covariates and Subgroups of Interest; paragraph 2. Revised sentence to more complete describe adjustments to statistical model.

Revised Text:

> Statisticalmodelswillbeadjustedfor**the covariates used in the original analysis,** baseline, subgroup,treatmentandtreatmentbysubgroupinteraction. Point estimates and **two-sided** 95%CIswillbeestimated(presentedonForestPlots)andthesubgroup bytreatmentinteractionp -valuecalculated.

Section 9.4.4.1. Exploratory Cardiovascular Safety Analysis. Added two-sided for 95% CI

Revised Text:

> Withfewerth an80firstMACE(definedasall- causemortality,non -fatalMI,ornon -fatal stroke)expectedtooccurduringthetrial,incidenceratesand**two -sided** 95%CIswillbe computedforthefollowingmortalityandCVcompositeorcomponentendpoints:1) MACE;2) MACEorathromboembolicevent(vascularaccessthrombosis,asymptomatic deepveinthrombosisorasymptomaticpulmonaryembolism);3)MACEor hospitalization for heart failure; 4) all cause mortality; 5) CV mortality; 6) MI (fatal and

non-fatal);7)str oke(fatalandnon -fatal);8)CVmortalityornon -fatalMI;9)allcause hospitalization

Section 9.4.7 Analysis of Patient Reported Outcomes Measures Paragraph 1. Updated study visit for interim data cut.
Revised Text:

Inordertoestablishandevaluate themeasurementpropertiesoftheCKD -QA,an interimcutofblindedobservationsofatleast50subjectswhocompletedtheWeek ~~52~~ **28** visitwillbetaken.Thedatacutwillrequirethefollowingvariablesthrough Week ~~52~~ **28**:PGI -C,PGI -S,Hgb,SF-36,demo graphicandbaselineclinicalcharacteristics.

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:

To further compare daprodustat and rhEPO on Hgb variability	• Hgb observed and change from baseline across all visits to end of treatment • % of time Hgb is above, within and below the analysis range (10-11.5 g/dL) during EP ~~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 g/dL during the EP • Number of times Hgb ≥ 12 g/dL during the EP • % of time Hgb ≥ 12 g/dL during the EP
To compare daprodustat to rhEPO on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, transferrin saturation, total iron, total iron binding capacity (TIBC) across all visits to end of

	treatment • Average quarterly TSAT • Average quarterly ferritin • Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria • ~~**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	• Number (%) of subjects who receive at least one RBC or **whole blood** transfusion by Week 52 • Number of RBC and **whole blood** transfusions per 100 patient years • Number of RBC and **whole blood** units per 100 patient years

To evaluate the dose adjustment schemes	• **Assigned dose by visit and at Day 1, Week 28, Week 52**
	• **Most recent dose prior to Week 28, Week 52, yearly and End of Treatment**
	• **Number (%) of patients with 0, 1, 2, or >2 dose adjustments during the following periods:**
	  ○ **Day 1 - < Week 28**
	  ○ **Week 28 - < Week 52**
	  ○ **Day 1 - < End of Treatment**
	• **Number of dose adjustments during the following periods:**
	  ○ **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~~ • Time dose held for Hgb ≥12 g/dL

*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		
Excessiveerythropoiesis (polycythemia)leadingtothrombosis and/ortissueischemia	Inanimalstudies,excessiveerythropoiesisattributedto daprodustatwasassociatedwithvascular congestion**/inflammation**,microthrombi,andtissueischemia inanumberoforgans. **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**. Followingreviewofclinicaldatareceivedtodate,thishasnot beenidentifiedasasafetyconcernfordaprodustat. Phase2dose -rangingstudies,andassociatedstatisticaland exposureresponsemod ellinghasinformedPhase3dose rationale,startingdoses,doselevels,anddoseadjustment schemetooptimizeHgbmanagement.	• Specificeligibilitycriteriarelated torequirementsforentryHgbare detailedinSection5.1 • Hgbwillbecloselymonitored throughoutthedosingperiodas outlinedintheTimeandEvents Table(Table6) • Specificguidancefordose adjustment,doseinterruption,or discontinuationofdaprodustat basedonachievedHgb(including rateofchange)isprovidedin Section6.2andSectio n6.11 • Unblindedmonitoringofsafety databyanIDMCin -stream throughoutthestudy.
RiskofDeath,MI,stroke,heart failure,thromboembolicevents,	MarketedrhEPOanditsanalogshavebeenassociatedwithan increasedriskfordeathandseriouscardiovascularevents	• Specificeligibilitycriteriarelated toCVriskareoutlinedinSection

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
thrombosisofvascularaccess atHgb levelswhicharewithinthenormal range(i.e.notpolycythemic conditions)	whenusedinpatientswithanemiaofCKD. Innon- clinicalstudiesconductedtodate,notobservedat tolerateddoseswhenhemo globin/hematocritwithinnormal rangeforspecies. Theclinicaldatareceivedtodateareinsufficienttoconcludeor refutethisrisk.	5.2 • Hgbwillbecloselymonitored throughoutth edosingperiodas outlinedintheTimeandEvents Table(Table6) • Unblindedmonitoringofsafety databyanIDMCin -stream throughoutthestudy
Esophagealandgastricerosions	Inanimalstudies,undesirableGIeffectsincludingemesis, abnormalfecesand/ordecreasedfoodconsumption/body weightlossandstomacherosions/ulcerswithhemorrhage wereobservedwithdaprodustat. Inrodents **rats** stomacherosionswereobservedwith intravenousandoraladministrationofdaprodustat. **Stomach erosions/ulcers also reported in rats with some marketed rhEPO and its analogs.** Gender-averagedsystemicexposure(AUC)atthenoobserved adverseeffectlevels(NOAEL)are3.3- fold(monkeys)and737-fold(rats)abovehumanexposure(25mgdaprodustat). Inclinicaltrialstodatewithdaprodustat,mild -moderateGI signsandsymptomsrepresentthemostfrequentlyreported	• SuspectedGIbleedingor significantsymptomsconsistent witherosionsorulcersshouldbe investigateddiagnostically(i.e. endoscopicexamination)as clinicallywarranted. • Unblindedmonitoringofsafety databy anIDMCin -stream throughoutthestudy.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	adverseevent,howevercausalassociationhasnotbeen established. Followingreviewofclinicaldatareceivedtodate,GIerosions havenotbeeniden tifiedasasafetyconcernfordaprodustat.	
Cancer-relatedmortalityandtumor progressionandrecurrence	Inclinicaltrials,useofrhEPO **and its analogs** inpatientswith cancerhasbeenassociatedwithincreasedriskofcancer relatedmorbidityandmortality. Administrationof60mg/kgdaprodustattomicecaused minimalincreasesincirculatingVEGFwhilesignificantEPO increaseswereobserved. Therewerenotestarticle-relatedneoplasticfindingsin2 -year rat(oraldaprodustat)ormouse(daprodustat+ subcutaneous injectionofthe3majorhumanmetabolites;M2,M3andM13) carcinogenicitystudies. In clinical studies with daprodustat up to 4 weeks duration, a dose-orderedincreaseinVEGFplasmaconcentrations,an angiogenicfactorthathasbeenimplic atedintumorgrowth, wasobservedatdosesrangingfrom10to150mg.Inclinical studies up to 24 weeks duration at doses up to 25mg, changes	• Specificeligibilitycriteriarelated topersonalhistoryofmalignancy orsubjectswithcomplexkidney cystareoutlinedinSection5.2.. • Stoppingcriteriaforsubj ectswith treatmentemergentmalignancy areoutlinedinSection5.5. • Unblindedmonitoringofsafety databyanIDMCin -stream throughoutthestudy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	inVEGFplasmaconcentrationswerevariablebutsimilar relativetocontrol. **In clinical studies conducted to date, administration of daprodustat has been associated with:** **<u>Once daily administration:</u>** • **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.** **<u>Three times weekly administration:</u>** • **In studies up to 4 weeks duration at doses of 10 to 30 mg:** o **Dose dependent increases in plasma VEGF and EPO concentrations were observed.** o **Pre-dose concentrations of EPO and VEGF were**	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	near or below baseline indicating no accumulation of EPO or VEGF after three times weekly dosing Followingreviewofclinical datareceivedtodate,thishasnot beenidentifiedasasafetyconcernfordaprodustat.	
Pulmonaryarteryhypertension(PAH)	AroleforHIF -regulatedpathwaysinthepathophysiologyof PAHhasbeensuggestedbasedonwell -establishedeffectsof acuteandchronichypoxiainmanonthepulmonary vasculature(vasoconstriction),andbyfindingsinpatientswith naturallyoccurringmutationsthatresultindecreasedHIF degradation[Smith,2006;Forment i,2011]. TherehavebeennohistopathologicfindingssuggestiveofPAH inpre -clinicalsafetystudieswithdaprodustatupto13 -weeks durationinmiceanddog**s** ,upto26weeks2 -yearsinrats **and mice**,andupto39 -weeksinmonkeys. Acutehypoxicchallenge(rats): Daprodustatproduced increasesinpeakrightventricularpressure(PRVP)duringacute hypoxiathatwereslightlyhigherthanthevehiclecontrol group.However,thesehypoxia -inducedPRVPchangeswere withintherangeofPRVPchangesnotedamong nonun -treated rats.	• Unblindedmonitoringofsafety databyanIDMCin -stream throughoutthestudy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Resultsfromaclinicalstudyofacutehypoxicchallengein healthyvolunteersdemonstratedthatshort-term(5days) therapywithdaprodustat5mgor100mghadnoclinically significanteffecton **transthoracic** echocardiographically **(ECHO)** estimatesdofpulmonaryarterysystolicpressure (sPA**S**P)undereithernormoxicorhypoxicconditions. ECHO assessments performed in Phase 2b studies (24 weeks treatmentduration)didnotidentifyanyclinicallymeaningful changesin**s** PASPinsubjectsnotondialysisfordaprodustat.In hemodialysissubjects,meanabsolutechangefrombaselinein **s**PA**S**Pwassimilarforbothtreatmentgroups;however,there wasanumericimbalance(daprodustatTotal:8[7%];Control0) insubjectsreachingthe**s** PA**S**PPCI(>20mmHgincreasefrom baseline). Regardingthisimbalance,therewereanumberof confounding factors in the study, most notably a 4.5:1 randomizationschemeandinconsistencyintimingofECHOs relativetodialysisday. Additionally,2of3subjectswith resolutionofsPA **S**Ponsafetyfollow -upECHOshad confoundingconditionsthatcouldcontributetoresolution otherthandiscontinuationofstudydrug;andtherewasno doserelationshipforsubjectsmeetingthesP **A**SPPCIcriterion. Overall,thereisinsufficientevidencetoconcludearelationship totreatmentwithdaprodustat. Followingreviewofclinicaldatareceivedtodate,thishasnot	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	beenidentifiedasasafetyconcernfordaprodustat.	
Cardiomyopathy	PublisheddatasuggestthatcardiaceffectsofHIFstabilization arelikelyafunctionofthemechanism,extent,anddurationof theeffects,andcanrangefromprotectivetodetrimental dependinguponthespecificmod elandexperimental conditionsutilized. Smallincreasesincardiactroponinin6monthratstudywith daprodustatwereconsistentwiththebackgroundfindingof spontaneousrodentcardiomyopathy.Therewereno elevationsobservedincardiactroponinin9 monthmonkey studywithdaprodustat. **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.** Cardiomyopathyhasnotbeenassociatedwithnaturally	• Unblindedmonitoringofsafety databyanIDMCin -stream throughoutthestudy.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	occurringmutationinmanwhichresultsinincreasedHIF stabilization. ECHO assessments performed in phase 2b studies (24 weeks treatmentduration)didnotidentifyanyclinicallymeaningful changesinLVEFwithdaprodustat. Followingreviewofclinicaldatareceivedtodate,thishasnot beenidentifiedasasafetyconcernfor daprodustat.	
Proliferativeretinopathy,macular edema,choroidalneovascularization	Increasesinlocal(ocular)VEGFproductionwithretinal neovascularizationandmacularedem aobservedindiabetic retinopathyandtochoroidalleakage,edemaand neovascularizationseeninage -relatedmaculardegeneration [Campochiaro,2006]. Administrationof 60mg/kgdaprodustattomicecaused minimalincreasesincirculatingVEGFwhilesignificantEPO increaseswereobserved. **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.** Noocularabnormalitieswithdaprodustatwereseeninnon -clinicalstudiesofupto13weeksdurationinmiceanddogs,26	• Suspectedp roliferative retinopathy,macularedema, choroidalneovascularizationor symptomsconsistentwiththese eventsshouldbeinvestigatedby ophthalmologic consultationas clinicallywarranted • Unblindedmonitoringofsafety databyanIDMCin -stream throughoutthestudy.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	weeksinrats,and39 -weeksinmonkeys. In clinical studies with daprodustat up to 4 weeks duration, a dose-orderedincreaseinVEGFplasmaconcentrationswas observedat dosesrangingfrom10to150mgadministered oncedailyandfrom10to30mgadministeredthreetimes weekly. In studies up to 24 weeks duration at doses up to 25mg,changesinVEGFplasmaconcentrationswerevariable butsimilarrelativetocontrol. Ophthalmologicassessmentsperformedinphase2bstudies (24 weeks treatment duration) did not identify any clinically meaningfulchangesinproliferativeretinopathy,macular edema,orchoroidalneovascularizationfordaprodustat. Followingreviewofclinicaldatareceivedtodate,thishasnot beenidentifiedasasafetyconcernfordaprodustat.	
Exacerbationofrheumatoidarthritis	Ininflamedrheumaticjoints,activationofHIF - relatedgenes secondarytodecreasedoxygenandpro -inflammatory cytokineshasbeenpostulatedtocontributetotheneo - angiogenesis,proliferationandinfiltrationofrheumatoid synovialfibroblasts[Westra,2010;Muz,2009]. Noabnormalitieswereseeninnon -clinicalstudiesconducted todatefordaprodus tat. Followingreviewofclinicaldatareceivedtodate,thishasnot	• Unblindedmonitoringofsafety databyanIDMCin -stream throughoutthestudy.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	beenidentifiedasasafetyconcernfordaprodustat.	
Drug-druginteractions	**Daprodustat is a substrate of CYP2C8:** Co-administrationof daprodustatwithastrongCYP2C8inhibitor**(gemfibrozil)** increased the Cmax and AUC of daprodustat, 4- and19 -fold, respectively,whileco -administrationofaweakinhibitor (trimethoprim)increasedtheCmaxandAUCofdaprodu statby 1.3- and1.5 -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.** daprodustatisaninhibitorofCYP2C8*in vitro,* withanIC $_{50}$ value of21μM. PopulationPKanalysisfromcompletedPhase2studies suggeststhatco -administrationofdaprodustatwith clopidogrel(amoderateCYP2C8 inhibitor)leadstoa~2 -fold increaseinAUC,withnoclinically -significantincreaseinthe measuredHgbresponse. Co-administrationofdaprodustat withmoderateCYP2C8inhibitors(i.e.,clopidogrel, teriflunomide,deferasirox)shouldbeperformedwit hcaution Co-administrationofdaprodustatwithpotent BCRPinhibitors	• Co-administrationofdaprodustatwith strongCYP2C8inhibitors(e.g., gemfibrozil)andinducers(e.g., rifampin/rifampicin)isnotpermitted asoutlinedinSection6.9.2 . • Co-administrationofdaprodustatwith moderateCYP2C8inhibitors(i.e., clopidogrel,teriflunomide, deferasirox)shouldbeperformed withcaution. Ifoneofthese medicationsisstarted,stoppedorthe doseischanged,Hgbshouldbe monitored every 4 weeks for 12 weeksasoutlinedinSection6.9.1. • Specificguidanceonthemanagement ofpotentialdrug- druginteractions andconcomitantmedicationsis providedinSection6.9.. • Hgbwillbecloselymo nitored throughoutthedosingperiodas outlinedintheTimeandEvents

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	hasthepotentialtoincreaseexposureofdaprodustat. Useof BCRPinhibitors(mostlyweak)wasfoundtoresultinasmall changeinmetaboliteexposure(20%increaseinAUC). DaprodustatisaninhibitorofOATP1B1/1B3*in vitro,* withIC 50 valuesof6µMand11 µM,respectively. Aclinicaldrug interactionstudybetween25mgdaprodustatwitheithera CYP2C8substrateoranOATP1B1/1B3substrateshowedthat thereisnoPKinteractionatth isdoseofdaprodustat. **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.** **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.** **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**	Table(Table6) •Specificguidancefordoseadjustment, doseinterruption,ordiscontinuationof daprodustatbasedonachievedHgbis providedinSection6.2.1andAppendix3. •Unblinded monitoringofsafetydataby anIDMCin -streamthroughoutthestudy.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. **<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.** **<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.** <u>DaprodustatisaninhibitorofOATP1B1/1B3:</u> Aclinicaldrug interactionstudybetween25mgand100mgdaprodustatwith anOATP1B1/1B3substrate(rosuvastatin)showedthatthereis noPKinteractionatthesedosesofdaprodustat	
Other		
rhEPOrisks(Control)	• Seerisksoutlinedintablefordaprodustatfor Excessive erythropoiesis(polycythemia)leadingtothrombosis and/ortissueischemia, Death,MI,stroke,thr omboembolic events,thrombosisofvascularaccess,andforIncreased cancer-relatedmortalityandtumorprogression.	•Seemitigationstrategiesoutlinedin tablefordaprodustatforExcessive erythropoiesis(p olycythemia)leadingto thrombosisand/ortissueischemia, Riskof death,MI,stroke,thromboembolic

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Uncontrolledhypertension • Pureredcellaplasia	events,thrombosisofvascularaccess,and forIncreasedcancer- relatedmortalityand tumorprogression. •Specificeligibilitycriteriarelatedto currentuncontrolledhypertensionare outlinedinSection5.2. •Specificeligibilitycriteriarelatedto personalhistoryofpureredcellaplasia areoutlinedinSection5.2.

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~~ MIU/**m**L **(≥23.0 IU/L)** and estradiol ≤10 pg/mL (or ≤37 pmol/L) is confirmatory).

Section 12.11, Appendix 11 is totally removed. Franceisnottakingpartinthisstudysothis Appendixisnolongerrelevant