TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-center, event driven study in dialysis subjects with anemia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoietin-stimulating agents.
Short Title:	**A**nemia **S**tudies in **C**KD: **E**rythropoiesis via a **N**ovel PHI **D**aprodustat-**D**ialysis **(ASCEND-D)**

Compound Number: GSK1278863

Development Phase: IIIA

Effective Date: 30-JUL-2020

Protocol Amendment Number: 04

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N226659_00	2016-MAY-27	Original
2015N226659_01	2016-JUN-09	Republishing
2015N226659_02	2016-SEP-20	Amendment No. 1
Amendment 1 applies only to Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Italy, Norway, Poland, Portugal, Romania, Spain, Sweden and the United Kingdom. • Text added to clarify when the end of the study will occur. • Removal of requirement to reduce ESA dose if Week -8 Hgb is >11.5 g/dL (study rationale and inclusion criteria). • Additional guidance added to iron management criteria • New exploratory objective to compare the effect of daprodustat to rhEPO on delayed graft function (DGF) after deceased donor kidney transplantation added.		
2015N226659_03	2016-OCT-12	Amendment No. 2
• Changes from country-specific Amendment 1 applied to global amendment • Country-specific requirements for France and Czech Republic added. • Section and 6 relating to darbepoetin alfa pre-filled syringe incidents, malfunctions and user errors. Section deleted as darbepoetin alfa pre-filled syringes are not subject to device reporting requirements. • Time and events Table 7 'Schedule of Assessments Year 1 to End of Study' modified. Main changes include new timepoints at Run-in (Week -4) and Week 2 for collection of information related to iron therapy; new timepoint at Week 52 for Kt/V_{urea} assessment; and transfusions and kidney transplant added to prompt completion of page in eCRF. • Time and Events Table 8 'Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies' modified. Main changes are changes to the ABPM sub-study assessments including prompts for the end of the 44hr ABPM assessments and prompts for recording the times the subject awakens and goes to sleep during this 44 hour ABPM period. • Time and events Table 9 'Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment' modified. Main changes include IRT system call removed at all visits except Early Treatment Discontinuation Visit and End of Study Visit; new timepoints for collection of information related to iron therapy, transfusions; and kidney transplant added to prompt completion of page in eCRF.		

- Text added to clarify those randomized to rhEPO who transition from HD to PD will change from epoetin alfa to darbepoetin alfa.
- Text relating to the timing of dialysis in relation to the study visit has been amended. The original text 'For subjects receiving PD or home HD >3x/week, study visits must occur within 48 hours of their last dialysis session' was inaccurate as PD is a daily treatment.
- For the negatively adjudicated events in 200807, the reporting process has been updated and the investigator-reported term (not the adjudicator-reported term) will be used.
- In addition to allowing a historical (last 6 months) kidney ultrasound to be used to assess entry criteria, a provision was added for a more sensitive imaging study (e.g., MRI, CT) to be used to assess entry criteria.
- Other changes include minor wording changes for clarity, updating of section numbering and cross referencing, formatting changes and administrative changes.

2015N226659_05	2017-OCT-05	Amendment No. 3

- Added retest values for Hgb and TSAT to determine eligibility at Week -8.
- 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.
- Provided guidance for those receiving HD two times a week who are randomized to the epoetin alfa arm and require three times a week epoetin alfa dosing.
- 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 new darbepoetin alfa dose strengths (not available in all countries).
- Added direction regarding randomized treatment and study continuation for subjects who will be away from the research site for an extended period of time.
- Clarified timeframe for iron management criteria.
- Clarified "frequency of dialysis" inclusion criterion and valid study visit days by dialysis type.
- Clarified baseline dose for the purposes of the rescue algorithm for subjects switching from HD to PD who are randomized to rhEPO.
- Shortened visit window for the Week 2 and 4 visits and clarified visit window for Week -4 and Day 1 visits.
- Modified Time and Events Table 7 'Schedule of Assessments Year 1 to End of Study'. Main changes include addition of Informed Consent activity; revised footnotes to remove Kt/V and URR measurement for daily HHD and allowance of extended timing to do Day 1 ECG and to do ultrasound and/or additional testing; more clarity around randomized treatment dispensing and compliance, including provisions for deferring dose changes till the next HD treatment; removed capture of rescue medications from unscheduled and early termination visits as rescue evaluation is triggered at scheduled visits; added footnote to clarify biomarkers will be stored for future analyses except if not permitted by IRB/EC or refused by subject;

addition of Argentina only pregnancy requirement; and removal of footnote at Week -4 visit for only collecting SAEs related to study participation or a GSK product as it did not apply.

- Modified Time and Events Table 8 'Schedule for Assessments for Patient Reported Outcomes, Genetics and Sub-studies' modified to add healthcare resource utilization data collection, to streamline ABPM assessments and to add timing for informed consent and additional eligible collection visits for PK sub-study.
- Modified Time and Events Table 9 "Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment" to remove capture of rescue medications (rescue evaluation is triggered at on-treatment scheduled visits), to add healthcare resource utilization data collection, and to complete ABPM assessments.
- Added direction to see CEC Site Manual for full scope of reporting requirements.
- Add clarifications for PD subjects as to how weight, blood pressure, and laboratory assessments are to be done.
- Clarified timing of assessments relative to dialysis for SBP, DBP, HR and laboratory assessments.
- Added reminder for the ordering of assessments for blood pressure and that the over-read of the Day 1 ECG is required to confirm eligibility.
- Updated PRO section to add healthcare resource utilization data being collected for completeness and updated endpoint labels for EQ-5D-5L & EQ-VAS.
- Revised statistical section to change from two-sided testing at the 5% level to one-sided testing at the 2.5% level; correct the comparator for the Null and Alternative hypotheses; to change significance levels to p-values; to add a more complete description of the adjustments to statistical model; to update hyporesponder analyses; and to add additional text regarding the interim analysis process.
- Added exploratory endpoints around Hgb variability, iron parameters, transfusions, and dose adjustment scheme.
- Edited Risk Assessment information to align with version 8 of the Investigator's Brochure.
- Updated FSH level to confirm menopause.
- Provision for possible adjustment to the Dose Adjustment Algorithm triggers for Hgb values 7.5 g/dL to <9.5 g//dL based on the review of blinded instream aggregate Hgb data.
- Changes to ABPM sub-study to add atrial fibrillation/flutter screening, remove home BP monitoring, change from 44- to 24-hour APBM, change in time-point for assessment (from Week 28 to Week 16), and adjustments to objectives, endpoints and analysis.
- Clarified additional inclusion and added additional eligible visits to collect PK samples in PK sub-studies.
- Other changes include spelling corrections or minor wording changes for clarity, formatting changes, a missing reference (epoetin alfa IV:SC conversion), and administrative changes.

2015N226659_07	30-JUL-2020	Amendment No. 4
• Revised MACE NI margin in order to align the NI margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO. • Revised target MACE as a result of the change to the non-inferiority margin. • Updated the analysis of the hemoglobin co-primary endpoint based on FDA feedback. • Updated terminology (i.e., use of 'supportive') to be consistent with ICH-E9 addendum. • Multiplicity adjustment strategy updated from Hommel to Holm-Bonferroni based on FDA feedback. • Added AESI of worsening of hypertension to footnote (included in IB, version 10). • Edited Risk Assessment information to include worsening of hypertension. • Updated pregnancy reporting timelines to align with revised Sponsor timings.		

PPD

From: PPD
Sent: Thursday, July 30, 2020 6:25 PM
To: PPD
Subject: FW: 200807-sponsign

From: Alex Cobitz PPD
Sent: Thursday, July 30, 2020 8:21 AM
To: PPD
Subject: RE: 200807-sponsign

PPD ,

I approve the protocol amendment.

Alex

From: PPD
Sent: Thursday, July 30, 2020 6:55 AM
To: Alex Cobitz PPD
Subject: 200807-sponsign

Dear Alex,

To approve the clinical protocol indicated below, reply to this email and state your approval.

PROTOCOL NUMBER: 200807

DOCUMENT IDENTIFIER: 2015N226659_07

AMENDMENT NUMBER: 04

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

Name of Sponsor Signatory: Alexander R. Cobitz, M.D., PhD

Title of Sponsor Signatory: Clinical Development Lead

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

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

Sponsor Legal Registered Address:

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

PPD is the contract research organization for this study.

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

IND Number: 101,291

EudraCT: 2016-000541-31

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200807

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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 200807

This Phase 3 study will evaluate the safety and efficacy of daprodustat (GSK1278863) compared to recombinant human erythropoietin (rhEPO) in the treatment of anemia associated with chronic kidney disease (CKD) in subjects on dialysis.

Primary Objective(s)/Endpoint(s)

Objectives	Endpoints
Co-primary (tested in parallel for non-inferiority)	
• To compare daprodustat to rhEPO for cardiovascular (CV) safety (non-inferiority)	• Time to first occurrence of **adjudicated** major adverse cardiovascular event (MACE) [composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke]
• To compare daprodustat to rhEPO for hemoglobin (Hgb) efficacy (non-inferiority)	• Mean change in Hgb between baseline and evaluation period (EP, mean over Weeks 28 to 52)

Overall Design

- This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center, event-driven study in dialysis subjects with anemia associated with CKD who are currently treated with erythropoiesis-stimulating agents (ESAs[1]).
- This study will comprise four study periods: a 4-week screening period, a 4-week placebo run-in period, a treatment period and a follow-up period. Prior ESA therapy continues during the screening and run-in periods.
- The total duration of the study is dependent upon the accumulation of 664 adjudicated first MACE (i.e., it is event-driven) unless review of interim data by the Independent Data Monitoring Committee (IDMC) recommends bringing the study to an earlier close.
- Subjects will be stratified by dialysis type, by region, and by participation in the ambulatory blood pressure monitoring (ABPM) sub-study.
- Following stratification, subjects will be randomized 1:1 to receive oral daprodustat or rhEPO [intravenous (IV) epoetin alfa or subcutaneous (SC) darbepoetin alfa].
- Both treatment arms (daprodustat and rhEPO) will follow a protocol-specified randomized treatment dose adjustment algorithm to achieve and/or maintain Hgb within the target range of 10-11g/dL. Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both randomized treatment arms.
- To ensure subjects remain iron replete and to minimize the potential for iron overload during the study, the investigator will follow the iron management criteria from randomization through the end of the study treatment period.

[1] ESAs refer to any rhEPO or methoxy PEG-epoetin beta.

- 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.
- GSK will provide randomized treatment: daprodustat or rhEPO (epoetin alfa or darbepoetin alfa).

Type and Number of Subjects

- This study will randomize approximately 3000 dialysis subjects (1500 per treatment arm) with anemia associated with CKD currently receiving an ESA and with a baseline HemoCue Hgb 8-11.5 g/dL.
- Subjects may be on hemodialysis (HD) or peritoneal dialysis (PD). PD subjects will be restricted to no more than 15% of the overall study population.

Analysis

The study's co-primary endpoints will each be tested for non-inferiority using a one-sided 2.5% significance level and the relevant confidence bound from a two-sided 95% confidence interval (CI) (upper bound for MACE and lower bound for the Hgb co-primary endpoint).

For CV safety, the primary question is whether daprodustat is non-inferior to rhEPO for adjudicated MACE. An Intent-to-Treat (ITT) analysis of time to the first occurrence of adjudicated MACE using a margin of 1.25 and a Cox Proportional Hazards regression model adjusting for treatment and prognostic randomization stratification factors (dialysis type and region), will be used.

For Hgb efficacy, the primary question is whether daprodustat is non-inferior to rhEPO for change from baseline in central laboratory Hgb. 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. An analysis of the ITT Population and an analysis of covariance (ANCOVA) model will be used. The model will include prognostic randomization stratification factors (dialysis type and region), and factors for baseline Hgb and treatment.

Non-inferiority needs to be met for both co-primary endpoints for the study to be considered successful.

2. INTRODUCTION

2.1. Brief Background

Daprodustat (GSK1278863) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) currently being investigated as a treatment for anemia associated with CKD in both dialysis and non-dialysis (ND) subjects, with adequate safety and efficacy having been demonstrated in clinical trials up to 24 weeks' duration. Both pre-clinical and clinical data show that daprodustat stimulates erythropoietin (EPO) production resulting in increased erythropoiesis and elevation in Hgb concentrations. These increases in Hgb are achieved with peak plasma EPO exposures substantially lower than those observed with rhEPO. Data from completed clinical and preclinical studies are provided in the current 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

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

A Phase 2B clinical trial 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. Data from completed clinical studies are provided in the current IB and IB supplement(s) (if applicable).

This Phase 3 study in dialysis subjects with anemia associated with CKD will evaluate the safety and efficacy of daprodustat compared to rhEPO, the current standard of care, as co-primary endpoints, following switch from ESAs. Both co-primary endpoints must meet non-inferiority of daprodustat to rhEPO for the study to be successful and for analyses to progress to testing principal secondary endpoints. Data from this trial are intended to support the use of daprodustat for the treatment of anemia associated with CKD in patients on dialysis.

3. OBJECTIVE(S) AND ENDPOINT(S)

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

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

• To compare daprodustat to rhEPO on the use of intravenous (IV) iron	• Average monthly IV iron dose (mg)/subject to Week 52
Safety	
• To compare the safety and tolerability of daprodustat to rhEPO	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest[1] • Reasons for discontinuation of randomized treatment • Absolute values and changes from baseline in laboratory parameters, BP and heart rate (HR)

1. Defined as thrombosis and/or tissue ischemia secondary to excessive erythropoiesis; worsening of hypertension;cardiomyopathy; pulmonary artery hypertension; cancer-related mortality and tumor progression and recurrence; esophageal and gastric erosions; proliferative retinopathy, macular edema, choroidal neovascularization; and exacerbation of rheumatoid arthritis

Additional 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, event-driven study in dialysis subjects with anemia associated with CKD who are currently treated with ESAs[2].

[2] ESAs refer to any rhEPO or methoxy PEG-epoetin beta.

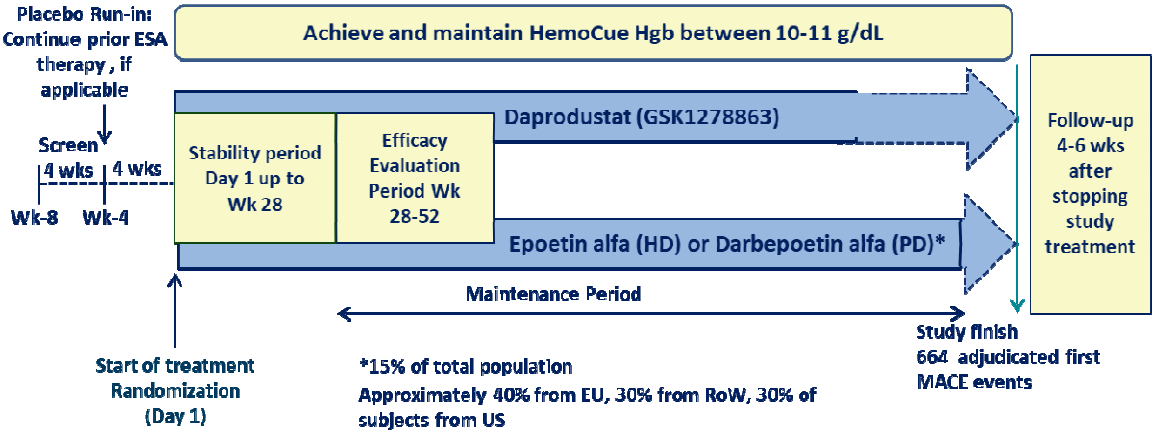
- This study will comprise four study periods (Figure 1): a 4-week screening period, a 4-week placebo run-in period, a treatment period and a follow-up period. Prior ESA therapy continues during the screening and run-in periods.
- The treatment period consists of :
  1. The stabilization period, defined as the period from Day 1 to Week 28 during which randomized treatment will be dose titrated to achieve the appropriate Hgb target
  2. The maintenance period, defined as the period from the end of the stabilization period (Week 28) to the end of treatment (variable per subject), to assess long term safety and efficacy.
     - The efficacy evaluation period (EP) is defined as the period from Week 28 to Week 52 during which Hgb efficacy will primarily be assessed.
- The total duration of the study is dependent upon the accumulation of 664 adjudicated first MACE (i.e., it is event-driven) unless review of interim data by the IDMC recommends bringing the study to an earlier close.
- All subjects will remain in the study (including subjects receiving kidney transplant), regardless of whether they continue with randomized treatment (unless consent for any further follow up is withdrawn), until the target number of first adjudicated MACE has occurred. At that point, the sponsor will notify investigators to have subjects come in for an End of Study visit within a pre-defined time period.
- The end of the study will occur after the accumulation of 664 adjudicated first MACE and the last subject has completed their last required study visit (Section 7.1).
- Subjects will be stratified by dialysis type [HD* or PD], by region (see Appendix 3), and by participation in the ABPM sub-study. Dialysis type and region are stratification factors considered to be potentially prognostically important, i.e., predictive of study endpoints while participation in the ABPM sub-study is an administrative stratification factor intended solely to ensure a similar number of sub-study subjects in each of the two randomized groups.

  ** HD group also includes hemodiafiltration (HDF) or hemofiltration (HF).*

- Following stratification, subjects will be randomized 1:1 to receive oral daprodustat or rhEPO (IV epoetin alfa for HD subjects and SC darbepoetin alfa for PD subjects). A central randomization approach will be used to protect against potential selection bias due to the open-label design. The sponsor is blinded to treatment assignment in the main study and ABPM sub-study.
- Both treatment arms (daprodustat and rhEPO) will follow a protocol-specified randomized treatment dose adjustment algorithm to achieve and/or maintain Hgb within the target range of 10-11 g/dL (Section 6.3.3). Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both randomized treatment arms.

- To ensure subjects remain iron replete and to minimize the potential for iron overload during the study, the investigator will follow the iron management criteria (Section 6.11.1) from randomization through the end of the study treatment period.
- 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 (Section 6.12).
- An overview of the study design is provided in Figure 1.

Figure 1 Study Schematic



- This study will include the following sub-studies:
  - ABPM sub-study (Appendix 12)
  - Pharmacokinetic (PK) sub-study (Appendix 13)
- An external independent Clinical Events Committee will conduct blinded adjudication of all events reported during this study that may meet the definition of the co-primary safety endpoint of MACE and additional endpoints as outlined in Section 7.4.1 and Section 10.8.2.
- An external IDMC will monitor the safety and efficacy data from the study (Section 10.8.1).

4.2. Type and Number of Subjects

- This study will randomize approximately 3000 dialysis subjects (1500 per treatment arm) with anemia associated with CKD currently receiving an ESA and with a baseline HemoCue Hgb 8-11.5 g/dL (Section 5.1).
- Subjects may be on HD or PD. PD subjects will be restricted to no more than 15% of the overall study population.

4.3. Design Rationale

This study includes both a 4 week screening and a 4 week placebo run-in period prior to randomization (Day 1). The screening period permits eligibility based on laboratory

assessments to be confirmed, while the run-in period will be used to establish compliance with placebo and study procedures in an attempt to minimize withdrawn consent post-randomization.

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 best opportunity for subjects to be titrated to their optimal dose of randomized treatment prior to the efficacy EP (Weeks 28 to 52). A percentage of subjects may still need dose titration during the EP. After Week 52, minimal dose changes may be required to maintain Hgb within the target range.

The selection of the rhEPO control (epoetin alfa for HD subjects; darbepoetin alfa for PD subjects) is based on clinical practice in the majority of participating countries.

This study will be open-label (sponsor blind) because it would be complex to double-blind due to the differing number of dose steps between randomized treatments, leading to potential dosing errors. Additionally, it is potentially unethical to blind the different route of administration of randomized treatment.

4.4. Dose Justification

Starting doses, dose steps, and elements of the dose adjustment scheme are provided in Section 6.3 and Appendix 6.

4.4.1. Daprodustat

Daprodustat starting doses were selected to reach the target Hgb concentration after approximately one red blood cell (RBC) lifespan of treatment (almost 3 months, pharmacodynamic steady-state), without the need for any individual dose adjustments. 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.

The daprodustat starting doses and dose steps (including the highest dose level, 24 mg) selected for this study are consistent with those utilized in the completed 6-month Phase 2B studies, and were 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. Simulations showed the effect of body-weight was not clinically important for dosing, but the relationship between prior ESA dose and response was used to determine starting doses of daprodustat relative to a subject's prior ESA dose.

Starting doses of 4, 6, 8 and 12 mg were selected and are estimated to maintain Hgb levels observed with their prior ESA therapy.

4.4.2. Randomized Treatment Dose Adjustment Scheme

A randomized treatment (daprodustat and rhEPO) 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 (Appendix 6).

4.5. Benefit:Risk Assessment

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

4.5.1. Risk Assessment

The potential risks of clinical significance including AEs of special interest (Section 7.4.4), and the mitigation strategies for this protocol taking into account the results of completed clinical and nonclinical studies with daprodustat, are outlined in Appendix 4. In addition to the mitigation strategies outlined, an 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. CCI [redacted] CCI [redacted] CCI [redacted]. Treatment of anemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated increases in EPO exposure with rhEPO [Szczech, 2008]; CCI [redacted]

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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 randomized subjects (See Appendix 4). 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 regarding warnings, precautions, contraindications, AEs, and other pertinent information on the randomized treatment is provided in the IB, IB

supplement(s) (if applicable), product labels for epoetin alfa and 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 (Week -8)** and **randomization (Day 1)** unless otherwise specified.

1. **Age (confirm at screening only):** 18 to 99 years of age (inclusive).
2. **ESAs**: Use of any approved ESA for at least the 6 weeks prior to screening and between screening and randomization.
3. **Hgb concentration measured by HemoCue (range is inclusive):**

	Hgb Range
Week -8	• Hgb 8 to 12 g/dL[1] (5 to 7.4 mmol/L). • If Hgb is 12.1 to 12.4 g/dL[2] (7.5-7.7 mmol/L), up to two retests are allowed; the retest value must be between 8 to 12 g/dL (5 to 7.4 mmol/L).
Day 1	• Hgb 8 to 11 g/dL (5 to 6.8 mmol/L) **and** receiving at least the minimum ESA dose[3]. • Hgb >11 g/dL to 11.5 g/dL (6.8 mmol/L to 7.1 mmol/L) **and** receiving greater than the minimum ESA dose[3].

1. Conversion from g/dL to g/L is 1:10, e.g., Hgb of 8 to 10 g/dL is equivalent to 80-100g/L.
2. The first retest will use the original Week -8 blood sample. If this value is >12 g/dL, one additional retest can be performed using a new blood sample on the study visit day. The **final** retest value is entered into the IRT system. For in-center HD, retests will be pre-dialysis, in between dialysis sessions for HHD subjects at the study visits, and at the study visits for PD subjects, as per standard of care.
3. **Minimum ESA dose:** epoetins (including biosimilars): 1500 units (U)/week intravenous (IV) or 1000 U/week SC; darbepoetin alfa: 20 μg/4 weeks SC/IV; methoxy PEG-epoetin: 30 μg/month SC/IV

4. **Dialysis:** On dialysis >90 days prior to screening and continuing on the same mode of dialysis from screening (Week -8) through to randomization (Day 1).
5. **Frequency of Dialysis:**
   a. HD (in-center): ≥2 times/week
   b. PD: ≥5 times/week
   c. Home HD: ≥2 times/week
6. **Compliance with placebo [randomization (Day 1) only]:** ≥80% and ≤120% compliance with placebo during run-in period (NOTE: this is in addition to ESA treatment).

7. **Informed consent (screening only):** capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

   Note: The country-specific requirements for France ONLY for the informed consent process are provided in Appendix 14 (see Section 12.14.1, Item 3 for details).

8. **Other study eligibility criteria considerations**: The country-specific requirements for France ONLY for inclusion in this study are provided in Appendix 14 (see Section 12.14.1 Item 1 for details).

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply at **screening (Week -8)** or **randomization (Day 1)**, unless otherwise specified.

CKD related criteria

1. **Kidney transplant:** Planned living-related or living-unrelated kidney transplant within 52 weeks after study start (Day 1).

Anemia related criteria

2. **Ferritin (screening only):** ≤100 ng/mL (≤100 μg/L).
3. **Transferrin saturation (TSAT) (screening only):** ≤20%. If TSAT is 18-20%, then a retest using a new blood sample can be obtained within 7 days of the final laboratory report; the final retest value must be >20% to confirm eligibility.
4. **Aplasias:** History of bone marrow aplasia or pure red cell aplasia.
5. **Other causes of anemia:** Untreated pernicious anemia, thalassemia major, sickle cell disease or myelodysplastic syndrome.
6. **Gastrointestinal (GI) bleeding:** Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding ≤4 weeks prior to screening through to randomization (Day 1).

CV disease-related criteria

7. **MI or acute coronary syndrome:** ≤4 weeks prior to screening through to randomization (Day 1).
8. **Stroke or transient ischemic attack:** ≤4 weeks prior to screening through to randomization (Day 1).
9. **Heart failure (HF):** Chronic Class IV HF, as defined by the New York Heart Association (NYHA) functional classification system.
10. **Current uncontrolled hypertension:** Current uncontrolled hypertension as determined by the investigator that would contraindicate the use of rhEPO.
11. **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

12. **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.
13. **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 (e.g. Bosniak Category II F, III or IV) >3cm. Note: The only exception is localized squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥4 weeks prior to screening.

Concomitant medication and other randomized treatment-related criteria

14. **Severe allergic reactions:** History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (refer to daprodustat IB), or epoetin alfa or darbepoetin alfa (refer to product labeling).
15. **Drugs and supplements:** Use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) or strong inducers of CYP2C8 (e.g., rifampin/rifampicin).
16. **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).
17. **Prior treatment with daprodustat:** Any prior treatment with daprodustat for treatment duration of >30 days.

General health-related criteria

18. **Females ONLY:** Subject is pregnant [as confirmed by a positive serum human chorionic gonadotrophin (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 listed in the List of Highly Effective Methods for Avoiding Pregnancy in Appendix 5.

    Note: See Section 12.14.2 for the country-specific requirements for the Czech Republic ONLY relating to acceptable contraceptive methods during participation in this study.
19. **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/ Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized. A minimum set of information must be collected from subjects that fail screening including Demography, Screen Failure details, Eligibility Criteria, and SAEs (Section 7.4.3.4).

Subjects that fail screening are eligible to be rescreened up to three additional times 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. The investigator (dependent on local regulations) should obtain the name and phone number of a relative or friend to assist in contacting 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
- Meets criterion to receive rescue (Section 6.12)
- 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 squamous cell or basal cell carcinoma of the skin.
- Need for more than 14 days use of prohibited medication (Section 6.10.2)

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 reapproached 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 study visits through the End of Study visit, according to the study visit schedule, unless consent is actively withdrawn. Complete details are provided in the Time and Events Table (Section 7.1).

- Early Treatment Discontinuation visit: This visit should occur within 2 weeks of stopping randomized treatment.
- Remaining in-clinic visits*:
  - Day 1 through Week 52: Study visits at Weeks 4, 16, 28, 40 and 52.
  - Week 52 through end of study: Study visits every 12 weeks.
  - End of Study visit: as defined by the sponsor within a pre-defined time period.

  *Phone visit acceptable in exceptional circumstances.

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

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 or study procedures, but states an expectation that follow up information will always be required. Subjects 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 expresses a wish to withdraw 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 contacts 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 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 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 Study visit with the following exception: subjects who die while on study are also considered as having completed the study.

6. PLACEBO RUN-IN AND RANDOMIZED TREATMENT

6.1. Placebo Run-in and Randomized Treatment

Prior to randomization, oral placebo tablets will be dispensed at Week -4 with instructions to take one tablet daily through the run-in period.

The term 'randomized treatment' is used throughout the protocol to describe either study treatment (i.e., daprodustat, darbepoetin alfa or epoetin alfa) received by the subject during the treatment period as per the protocol design. Randomized treatment will be provided by GSK[3].

During the treatment period, iron therapy (supplied locally) will be administered as per the iron management criteria (Section 6.11.1).

[3] 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.

Daprodustat will be supplied as film coated tablets for oral administration containing 1, 2, 4, 6, 8, and 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. Subjects are to take the daprodustat tablet(s) daily with water, and these tablets can be taken without regard to food.

Table 1 Description of Daprodustat and Placebo Tablets

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

GSK will provide randomized treatment for the rhEPO control arm:

- Epoetin alfa using vials for IV administration. Doses from 1500 to 60000 U will be administered using the following vial strengths: 2000 U/ml, 3000 U/ml, 4000 U/ml and 10000 U/ml.

- Darbepoetin alfa as prefilled syringes (PFS) for SC or IV (for subjects transitioning to HD) injection. Doses from 20 µg to 400 µg will be administered using the strengths below (Table 2).

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.

See Section 6.3.2 for rhEPO dose steps and dosing frequency details. Additional details on rhEPO strengths to deliver the total dose are captured in the SRM.

6.2. Randomized Treatment Assignment

Subjects will be stratified as outlined in Section 4.1 and randomized 1:1 to receive oral daprodustat or rhEPO (IV epoetin alfa or SC darbepoetin alfa).

Subjects will discontinue their ESA therapy prior to randomization so that the randomization date (Day 1) should coincide, as closely as possible, with the date of next scheduled ESA administration. Examples of switching are provided in the SRM.

6.3. Randomized Treatment Starting Dose and Dose Adjustment

6.3.1. Daprodustat Dosing Information

Daprodustat Starting Dose:

The starting dose of daprodustat will be assigned based on prior ESA dose at randomization (Day 1) (Table 3).

Table 3 Daprodustat Starting Dose

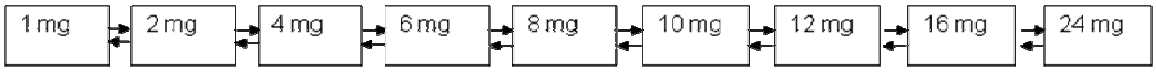
ESA Dose at Randomization(Day 1)			Daprodustat Starting Dose
epoetins (incl biosimilars) (U/week IV) [1]	darbepoetin (μg/4week SC/IV) [2]	methoxy PEG-epoetin beta (μg/month SC/IV) [3, 4]	(mg, once daily)
1500 to 2000	20 to 30	30 to 40	4
>2000 to <10000	>30-150	>40 to 180	6
≥10000 to <20000	>150-300	>180 to 360	8
≥20000	>300	>360	12

PEG=polyethylene glycol

1. Standardized rhEPO IV dose (U/week) = 161/113 * (epoetin SC dose (units)) / (frequency) [Beserab, 2002]
2. Conversion of 250 U:1 μg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008]
3. Conversion of 1:1.2 μg (darbepoetin alfa:methoxy PEG-epoetin beta)) utilized and rounded to the nearest available dose strength [Choi, 2013]
4. Conversion of 208 U:1 μg (epoetin IV: methoxy PEG-epoetin beta)

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. 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.



6.3.2. rhEPO Dosing Information

rhEPO *Starting Dose*:

The starting dose for subjects receiving rhEPO is as follows:

- For subjects with a baseline (Day 1) Hgb ≤11 g/dL

- For subjects already on epoetin alfa (HD subjects) or darbepoetin alfa (PD subjects), the starting dose will be the same as their currently scheduled dose, rounded to the nearest study dose.
- For subjects receiving other types of ESAs, the starting dose will be an IV epoetin alfa (HD subjects) or SC darbepoetin alfa (PD subjects) equivalent dose, rounded to the nearest study dose.

- For subjects with a baseline (Day 1) Hgb >11 g/dL and ≤11.5 g/dL
  - The starting dose of IV epoetin alfa (HD subjects) or SC darbepoetin alfa (PD subjects) will be reduced to the next lowest starting dose with the aim of maintaining Hgb within the range of 10-11 g/dL.

rhEPO Dose Steps:

Dose-steps of rhEPO are pre-defined in this study (Table 4 and Table 5). The IV epoetin alfa dose steps consist of stepwise increase or decrease in weekly dose of 20 to 33% for most steps, except when weekly doses of 3000 U or when weekly doses are >21000 U per week when further increases are within the 10 to 15% range. The darbepoetin alfa dose adjustment increases and decreases will be in similar steps as compared to epoetin alfa, generally within the 20 to 33% range with a few increases of 50% based on available dose strengths. In some cases, a partial amount of a darbepoetin alfa pre-filled syringe (PFS) will be used to deliver the total 4-weekly dose.

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.

For subjects who are on HD two times a week and are randomized to the epoetin alfa arm and require three times a week epoetin alfa dosing, the weekly dose should be split as close to equally, using the study-allocated dose vials of epoetin alfa, across the two dialysis treatments.

Table 4 Epoetin Alfa Dose Steps

Total Weekly Dose	Dose and Frequency
1500	1500 U once a week
2000	2000 U once a week
3000	3000 U once a week
4000	4000 U once a week
5000	5000 U once a week
6000	6000 U once a week
8000	8000 U once a week
10000	10000 U once a week
12000	4000 U three times a week
15000	5000 U three times a week
18000	6000 U three times a week
21000	7000 U three times a week
24000	8000 U three times a week
27000	9000 U three times a week
30000	10000 U three times a week
36000	12000 U three times a week
42000	14000 U three times a week
48000	16000 U three times a week
60000	20000 U three times a week

Table 5 Darbepoetin Alfa Dose Steps

Total 4-Weekly Dose	PFS Dose and Frequency
20 µg	20 µg every 4 weeks
30 µg	30 µg every 4 weeks
40 µg	40 µg every 4 weeks
60 µg	60 µg every 4 weeks
80 µg	80 µg every 4 weeks
100 µg	100 µg every 4 weeks
150 µg	150 µg every 4 weeks
200 µg	100 µg every 2 weeks
300 µg	150 µg every 2 weeks
400 µg	100 µg once a week

6.3.3. Daprodustat and rhEPO Dose Adjustment Algorithm

The protocol-specified randomized treatment (daprodustat or rhEPO) dose adjustment algorithm is provided in Appendix 6. Dose adjustments (i.e., increase, decrease, maintain, or withheld if ≥12 g/dL) will be made programmatically for both the daprodustat and rhEPO arms by the IRT system to maintain Hgb concentrations within the range of 10-11 g/dL based on the HemoCue Hgb value measured at least every 4

weeks (Day 1 through Week 52) or at least every 12 weeks (post-Week 52 through end of treatment) disclosed to the IRT system by the investigator.

From Week 52 onwards, additional study visits to check Hgb and dispense randomized treatment (where directed by the IRT system) will be required under the circumstances outlined in Appendix 6.

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 6 based on the review of blinded instream aggregate Hgb data.

6.3.4. Randomized Treatment Temporary Interruption

Every effort must be made to continue randomized treatment and to complete study visits, where able; however, sites should contact PPD Remote Site Monitor-Local 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.
- HD or PD subjects receiving oral daprodustat or PD subjects receiving SC darbepoetin alfa who cannot return to the site for a period >5 weeks
- HD subjects receiving IV rhEPO who cannot return to the site in time for the next dosing interval.

In exceptional circumstances, local 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.

6.3.5. Randomized Treatment Discontinuation

The sponsor will inform investigators when they should have subjects come in for an End of Study visit based on the projected occurrence of 664 first MACE. Subjects will stop taking randomized treatment the day of the End of Study visit.

For those subjects who permanently discontinue randomized treatment, see Section 5.5.1 for study visit details.

Anemia therapy may recommence, as required, once randomized treatment has been discontinued.

6.4. Blinding

This is an open-label study; however, the sponsor is blinded to treatment assignment for both the main study and ABPM sub-study. Randomized treatment will have the dose strength on the label. 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.

6.5. Packaging and 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.

6.6. Preparation/Handling/Storage/Accountability

No special preparation of placebo run-in or randomized treatment is required.

Only subjects enrolled in the study may receive placebo run-in and subsequently, randomized treatment and only authorized site staff may supply placebo run-in and randomized treatment. All placebo run-in and randomized treatment 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 placebo run-in and randomized treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

Further guidance and information for final disposition of unused placebo run-in and randomized treatment is provided in the SRM.

Under normal conditions of handling and administration, placebo run-in and randomized treatment are 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.

6.7. Compliance with Randomized Treatment Administration

Randomized subjects, who administer randomized treatment (daprodustat or rhEPO [darbepoetin alfa or epoetin alfa]) 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.

For subjects randomized to rhEPO (darbepoetin alfa or epoetin alfa) who have randomized treatment administered in the clinic, the details of each administered rhEPO dose 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/reductions, will be recorded in the eCRF.

6.8. 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 and these are not effective methods 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 CV events, increased HR and hematologic abnormalities.

Consult the approved product label for information on overdose for darbepoetin alfa and epoetin alfa.

6.9. 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.

6.10. Concomitant Medications and Non-Drug Therapies

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 or termination) will be recorded for certain medications at each visit (e.g., iron and anti-hypertensive medications).

6.10.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.10.2, 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 (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should subsequently be monitored every 4 weeks for the following 12 weeks.

6.10.2. Prohibited Medications and Non-Drug Therapies

Use of any of the following prescription drugs from screening (Week -8) 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)

No other investigational agents or devices are permitted from study entry through completion of the study, with the exception of the randomized treatment administered for this study.

6.11. Standard of Care

During the study (from screening), investigators are expected to monitor the subject's overall clinical status to ensure standards of care are met to enable consistency of practice with Kidney Disease Improving Global Outcomes (KDIGO) guidelines or local equivalent (e.g., phosphate and albumin).

For this study, specific iron management criteria and a dose adjustment algorithm for randomized treatment will apply. These were developed to reflect global clinical practice.

6.11.1. 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 10.8.4) will monitor blinded subject iron data in an ongoing fashion to ensure compliance.

6.12. 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 6.

This rescue algorithm **does not** apply to subjects with a low Hgb as a result of an acute or subacute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or vascular access). 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 6 Rescue Algorithm for Anemia Management

Evaluate Subject for Rescue if: HemoCue Hgb remains <9 g/dL (at a scheduled study visit, Week 4 onwards) despite three[1] consecutive dose increases above the starting[2] or post-rescue[3] dose (where HemoCue Hgb is <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 <u>one or more</u> 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,** - If HemoCue Hgb remains <9 g/dL despite initial intervention based on the average of two HemoCue Hgb values[4] ***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, epoetin alfa 42000 U per week, or darbepoetin alfa 200 µg over 4 weeks; one dose increase if starting/post-rescue dose is daprodustat 16 mg, epoetin alfa 48000 U per week, or darbepoetin alfa 300 µg over 4 weeks; and no prior dose increase if starting/post-rescue dose is daprodustat 24 mg, epoetin alfa 60000 U per week, or darbepoetin alfa 400 µg over 4 weeks (top dose).
2. For subjects who have switched from HD to PD who are randomized to rhEPO, the baseline dose for the purposes of the rescue algorithm is the new darbepoetin alfa dose.
3. For subjects who previously were 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.
4. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample); take average of 2 values.

6.13. Subjects Changing Dialysis Modality

Subjects changing dialysis modality should not be withdrawn from the study, and will continue in the same randomized treatment arm (daprodustat or rhEPO) they were originally assigned. Those subjects randomized to rhEPO who transition from PD to HD (in-center or home HD) will continue on darbepoetin alfa. However, subjects randomized to rhEPO who transition from HD to PD will switch from epoetin alfa to darbepoetin alfa at their next study visit from Week 4 onwards. If this occurs from Week 52 onward, additional visits are required as outlined in Appendix 6.

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.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

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

- For subjects on 3-5x/week HD, the designated study visit must not occur on the first dialysis session of the week, i.e., immediately following the longest interval between HD sessions. 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 study visit must occur on the day of the dialysis session that is closest to the previous 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).

The Week -4 and Day 1 visits should be completed 4 weeks ±1 week after the last visit; however, the total duration of the Screening and Run-In periods (from Week -8 to Day 1) should be 8 weeks ±1 week (i.e., 7-9 weeks).

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 8 onwards is ±1 week. However, during the first 52 weeks, to ensure continuity of randomized treatment, study visits must be no more than 5 weeks apart. In exceptional circumstances, minor changes to visit structure may be permitted after consultation with the PPD Medical Monitor.

Study assessments should preferably be done at dialysis centers; however, in some circumstances (i.e., where the dialysis center and research site are not co-located) 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 Table

Table 7 Schedule of Assessments Year 1 to End of Study

Protocol activity (visits ±1 week, except Weeks 2 and 4 which are ±3 days) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
Informed consent (main study)	X[22]							
IRT system transaction[17]	X	X	X	X	X	X	X	X
Subject reminder, inform site staff of changes in health[1]			X				X	
Check/confirm entry criteria	X		X					
History: medical, hospitalization, transfusion demography, height	X							
Weight (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; at study visits per standard of care for PD) and EDW	X	X	X	X	X	X	X	X
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; at study visits per standard of care for PD) (single readings unless otherwise indicated)	X	X	X (triplicate)	X	X	X	X (triplicate)	X
Kt/V_{urea} [18]			X		X		X	
ECG [2]			X[2]				X	
Ultrasound of kidneys and adrenal glands		X[16]						
Placebo run-in or randomized treatment dispensing (start administration on date treatment dispensed)[19]		X (placebo)	X	X[9]	X	X	X	X[9]
Placebo run-in or randomized treatment compliance[19]			X (placebo)	X[11]	X	X	X	X[11]
Iron therapy, transfusions[3]	X	X	X	X	X	X	X	X
Rescue medication(s) for Initial Intervention[3,4]					X	X	X	
Females only: estradiol and FSH (if required)	X							
FRP only: Serum pregnancy test [5,20]		X	X		X		X	
HemoCue Hgb	X	X	X	X	X	X	X	X
Hematology[6]	X	X	X		X	Hgb only	X	X
Clinical chemistry[6]	X		X		X		X	X

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

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

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

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

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

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

provided the size and cyst category has been reported. If a more sensitive imaging study [e.g., magnetic resonance imaging (MRI), computed tomography (CT)] has been performed within this timeframe and a report is available, this may be used in place of the ultrasound. See Section 7.4.10.

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

Table 8 Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies

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

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

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

Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment

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

Note: see footnotes on next page

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

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

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

7.2. Screening and Critical Baseline Assessments

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

Demography and medical history (including CV medical history/risk factors) will be assessed at screening (Week -8).

Randomization requires a Hgb on Day 1 in the range as defined by ESA use and region (Section 4.1).

Full details of screening (Week -8) and baseline (Day 1) assessments are provided in the Time and Events Table Section 7.1.

7.3. Efficacy

Planned time points for all Hgb efficacy assessments are listed in the Time and Events Table (Section 7.1).

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

Blood samples for measurement of Hgb via HemoCue and also by the central laboratory will be collected as specified in Time and Events Table (Section 7.1).

7.4. Safety

Planned time points for all study safety assessments are listed in the Time and Events Tables (Section 7.1). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

Safety endpoints will include monitoring of safety endpoint events including deaths (Section 7.4.1), other CV events (Section 7.4.2), AEs of special interest (Section 7.4.4), AEs, SAEs and AEs leading to discontinuation of randomized treatment, laboratory parameters, BP and HR.

Pre-specified events leading to permanent discontinuation of randomized treatment are described in Section 5.5. Liver chemistry stopping and follow-up criteria are described in Section 7.4.12 and Appendix 8.

7.4.1. Events Referred to the Clinical Events Committee

Investigators should refer any event suspected to be one of the events below to the Clinical Events Committee for adjudication. See CEC Site Manual for full scope of reporting requirements.

- All-cause mortality (CV and non-CV mortality)
- Non-fatal MI

- Non-fatal stroke
- Hospitalization for HF
- Thromboembolic events (vascular access thrombosis, deep vein thrombosis, pulmonary embolism)

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

Source documentation required to support the adjudication of the events is described in the CEC Site Manual. Recording of potential endpoint events in the eCRF and submission of source documentation will be required.

Positively adjudicated events will be reported separately (Section 7.4.3). Negatively adjudicated events will be reported as AEs or SAEs using the investigator-reported event term.

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 CV AEs and SAEs or any event that may potentially be one of the categories listed:

- Arrhythmias
- Pulmonary hypertension (also an AE of special interest see Section 7.4.4 for further details).
- Valvulopathy
- Revascularization

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

The definitions of an AE or SAE can be found in Appendix 7.

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

For this study, events referred to the Clinical Events Committee (Section 7.4.1) will be subjected to blinded adjudication using pre-specified diagnostic criteria. Positively adjudicated events will be reported separately. Negatively adjudicated events will be reported as AEs or SAEs using the investigator-reported event term.

Events should be reported as an AE or SAE according to the definitions in Appendix 7.

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

- Any SAEs 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 in the subject's eCRF from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs and SAEs will be collected from the start of placebo run-in until the Follow-up visit (or the "End of Study" visit for subjects that discontinue study treatment early) (Section 7.4.3.2), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of placebo run-in but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions Section of the eCRF.
- All SAEs will be recorded in the eCRF and reported to PPD within 24 hours, as indicated in Appendix 7.
- 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 7.

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 endpoint events (as defined in Section 7.4.1), 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 5.5). Further information on follow-up procedures is given in Appendix 7.

7.4.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to PPD of SAEs related to placebo or 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 events that may represent the AEs of special interest listed below (using preferred terms):

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Worsening of hypertension
- Cardiomyopathy
- Pulmonary artery hypertension (see also Section 7.4.2)
- 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 the relevant AE of special interest page of the subject's eCRF.

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 from the start of dosing and until seven days after the last dose.

If a pregnancy is reported then the investigator should inform PPD within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.

7.4.7. Height and Weight

Height and weight will be measured as specified in the Time and Events Table (Section 7.1). Weight will be measured with the subject wearing indoor daytime clothing with no shoes. For in-center HD subjects, weight will be measured pre and post-dialysis. For HHD subjects, weight will be done at study visits between dialysis sessions. For PD subjects, this assessment will be done at study visits, as per standard of care.

EDW will be reported at each study visit as specified in the Time and Events Table (Section 7.1).

7.4.8. Blood Pressure and Heart Rate

Measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR will be taken at the time points specified in the Time and Events Table Section 7.1.

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

For in-center HD subjects, SBP, DBP and HR will be measured pre and post-dialysis. For HHD subjects, these assessments will be done at study visits between dialysis sessions. 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 (e.g., would not apply for post-HD measurement).

7.4.9. Electrocardiogram (ECG)

ECG measurements will be taken at the time points specified in the Time and Events Table (Section 7.1). Full 12-lead ECGs will be recorded with the subject in a supine position. HR, 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 (see Section 5.2) using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility (see Section 5.2). 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, and HR and **before** collection of blood samples for laboratory testing, where applicable (e.g., would not apply if ECG is performed post-HD).

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 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 (see 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 10, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Section 7.1). Laboratory assessments will be done pre-dialysis for in-center HD subjects, in between dialysis sessions for HHD subjects at the study visits, 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 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 10 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]	Potassium (serum)	AST	Albumin (serum)
	Calcium (total and albumin-adjusted)	ALT	Urea (serum)
	Inorganic phosphate	Bilirubin (total and direct/indirect)	
Iron parameters	Iron (serum)	Ferritin	UIBC
	Hepcidin	TIBC	TSAT
Lipid parameters	Total cholesterol	LDL-C (direct)	HDL-C
Other laboratory tests	Serum pregnancy test[2]	FSH[3]	Estradiol[3]
	HemoCue Hgb	HbA1c[4]	hsCRP
	iPTH	Stored sample (blood)	

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; LDL-C, low density lipoprotein-C; HDL-C, high density lipoprotein-C; TIBC, total iron binding capacity

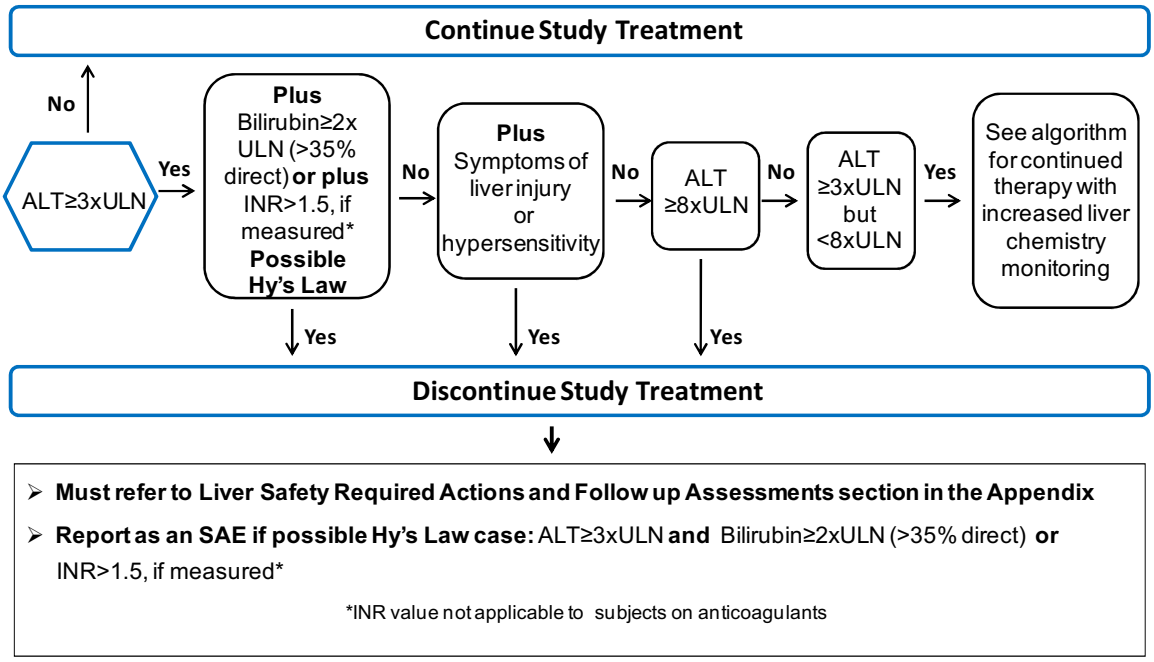
1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 7.4.12 and Appendix 8.
2. For females of reproductive potential only.
3. Screening only. As needed in postmenopausal women where their menopausal status is in doubt (see Inclusion Criteria Section 5.1).
4. Only subjects with diabetes.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within seven 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 sponsor should be notified.

7.4.12. Liver Chemistry Stopping Criteria

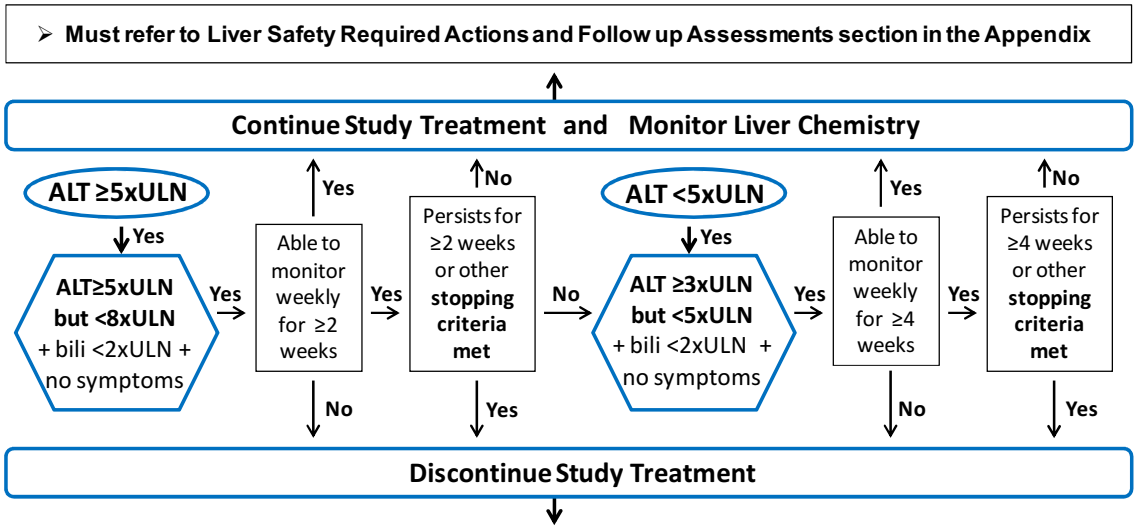
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology [in alignment with the Food and Drug Administration (FDA) premarketing clinical liver safety guidance]. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase 3-4 Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 8.

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



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 8.

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

Refer to Appendix 9 for full guidance.

7.5. Genetics

Information regarding genetic research is included in Appendix 11.

Samples for genetic analysis will be taken at the time points specified in the Time and Events Table (Section 7.1).

7.6. Storage Biomarkers

Blood (serum and plasma) samples will be collected as outlined in the Time and Events Table (Section 7.1) for potential future analysis of biomarkers of CV risk and iron metabolism.

7.7. Patient Reported Outcomes

The patient-reported effect of daprodustat and rhEPO on symptom, health-related quality of life (HR-QoL), and health status (e.g. utility) will be assessed. 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 outpatient visits.

All questionnaires used in this study have been translated, and culturally adapted for use in local country languages and will be administered electronically. Specific instructions on how the subject is to complete the scales and the process for data entry is provided in the SRM. If there are exceptional circumstances whereby the electronic PRO assessments cannot be conducted, the completion of these assessments will be discussed with the sponsor on a case-by-case basis.

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

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

The PGI-S is a 1-item questionnaire designed to assess subject'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 PGI-C is a 1-item questionnaire designed to assess a subject's impression of symptoms 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.

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

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

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

The EQ-5D-5L consists of 2 concepts – the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale (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.

The EQ-5D-5L and EQ VAS will only be completed by subjects in selected countries which require this data as part of their reimbursement assessment process as noted in Appendix 3.

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.
- AE and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK-Drug, 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

The study has two co-primary objectives and endpoints:

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

The co-primary endpoints will each be tested using a one-sided 2.5% significance level and the relevant confidence bound of the two-sided 95% CI (upper bound for MACE and lower bound for the Hgb co-primary endpoint). The type I error rate will be strictly controlled at the one-sided 2.5% level across the co-primary analyses as both non-inferiority tests need to be met for the trial to be considered successful and for statistical analysis to proceed to evaluate MACE superiority and superiority for the principal secondary objectives/endpoints.

9.1. Hypotheses

9.1.1. CV Safety (MACE) Co-Primary Hypothesis

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

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

The non-inferiority margin is pre-defined as the hazard ratio of 1.25; supported by a review of evidence reported in historical randomized trials of rhEPO in dialysis and ND CKD subjects and after consideration of the largest point estimate that, by design, would meet the statistical criterion for non-inferiority.

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

9.1.2. Hgb efficacy Co-Primary Hypothesis

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

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

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

The non-inferiority margin is pre-defined as -0.75 g/dL; determined based upon a combination of clinical judgment, statistical reasoning and regulatory guidance for designing non-inferiority trials.

Statistical significance of non-inferiority will be assessed at the one-sided 2.5% level. An ANCOVA model including prognostic randomization stratification factors (dialysis type and region), baseline Hgb and treatment will be used to obtain a point estimate and 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.

The co-primary endpoints will be tested first. Non-inferiority needs to be established for both co-primary's to proceed to evaluate MACE for superiority as well as the principal secondary endpoints for superiority. Principal secondary endpoints include prioritized composites for MACE (including thromboembolic events and hospitalizations for HF) and IV iron utilization (defined as the average monthly IV iron dose used to Week 52). Statistical testing of MACE for superiority as well as the principal secondary endpoints will be adjusted for multiplicity (Section 9.4.3).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The size of this event driven trial is based on the co-primary CV safety objective and is determined by a fixed event target of 664 adjudicated first MACE. This provides approximately 90% power to establish non-inferiority assuming a true underlying 3% lower relative risk of MACE in favor of daprodustat compared to rhEPO (i.e., hazard ratio=0.97) and 82% power for non-inferiority under the assumption that the true underlying risk of MACE is the same in both arms (i.e., hazard ratio=1.00). Other assumptions behind the sample size calculation include:

- Projected annual adjudicated first MACE rate of 11%. All-cause death is expected to be the most prevalent component, followed by non-fatal MI and then non-fatal stroke (projected break down of 60%, 30% and 10% respectively).
- Variance under the alternative hypothesis (i.e. hazard ratio=0.97)
- 1% annual lost to follow-up without vital status
- A two-sided 95% CI is used for analysis

The target of 664 adjudicated first MACE will permit a two-sided 95% CI of (0.859, 1.164) to describe the results for an observed hazard ratio of 1. The largest hazard ratio point estimate (two-sided 95% CI) that would meet the statistical criterion for non-inferiority is 1.074 (0.922, 1.250) and for superiority, the minimum observable effect would be a 14.1% relative risk reduction in favor of daprodustat, corresponding to a hazard ratio of 0.859.

Conditional on both co-primary endpoints achieving non-inferiority at the one-sided 2.5% level, statistical testing will progress to evaluate MACE and the principal secondary endpoints for superiority. These tests will be multiplicity adjusted, details are provided in Section 9.4.3.

Based on an annual MACE rate of 11%, it is anticipated that the 664 adjudicated first MACE target will be reached approximately 3.3 years from when the first subject is randomized. All subjects will have the opportunity for a minimum of 1 year exposure to treatment and thus the opportunity to complete the EP (Weeks 28 to 52). Exposure to daprodustat is expected to be in the region of 3,500 patient years with median patient follow-up expected to exceed 2 years.

Note: The country-specific requirements for France ONLY for the sample size consideration are provided in Appendix 14 (see Section 12.14.1, Item 2 for details).

9.2.2. Sample Size Sensitivity

The estimated 11% annual MACE rate is based on a blinded summary of ASCEND-D data as of April 20, 2020. Table 11 illustrates the impact on power if the true underlying treatment effect is not a hazard ratio of 0.97.

Table 11 Sensitivity Based on a Different True Underlying Treatment Effect

Underlying hazard ratio for MACE rate	Power for non-inferiority
0.90	99%
0.95	94%
0.97 (base case)	**90%**
1.00	82%
1.03	70%
1.05	61%

Impact of Sample Size for Hgb Efficacy Analysis

Subjects will be treated to achieve and maintain a Hgb between 10 and 11 g/dL. The expected difference in mean Hgb change from baseline between arms and the EP is 0 g/dL and the anticipated standard deviation (SD) is 1.5 g/dL, based on historical rhEPO trials and daprodustat clinical trial experience to date.

For 90% power to test the co-primary non-inferiority Hgb hypothesis, with a two-sided 95% CI, pre-specified margin of -0.75 g/dL and a two-sample T-test, a total of 86 evaluable subjects per treatment group are required. The planned study size far exceeds this requirement and provides more than 99% power for non-inferiority and a high level of precision to estimate the treatment effect (two-sided 95% CI half width of 0.128 g/dL, assuming 30% of subjects will be non-evaluable for efficacy). The largest (most negative) difference between arms that would meet the statistical criterion for non-inferiority would be -0.622 g/dL. If the two-sided 95% CI is completely negative (i.e. lies fully within the range -0.75 to <0g/dL) non-inferiority would still be concluded.

9.2.3. Sample Size Re-estimation or Adjustment

At the time of this protocol amendment, the study was fully enrolled, and as such no sample size re-estimation was performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The primary population for analyses of MACE and other time to event outcomes will be the All Randomized (ITT) Population. Subjects will be analyzed according to the treatment to which they were randomized.

The primary population for the Hgb efficacy analyses will also be the ITT Population. A supportive analysis of the primary efficacy endpoint 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.

The primary population for safety will be based on 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, including sub-study populations.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

9.4.1.1. Primary CV Safety Analysis (co-primary)

MACE: The co-primary cardiovascular safety analysis is to assess the comparative treatment effect for time to first occurrence of adjudicated MACE in all randomized subjects. Time to the first occurrence of a primary endpoint event will be computed as (event date – randomization date) +1. Subjects who do not have the event during the trial period will be censored in the analysis, with details provided in the RAP. The statistical model is a Cox Proportional Hazards regression model, adjusting for treatment and the prognostic randomization stratification factors (dialysis type and region), to estimate the hazard ratio, two-sided 95% CI and one-sided p-value for the statistical non-inferiority test. Non-inferiority will be established if the upper limit of the two-sided 95% CI is less than the margin of 1.25. Cumulative time from randomization to first event or end of trial will be evaluated using Kaplan-Meier methodology and displayed graphically. Treatment comparisons from the Cox regression model will be presented as hazard ratios and two-sided 95% CIs and displayed on forest plots. The validity of the proportional hazards assumption will be assessed. All adjudicated events will be used for the primary analysis and concordance between investigator reported and adjudicated events will be summarized.

Sensitivity and Supportive Analyses: A sensitivity analysis will be performed to address potential effects of drop outs and to evaluate the robustness of the co-primary

MACE analysis. A sensitivity "tipping point" analysis utilizing multiple imputation for randomized subjects who have withdrawn from the study will be performed, as well as a supportive "on-drug" analysis to evaluate the comparative treatment effect during the time that subjects remain on randomized treatment (plus a window of 28 days). Full details will be provided in the RAP.

In addition, analyses will be performed for each component of MACE (all-cause mortality, MI and stroke) to understand individual contributions to the overall MACE result and to assess component directional consistency. These analyses will not be multiplicity adjusted. Further subgroup and covariate adjusted analyses of specific clinical interest are detailed in Section 9.4.4 and the RAP.

9.4.1.2. Primary Efficacy Analysis (co-primary)

Mean change in Hgb between baseline and the EP (Weeks 28 to 52): The primary efficacy estimand is the effect of daprodustat relative to rhEPO on the change in Hgb from baseline to the average of all values in the EP, regardless of adherence to treatment including interruptions and discontinuation, the use of non-randomized ESA medication for any reason including rescue therapy, or the use of blood transfusions, in subjects on dialysis currently treated with an ESA with anemia secondary to CKD and assuming subjects do not die before the end of the EP. The analysis will use an ANCOVA model. For each subject, 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 and imputed Hgb values between Weeks 28 to 52 inclusive regardless of adherence to randomized treatment. The ANCOVA model will include prognostic randomization stratification factors (dialysis type and region), 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. Imputation will be used for missing Hgb data; further details will be provided in the RAP.

Sensitivity and Supportive 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 supportive 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 supportive "tipping point" analysis as that described above for the primary analysis will be performed for this "on-drug" analysis. In addition, a per-protocol supportive analysis will estimate the treatment effect in subjects who strongly adhere to the protocol, and supportive analyses to explore a shorter EP (Weeks 28 to 36) will be performed for the co-primary effectiveness estimand and "on-drug" efficacy estimand. Full details of all sensitivity and supportive analyses will be provided in the RAP.

9.4.2. Secondary Analyses

9.4.2.1. Principal Secondary Analyses

Conditional on the co-primary endpoints achieving at least non-inferiority at the one-sided 2.5% level, statistical testing will progress to superiority for MACE and the principal secondary endpoints. The hypotheses to be tested for these endpoints are as follows:

- **Null:** daprodustat is not superior to rhEPO (i.e. the hazard ratio is greater than or equal to 1.0 for time-to-event endpoints, or the mean difference is greater than or equal to 0 for continuous endpoints)
- **Alternative:** daprodustat is superior to rhEPO (i.e. the hazard ratio is less than 1.0 for time-to-event endpoints, or the mean difference is less than to 0 for continuous endpoints)

These tests will be multiplicity adjusted based on a family-wise Type I error rate set at the one-sided 2.5% level, see Section 9.4.3 for further details.

For "time to event" endpoints: The statistical modeling approach described for MACE in Section 9.4.1.1 will be repeated for the adjudicated composite endpoints of:

- MACE or a thromboembolic event (vascular access thrombosis, symptomatic deep vein thrombosis or symptomatic pulmonary embolism).
- MACE or hospitalization for HF.

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 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 prognostic randomization stratification factors.

Additional secondary endpoints are listed in Appendix 2. All analyses of secondary endpoints are of exploratory nature, summary statistics and nominal one-sided p-values will be used for any treatment comparisons.

9.4.2.2. Analysis Patient Reported Outcomes

Analysis to compare the subject reported effects of daprodustat and rhEPO on symptoms, health related quality of life, and health status, as discussed in Section 7.7, will be described in the RAP.

9.4.2.3. Safety Analyses

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

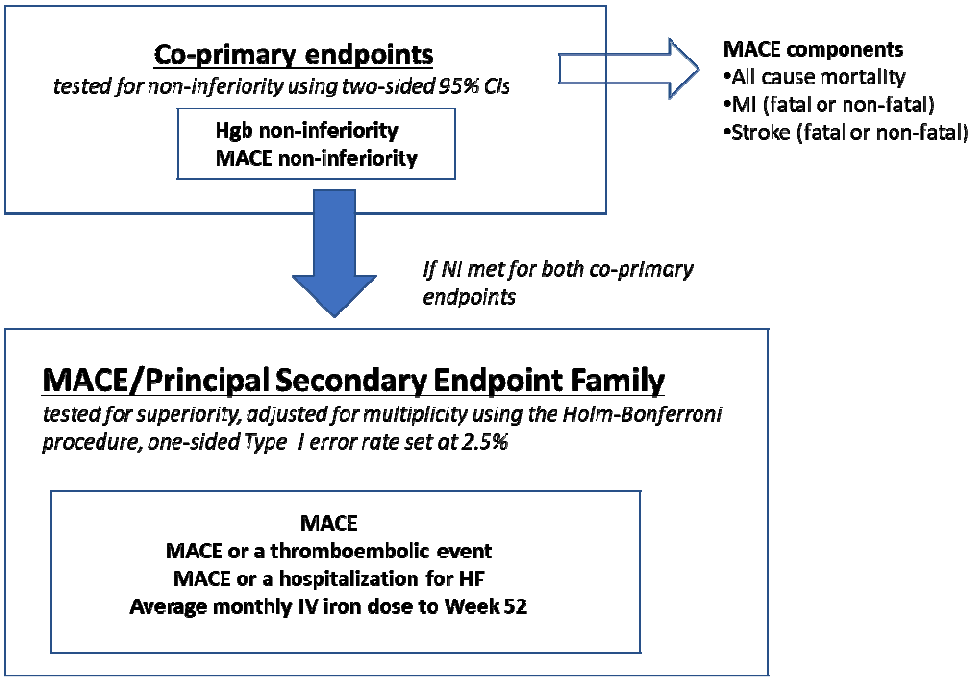
9.4.3. Multiplicity Strategy

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

Figure 2 illustrates the structure of the statistical testing plan. First, the co-primary endpoints will be evaluated for non-inferiority by comparing each two-sided 95% CI to the appropriate non-inferiority margin. Conditional on both co-primary endpoints achieving non-inferiority (i.e., passing the gatekeeper), the family of MACE and the principal secondary endpoints will be formally tested for superiority using the widely known Holm-Bonferroni procedure [Holm, 1979]. The procedure will be conducted based on a family-wise Type I error rate set at the one-sided 2.5% level. Details of the Holm-Bonferroni procedure will be fully described in the RAP.

Section 9.4.5 describes the planned interim analysis for the assessment of MACE futility. While this analysis will have a small impact on reducing the study-wise Type I error rate, there are no plans to adjust the alpha level used for end-of-study analyses. There are no prospectively defined plans to stop this study early for benefit.

Figure 2 Multiplicity controlled statistical testing plan



9.4.4. Covariates and Subgroups of Interest

The co-primary and principal secondary endpoints will be evaluated for a set of pre-specified subgroups to support the proposed indication. For the co-primary efficacy endpoint, these subgroups will be evaluated for both the primary ITT analysis of Hgb values during the EP regardless of adherence to treatment, as well as the sensitivity analysis limited to on-treatment Hgb values during the EP.

Although subgroup analyses aim to assess for consistency with the overall results, they may have low power, especially if the subgroup is small or has a low number of events. Statistical models will be adjusted for the covariates used in the original analysis, 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	Appendix 3
Country	Appendix 3
Dialysis type	HD, PD (repeat using HD, HDF/HF, PD)
Dialysis vintage	0 to <2 years, 2 to <5 years, ≥5 years
Prior rhEPO dose	<7,000 U/week, ≥7,000 U/week
rhEPO Hypo-responsiveness	No, yes (see below for definition)
Baseline Hgb	<9, 9 to <10, 10 to 11, >11 g/dL
BMI	<30, ≥30 kg/m^2
Weight	< 75kg, ≥75kg
Baseline hsCRP	≤3 mg/L, >3 mg/L
United states	US, Non-US

rhEPO hyporesponder subgroup definition: rhEPO hyporesponders will be identified either by the ESA Resistance Index (ERI) [HERO study, Johnson, 2015] or by treatment at baseline with a very high dose of IV epoetin alpha. For each subject, baseline ERI will be calculated as the dry weight adjusted weekly mean ESA dose during the 8 week screening period divided by baseline Hgb concentration. Subjects with baseline ERI ≥2 U/kg/wk/g/L for epoetin-treated subjects; ≥0.008 µg/kg/wk/g/L for darbepoetin-treated subjects and ≥0.01 µg/kg/wk/g/L for methoxy-PEG-epoetin-treated subjects will be included in the pre-specified subgroup. In addition, subjects will be included if being treated at baseline with greater than or equal to the equivalent of 450 U/kg/week of IV epoetin alpha. This latter criterion covers subjects at higher body weight for which the ERI calculation is less accurate and is based on the NICE anemia guidelines of June 2015 [NICE, 2015]. Sensitivity analyses will explore alternative subgroup definitions: an ERI cut-point of ≥1.5 (or equivalent depending on ESA treatment) or using baseline prior rhEPO dose above the top 20th percentile for the study population.

rhEPO hyporesponder subgroup analysis plan: It is anticipated that approximately 10-15% of subjects may be classified as rhEPO hyporesponders according to this

definition, thus resulting in a subgroup size of potentially 300-450 subjects. The subgroup efficacy analysis will follow the same structure as that defined for the full study, assessing the comparative treatment effect in mean Hgb change between baseline and EP in subjects regardless of adherence to study treatment as well as in subjects who adhere to randomized treatment and using the same non-inferiority margin of -0.75 g/dL. For at least 90% power to demonstrate non-inferiority, 86 evaluable rhEPO hyporesponders are required per arm. The statistical model (ANCOVA) will include terms for prognostic randomization stratification factors, baseline Hgb, treatment, hyporesponder subgroup and treatment by subgroup interaction. Point estimates and two-sided 95% CIs will be generated to describe the treatment effect separately for rhEPO hyporesponders and the complement set of rhEPO non-hyporesponders; non-inferiority would be established if the lower limit of the two-sided 95% CI is greater than -0.75 g/dL. In addition, a nominal one-sided non-inferiority p-value and a nominal one-sided superiority p-value for the difference between the two groups will be generated.

While it is unlikely, given the sample size, that a sufficient number of adjudicated first MACE will occur to support a robust model-based analysis, subgroup analyses are planned for the co-primary MACE and principal secondary CV endpoints. The statistical analysis model (Cox Proportional Hazards) will include terms for prognostic randomization stratification factors, treatment, hyporesponder subgroup and treatment by subgroup interaction. Point estimates and two-sided 95% CIs for the hazard ratio will be generated to describe the treatment effect separately for rhEPO hyporesponders and the complement set of rhEPO non-hyporesponders; non-inferiority would be established if the upper limit of the two-sided 95% CI is less than 1.25. At a minimum, the incidence of MACE, its components and the principal secondary CV endpoints will be descriptively summarized by treatment group.

9.4.5. Interim Analysis

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

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

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

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

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 favorable 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/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.

- All study investigators will be provided with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

10.8. Review Committees

In addition to GSK, medical governance will also be provided by the following independent committees. Additional information about each committee is included in the respective committee charter which is available upon request.

10.8.1. Independent Data Monitoring Committee

An IDMC 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 schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter.

10.8.2. Clinical Events Committee

An external independent Clinical Events Committee blinded to treatment allocation will adjudicate all events reported during this study that constitute the co-primary CV safety endpoint of MACE [composite of all-cause mortality, non-fatal MI and non-fatal stroke], the principal CV secondary composite endpoints of MACE plus additional components including events of vascular access thrombosis, symptomatic deep vein thrombosis, symptomatic pulmonary embolism, CV mortality and hospitalization for HF.

10.8.3. Executive Steering Committee

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.

10.8.4. Steering Committee

The Steering Committee in collaboration with the Executive Steering Committee is responsible for the scientific oversight of all aspects of study conduct and will provide advice to the National Leader Committee.

10.8.5. 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

ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
ANSM	L'Agence nationale de sécurité du médicament et des produits de santé
AST	Aspartate transaminase
BP	Blood pressure
CEC	Clinical Events Classification
CI	Confidence interval
CKD	Chronic kidney disease
CNIL	Commission Nationale de I'Informatique et des Libertés
CPK	Creatine phosphokinase
CRA	Clinical Research Assistant
CT	Computed tomography
CTR	Clinical Trials Register
CV	Cardiovascular
DBP	Diastolic blood pressure
DGF	Delayed graft function
ECG	Electrocardiogram
eCRF	Electronic case report form
EDW	Estimated dry weight
EP	Evaluation period
EPO	Erythropoietin
EQ-5D-5L	EuroQol 5 Dimension 5 Level Health Utility Index
EQ-VAS	EuroQol Visual Analogue Scale
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FRP	Females of reproductive potential
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
HbA1c	Glycated hemoglobin
hCG	Human chorionic gonadotrophin
HD	Hemodialysis
HDF	Hemodiafiltration
HDL-c	High density lipoprotein-C
HDPE	High density polyethylene
HF	Heart failure

Hgb	Hemoglobin
HHD	Home hemodialysis
HIF	Hypoxia-inducible factor
HIF-PHI	Hypoxia inducible factor prolyl hydroxylase inhibitor
HR	Heart rate
HR-QoL	Health Related Quality of Life
HRT	Hormone replacement therapy
hsCRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
iPTH,	Intact parathyroid hormone
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein-C
MACE	Major adverse cardiovascular event
MAP	Mean arterial pressure
MCH	Mean corpuscular hemoglobin;,
MCHC	Mean corpuscular hemoglobin concentration
MCS	Mental Component Score
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NYHA	New York Heart Association
PASP	Pulmonary Artery Systolic Pressure
PCS	Physical Component Score
PD	Peritoneal dialysis
PEG	Polyethylene glycol
PFS	Pre-filled syringe
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PP	Per protocol
PPD	Pharmaceutical Product Development, LLC
PRBC	Packed red blood cells
PRS	Project specific requirement
PSRAE	Possible Suicidality Related Adverse Events

QC	Quality control
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RDW	Red blood cell distribution width
rhEPO	Recombinant human erythropoietin
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDAC	Statistical Data Analysis Center
SRM	Study Reference Manual
TIBC	Total iron binding capacity
TSAT	Transferrin saturation
U	Units
UIBC	Unsaturated iron binding capacity
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WBC	White blood cells;

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 and Exploratory Objectives/ Endpoints

Objectives	Endpoints
Secondary Objectives	**Secondary Endpoints (tested for superiority[1], no multiplicity adjustment)**
• To compare daprodustat to rhEPO on additional CV safety endpoints	• All-cause mortality, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke[2] • MACE or hospitalization for HF[2] (recurrent events analysis) • CV mortality or non-fatal MI[2] • All-cause hospitalization • All cause hospital re-admission within 30 days • MACE or hospitalization for HF or thromboembolic events[2] • Hospitalization for HF[2] • Thromboembolic events[2]
• To compare daprodustat to rhEPO on Hgb variability	• Hgb change from baseline to Week 52[1] • N (%) responders, defined as mean Hgb within the Hgb analysis range 10-11.5 g/dL during EP • % time Hgb in analysis range (10-11.5 g/dL) during the evaluation period (EP, Week 28 to 52) and during the maintenance period (MP; Week 28 to end of trial) *(non-inferiority analysis that will use a margin of 15% less time in range)* [1]
• To compare daprodustat to rhEPO on BP	• Change from baseline in SBP, DBP and MAP at Week 52 and at end of treatment • Number of BP exacerbation events per 100 patient years • N (%) with at least one BP exacerbation event during study
• To compare daprodustat to rhEPO on the time to rescue (defined as permanently stopping randomized treatment due to meeting rescue criteria).	• Time to stopping randomized treatment due to meeting rescue criteria
• To compare daprodustat to rhEPO on HRQoL and Utility score	• Mean change in SF-36 HRQOL scores (Physical Component Score (PCS), Mental Component Score (MCS) and 8 health domains) between baseline and Weeks 8, 12, 28, 52, of particular interest are the changes from baseline in the vitality and physical functioning domains at Wk 28 and 52 • Change from baseline in Health Utility (EQ-5D-5L) score at Week 52 • Change from baseline in EQ VAS at Week 52
• To compare daprodustat to rhEPO on the symptom severity and change	• Change from Baseline at Wk 8,12, 28, 52 in PGI-S

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints (statistical testing not planned)**
• To further compare daprodustat and rhEPO on Hgb variability	• Hgb observed and change from baseline across all visits to end of treatment • % of time Hgb is above, within and below the range of 10-11.5 g/dL during EP and MP • Number (%) of subjects with mean Hgb above, within and below the Hgb analysis range during EP and at the end of treatment • Number (%) of subjects with a Hgb <7.5 g/dL during the EP and MP • Number of times Hgb < 7.5 g/dL during the EP and MP • Number (%) of subjects with a >1g/dL increase in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL increase in Hgb within any 4 week period from Week 4 to Week 52 • Number (%) of subjects with a >1g/dL decrease in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL decrease in Hgb within any 4 week period from Week 4 to Week 52 • N (%) of subjects with a Hgb value ≥ 12 g/dL during the EP and MP • Number of times Hgb ≥ 12 g/dL during the EP and MP • % of time Hgb ≥ 12 g/dL during the EP and MP
• To compare daprodustat to rhEPO on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, TSAT, total iron, TIBC across all visits to end of treatment • Average quarterly ferritin • Average quarterly TSAT • Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria • N (%) of subjects who reduced IV iron supplementation relative to baseline (defined as total iron (mg) over 4 weeks prior to randomization) during EP (defined as average monthly IV iron dose (mg) over Weeks 28 to 52)
• To further compare daprodustat to rhEPO on BP and BP medication changes	• Observed and change from baseline in SBP, DBP and MAP by visit • Number of BP medications per subject by visit • Change from baseline in the number of BP medications per subject by visit • N (%) of subjects who had no change, an increase or a decrease in the dosage or number of BP medications from baseline by visit
• To compare daprodustat to rhEPO on the need for RBC and whole blood transfusions	• Number (%) of subjects who receive at least one RBC or whole blood transfusions by Week 52 and by end of treatment

Objectives	Endpoints
	• Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years
• To compare daprodustat to rhEPO on lipid parameters.	• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)]
• To compare the effect of daprodustat to rhEPO on delayed graft function (DGF) after deceased donor kidney transplantation	• Number (%) of subjects experiencing DGF after deceased donor kidney transplantation (where DGF is defined as the use of dialysis within 7 days of the transplant) • Length of time that subjects experience DGF after deceased donor kidney transplantation
• Evaluate the dose adjustment schemes	• Assigned dose by visit and at Day 1, Week 28, Week 52, and yearly • Most recent dose prior to Week 28, Week 52, yearly and End of Treatment • Number (%) of patients with 0, 1, 2, or >2 dose adjustments during the following periods: o Day 1 - < Week 28 o Week 28 - < Week 52 o Day 1 - < End of Treatment • Number of dose adjustments during the following periods: o Day 1 - < Week 28 o Week 28 - < Week 52 o Day 1 - < End of Treatment • Number of dose adjustments per year during Day 1 - < End of Treatment • Time dose held for Hgb≥12 g/dL
• To further compare daprodustat to rhEPO on HRQoL and Utility score	• Change from baseline in Health Utility I (EQ-5D-5L) score at Weeks 8,12, 28, 52, yearly, EOS • Change from baseline in EQ VAS at Weeks 8, 12, 28, 52, yearly, EOS
• To further compare daprodustat to rhEPO on the symptom severity and change	• Shift tables (Baseline to Weeks 8, 12, 28, and 52) in PGI-S • N(%) of patients within each PGI-C symptom change level at Weeks 8, 12, 28, 52.

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

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

12.3. Appendix 3: Stratification by Region- Region Groupings

Region	Countries[2]			
1	• Thailand[1] • Republic of Korea[1]	• India • Singapore[1]	• Malaysia[1] • Taiwan[1]	• Philippines
2	• Bulgaria • Hungary • Ukraine	• Turkey • Poland • Slovakia	• Czech Republic • Romania • South Africa[1]	• Estonia • Russian Federation
3	• Australia[1] • Denmark[1] • Italy • Norway[1] • United Kingdom[1]	• Austria • France • Israel • Portugal	• Belgium • Germany • Netherlands[1] • Spain[1]	• Canada[1] • Greece • New Zealand[1] • Sweden[1]
4	• Argentina	• Brazil[1]	• Mexico	
5	• US[1]			

1. Countries which will collect the EQ-5D-5L and EQ VAS
2. Countries that do not participate or do not randomize any subjects will be removed from the regional grouping.

12.4. Appendix 4: 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. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat. Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose steps, and dose adjustment scheme to optimize Hgb management.	• 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 Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb (including rate of change) is provided in Section 6.3 and Section 6.12. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Worsening of hypertension	In a dog cardiovascular study, single oral doses of daprodustat (up to 90 mg/kg) did not produce effects on blood pressure. Marketed rhEPO and its analogues have been associated with risks related to uncontrolled hypertension, including the need for initiation of or increases in antihypertensive therapy when used in patients with anemia of CKD (i.e. 25% Epogen, 27% Mircera, and 40% Aranesp treated patients with renal anemia required initiation or increase in their anti-hypertensive medications; hypertensive encephalopathy and seizures have been reported. The contribution of rhEPO-associated hypertension to the unfavourable effects on cardiovascular outcomes remains uncertain). Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese	• Blood pressure will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • 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
	phase 3 studies (52-week treatment duration)]: ○ The majority (>90%) of subjects had a baseline history of hypertension. ○ No meaningful difference was seen between treatment groups in AEs (preferred term) of "hypertension" [29/688 (4%) daprodustat vs. 19/404 (4%) rhEPO; 0.91 relative risk (RR) (95% confidence interval: 0.5, 1.67)] or "blood pressure increased" [16 (2%) daprodustat vs. 7 (2%) rhEPO; RR 1.22 (0.48,3.11)]. Results were not substantively different between non-dialysis and haemodialysis subjects. ○ Although no clinically meaningful changes in blood pressure were observed, subjects in both treatment groups required increases in anti-HTN medications: ○ In the 24-week global phase 2b studies, 25/170 (15%) of ND subjects receiving daprodustat vs. 18/80 (14%) control and 22/177 (12%) of HD subjects receiving daprodustat vs. 2/39 (5%) control. ○ In the 52-week Japan phase 3 studies, 57/149 (38%) of ND subjects receiving daprodustat vs. 68/150 (45%) rhEPO and 51/136 (38%) of HD subjects receiving daprodustat vs. 66/135 (49%) for rhEPO. The data received to date from completed clinical trials with daprodustat are insufficient to refute this risk.	
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	• 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 Section 7.1. • Unblinded monitoring of safety data by an

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	this risk.	IDMC in-stream throughout the study. • Planned formal interim analyses with stopping guidelines for evidence of increased CV risk as outlined in Section 9.4.5.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 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.	• 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.
Cancer-related mortality and tumor progression and recurrence	Marketed rhEPO and its analogs have been associated with increased risk of cancer related morbidity and mortality when used in patients with cancer. 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 a 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	• 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
	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 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.	
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. <u>Acute hypoxic challenge (rats):</u> Daprodustat produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. However, these hypoxia-induced PRVP changes were within the range of PRVP changes noted	• 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
	among untreated 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 has 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: 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 treatment; 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 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	• 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
	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 for daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
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. 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 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 30 mg administered three times weekly. In studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but	• 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
	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 with daprodustat. Following review of clinical data with daprodustat received to date, this has not been identified as a safety concern for daprodustat.	
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 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. Daprodustat is an inhibitor of CYP2C8: A clinical drug interaction study between 25mg and 100mg daprodustat with a CYP2C8 substrate (i.e., 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	• Co-administration of daprodustat with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.10.2. • 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 6.3 and Appendix 6. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.10. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb is provided in Section 6.3 and Appendix 6. • 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
	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, heart failure, thromboembolic events, thrombosis of vascular access, and for 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; death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access; and for 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.

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12.5. Appendix 5: Female Eligibility Criteria

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

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

    1. Contraceptive subdermal implant that meets effectiveness criteria.
    2. Intrauterine device or intrauterine system.
    3. Combined estrogen and progestogen oral contraceptive
    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.

Note: See Section 12.14.2 for the country-specific requirements for the Czech Republic ONLY relating to acceptable contraceptive methods during participation in this study.

- Non-reproductive potential defined as either:

    1. Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;

2. Postmenopausal defined as 12 months of spontaneous amenorrhea. In questionable cases, a blood sample with simultaneous FSH and estradiol consistent with menopause is confirmatory (FSH ≥23.0 MIU/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.

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12.6. Appendix 6: Randomized Treatment Dose Adjustment Schemes

HemoCue Hgb (g/dL) at current study visit[1]	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[7]	Increase to the next higher dose step
7.5 to <9.5	Increasing[8]	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 mandated study visits (every 4 weeks through Week 52; then every 12 weeks). From Week 52 onwards, additional study visits to check Hgb and dispense randomized treatment (where directed by the IRT system) are required under the following circumstances (additional visits have a visit window of ±1 week):

- When Hgb at last study visit is outside of the target range, i.e., <10 or >11 g/dL: Visit 4 weeks later to assess for dose adjustment.
- When the dose of randomized treatment is changed or restarted in the previous 12 weeks ±1 week: Visits every 4 weeks for 12 weeks.
- When a medication that is a moderate CYP2C8 inhibitor (i.e., clopidogrel, teriflunomide, deferasirox) is started, stopped, or the dose is changed: Visits every 4 weeks for 12 weeks.
- When the investigator determines it clinically necessary to evaluate a subject sooner than 12 weeks later: Visit 4 weeks later to assess for dose adjustment.
- For subjects changing dialysis modality from HD to PD: Visits every 4 weeks for 12 weeks.

2.This rule applies to any mandated visit or 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 Week 2 and Week 4 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.

7.No change may be redefined as an increase of <0.5 g/dL based on the review of blinded instream aggregate Hgb data.

8.Increasing may be redefined as an increase of ≥0.5 g/dL based on the review of blinded instream aggregate Hgb data.

12.7. Appendix 7: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.7.1. 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, SBP, DBP or HR measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment 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 placebo run-in or 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 placebo run-in, 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 fulfill 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.

12.7.2. 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.

12.7.3. 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 eCRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to PPD in lieu of completion of the GSK, AE/SAE eCRF 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.

12.7.4. 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 placebo run-in or 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 placebo run-in or randomized treatment will be considered and investigated.
- The investigator will also consult the 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.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to PPD within the designated reporting time frames.

12.7.5. 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 can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.8. Appendix 8: Liver Safety Required Actions and Follow up Assessments

Phase 3-4 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 3-4 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 eCRF 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** (refer to Appendix 9) • If restart **not allowed or not granted**, permanently discontinue randomized treatment and may continue subject in the study for any protocol specified follow up assessments	• 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 PK analysis, obtained within 24 hour 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 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
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • 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]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF 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 Gal, 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 eCRF. 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 PPD 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

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12.9. Appendix 9: 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** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for randomized 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 requested to 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 7.

12.10. Appendix 10: 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 24 hours of learning of a subject's pregnancy.
- The 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 by the investigator reasonably related to the randomized treatment, will be reported to PPD as described in Appendix 7. 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.

12.11. Appendix 11: 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 randomized 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 consent 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

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12.12. Appendix 12: A Sub-study of the Effect of Daprodustat Compared to rhEPO on BP in Hemodialysis Dependent Subjects with Anemia Associated with Chronic Kidney Disease who Switch from ESAs

12.12.1. Introduction and Rationale

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

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

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

12.12.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare daprodustat to rhEPO for effect on SBP (superiority) by ABPM in subjects receiving maintenance hemodialysis in the ABPM ITT population	• Change in 24 hour average SBP from baseline to end of sub-study[1] between treatment groups
Secondary	
• To assess the effect of daprodustat and rhEPO independently within treatment group on SBP, DBP and mean arterial blood pressure (MAP) by ABPM in the ABPM ITT population	• Change in 24 hour average SBP from baseline to end of sub-study[1] within each treatment group • Change in 24 hour average DBP from baseline to end of sub-study[1] within each treatment group • Change in 24 hour average MAP from baseline to end of sub-study[1] within each treatment group
• To compare the effect of daprodustat to rhEPO on DBP and MAP by ABPM in the ABPM ITT population	• Change in 24 hour average DBP from baseline to end of sub-study[1] between treatment groups • Change in 24 hour average MAP from baseline to end of sub-study[1] between treatment groups
• To compare the effect of daprodustat to rhEPO on BP parameters in the ABPM per-protocol population	• Change in: ○ 24 hour average SBP ○ 24 hour average DBP ○ 24 hour average mean arterial pressure from baseline to end of sub-study[1] between treatment groups

Objectives	Endpoints
• To assess the effect of daprodustat and rhEPO on BP parameters in the ABPM per-protocol population	• Change in: ○ 24 hour average SBP ○ 24 hour average DBP ○ 24 hour average mean arterial pressure from baseline to end of sub-study[1] within each treatment group
• To compare the percentage of subjects in each treatment group requiring a change in antihypertensive medications in the ABPM ITT population	• Difference between treatment groups in percentage of subjects requiring no change in number or dosage of antihypertensive medications • Difference between treatment groups in percentage of subjects requiring an increase in number or dosage of antihypertensive medications • Difference between treatment groups in percentage of subjects requiring a decrease in number or dosage of antihypertensive medications
• To characterize the dipping pattern of sleeping BP in each treatment group in the ABPM ITT and ABPM per-protocol populations	• 24 hour BP profile as measured by ABPM, with subjects categorized according to their sleeping BP behaviors as: ○ dippers (normal) when the reduction in the average SBP during the sleeping period was >10% to 20% of mean SBP during waking hours, ○ extreme dippers when this reduction was >20%, ○ non-dippers when the reduction was <10%, and ○ reverse dippers when the mean sleep SBP was higher than the awake SBP [Bakris, 2014]
• To compare the percentage of subjects that convert from non-dipper status to dipper status between treatment groups in the ABPM ITT and ABPM per-protocol populations	• Difference between treatment groups in percentage of subjects that convert from non-dipper status at baseline to dipper status at end of sub-study[1]
• To compare the percentage of subjects that convert from dipper status to non-dipper status between treatment groups in the ABPM ITT and ABPM per-protocol populations	• Difference between treatment groups in percentage of subjects that convert from dipper status at baseline to non-dipper status at end of sub-study[1]
• To compare the effect of treatment with daprodustat to rhEPO on heart rate by ABPM in the ABPM ITT population	• Change from baseline to end of sub-study[1] in 24 hour average heart rate between treatment groups as measured by ABPM relative to time since administration of medication

1. The end of the sub-study is defined as Week 16, or Week 28 for subjects completing the sub-study prior to Amendment 2.

12.12.3. Study Design

This is a multicenter sub-study of the main ASCEND-D study. Subjects who qualify for the main study will be assessed for enrolment. Approximately 136 subjects from centers in selected countries that are participating in the main study will be randomized.

Note: if the target number of randomized subjects in the ABPM sub-study is not achieved when the main study is fully enrolled, recruitment may be extended to allow randomization in the ABPM sub-study to complete.

12.12.3.1. ABPM Quality Control Criteria

Subjects will need to wear the ABPM device for two 24-hour sessions during the study: at a mid-week dialysis visit starting at Week -4 until 1 week prior to randomization (baseline ABPM) and then at Week 16. The ABPM device will be placed after assessments for the main study have been completed. Subjects will be expected to wear the ABPM device for 24 hours at each session. The ABPM device will measure BP and heart rate every 30 minutes during both awake and asleep hours. The times the subject awakens and goes to sleep during this 24 hour period will be recorded.

For each session the ABPM Quality Control (QC) criteria as defined in the Project Requirement Specification (PRS) for ABPM must be met. If these criteria are not met the ABPM may be repeated (see Section 12.12.3.3).

12.12.3.2. Eligibility Criteria – Screening

Additional Inclusion Criteria

In addition to meeting entry criteria for the main study, a subject will be eligible for inclusion in this sub-study only if all of the following criteria apply.

1. Signed written informed consent prior to beginning sub-study-related procedures. **Note:** Consent to participate in this sub-study is separate from consent to participate in the main study, and will be signed either at Week -8 or at Week -4 prior to ABPM assessments.
2. Use of the same antihypertensive treatment for the 6 weeks prior to the Screening visit, through the entire Screening period and at randomization.
3. SBP of ≤170 mmHg based on the average of pre-dialysis clinic values obtained at Week -8 and Week -4 using the methodology described in the SRM.
4. Willing and able to wear ABPM device for 24 hours on two separate sessions.
5. Valid ABPM at baseline **[randomization (Day 1) only]**.
6. Dialysis schedule of three times per week.
7. Average awake-time SBP of ≤150 mmHg as assessed by a valid baseline ABPM **[randomization (Day 1) only]**.

Additional Exclusion Criteria

A subject will not be eligible for inclusion in this sub-study if any of the following criteria apply:

1. Receiving peritoneal dialysis or home HD.
2. Subjects who are at high risk for loss to follow-up (e.g., subjects who are known to not regularly attend dialysis, subjects who may require frequent hospitalizations or vascular access interventions).
3. Evidence of atrial fibrillation or atrial flutter at time of baseline ABPM assessment (see Section 12.12.3.3).
4. Oscillometer/sphygmomanometer cuff cannot accommodate their upper arm circumference.
5. BP cannot be measured in the arm opposite of current vascular access.
6. Subjects who experience, on average, >5% increase in weight above EDW between mid-week dialysis treatments between Week -8 and baseline ABPM reading.

12.12.3.3. Study Assessments

Week -8 Study Visit:

Subject's consent for ABPM is obtained (Note: if missed this may be obtained at Week -4 prior to ABPM assessments).

Week -4 Study Visit:

A baseline ABPM reading must be initiated at a mid-week dialysis visit and may be performed following completion of the Week -4 study assessments or at a subsequent mid-week dialysis visit provided it occurs at least 1 week prior to randomization.

Post-dialysis and prior to ABPM, subjects will be assessed for the presence of atrial fibrillation/flutter as follows: subjects with an irregular heart beat detected during heart rate measurement will undergo an ECG and those with documented atrial fibrillation or atrial flutter will not be eligible for ABPM.

The ABPM device will be placed on the arm opposite current vascular access, and will be removed by the subject at home after a minimum of 24 hours of wear; the device will be returned to the research staff at the next visit, which ideally is no later than 1 week prior to randomization to allow for QC of the ABPM. See SRM for guidance on placement of ABPM device.

If the subject fails to meet the baseline ABPM QC criteria and agrees to repeat the ABPM procedure, then:

- The baseline ABPM procedure can be repeated at the next mid-week dialysis visit. *Note: the atrial fibrillation/flutter assessment should be repeated prior to device placement.*
- Day 1 (randomization) may be delayed.
- If the baseline ABPM fails the QC criteria after three attempts, then the subject will not be enrolled in this ABPM sub-study.

Subjects will have their body weight measured and recorded in the eCRF both pre- and post-dialysis (see SRM for guidance on body weight measurement).

Day 1 (Randomization):

If the ABPM measurements meet the QC criteria, the subject can be randomized.

Subjects who either do not qualify for entry into the ABPM sub-study after failing QC criteria a third time or who do not desire to continue in the ABPM sub-study although they pass the QC criteria, should continue with randomization into the main study following the schedule of assessments as outlined in Table 7 of the main protocol if appropriate.

Week 16 Study Visit:

At Week 16, at the mid-week dialysis visit and after all main study assessments have been completed, the subject's pre- and post-dialysis weight will be measured and the EDW will be recorded.

The ABPM device will be placed on the subject's arm by site personnel. After a minimum of 24 hours of wear, the device will be removed by the subject at home and returned to the research staff at the next visit. The time and date of study medication administration, before and while wearing the ABPM device, will be recorded.

If the ABPM fails the QC criteria (same as baseline), up to two additional attempts may be made at subsequent, mid-week dialysis visits. No further attempts are allowed. The subject will continue study visits in the main study as scheduled.

12.12.3.4. Permanent Discontinuation of Randomized Treatment

A subject who permanently discontinues randomized treatment prior to completing the ABPM sub-study should remain in the sub-study and complete the Week 16 ABPM assessment unless consent to participate in the ABPM sub-study is withdrawn (see also Section 5.5).

12.12.3.5. Estimated Dry Weight and Antihypertensive Medication Changes

It is preferred that no changes are made to EDW and antihypertensive medications while the subject is part of the sub-study.

If changes in EDW and/or antihypertensive medications are necessary, these must be documented in the eCRF along with the reasons. Subjects will remain in the sub-study regardless of any changes.

12.12.3.6. Withdrawal from ABPM Sub-Study

If a subject participating in this sub-study withdraws from the sub-study, the reason for the withdrawal must be recorded in the eCRF. The subject will remain in the main study unless the subject withdraws consent from the main study.

12.12.4. Sample Size and Power Calculations

The sample size of this sub-study has been designed based on the primary sub-study objective to demonstrate superiority in average SBP change from baseline to end of sub-study between arms (daprodustat versus rhEPO), measured by ABPM over a 24 hour assessment period. Assuming a one-sided 2.5% significance level, a true standard deviation for SBP change from baseline measured by ABPM of 11 mmHg [Peixoto, 2000], and up to a 20% withdrawal rate from the sub-study, a sample size of 68 subjects per group (136 subjects in total) will provide greater than 80% power to detect a -6 mmHg difference in treatment groups (i.e., achieve superiority). Under these assumptions, superiority will be established if there is more than a 4.2 mmHg mean difference observed in favor of daprodustat.

Assuming a 40% screen failure rate for the additional ABPM entry criteria, approximately 228 subjects that are eligible for the main study will need to be screened for the sub-study in order to randomize approximately 136 subjects. See Section 9.2.3 for more information about sample size adjustments.

Unblinded ABPM data will be reviewed by the IDMC during the conduct of the trial as part of their data monitoring responsibilities. No formal interim analysis is planned.

12.12.5. Statistical Analysis

The primary sub-study estimand is to compare the treatment effect on change from baseline in 24 hour average SBP at end of sub-study, in all randomized sub-study subjects. The statistical model for analysis will be an ANCOVA with terms for treatment and baseline 24 hour average SBP. This model will provide a point estimate and two-sided 95% CI for the treatment effect and a one-sided p-value for the superiority assessment. Superiority will be established if the p-value is <0.025. The primary analysis population will be the ABPM sub-study-ITT population defined as randomized subjects who were also entered into the ABPM sub-study.

Given the nature of ABPM measurement, a high degree of dropout unrelated to randomized treatment is anticipated. The potential high level of missing data poses a challenge in the interpretation of the primary ABPM sub-study analysis. The reason for missing ABPM data will be examined to explore the impact of missing data on the sub-study primary efficacy conclusions. If the majority (defined as >70%) of the missing data is due to either subject unwillingness to repeat the ABPM procedure or due to an un-evaluable reading, then data will be treated as missing at random and the primary analysis

will be considered sufficient. Otherwise, a sensitivity analysis may be performed that will use multiple imputation from the active control arm to replace data from both treatment groups that was missing due to reasons other than subject unwillingness or un-evaluable readings. Further supplementary analyses may include an ABPM per-protocol population (PP) analysis, utilizing all ABPM-ITT subjects who are not major protocol violators or who did not change BP medications during the sub-study. Further details of sensitivity and supplementary analyses will be described in the RAP.

In order to contextualise the primary between-group comparison, a key secondary objective is to assess within-group changes from baseline over the sub-study. Assessment of within-group changes will support interpretation of the primary analysis by identifying whether there was an absence of an increase in BP in one or both treatment groups. To that end, two-sided 95% confidence intervals will be calculated for change from baseline in each ABPM parameter separately for each treatment group. For either treatment group, a lack of adverse effect on the primary endpoint of average SBP at end of sub-study will be concluded if the upper 95% confidence limit is no more than 4 mmHg. This margin was chosen as it is less than the clinically meaningful change of 5 mmHg [Whelton, 2002] and it is half the historical increase in SBP observed with rhEPO [Krapf, 2009].

The mean and two-sided 95% CI will be estimated from the primary statistical model for within treatment arm SBP change from baseline to end of sub-study.

The change from baseline 24 hour average DBP, mean arterial pressure and heart rate at end of sub-study will be assessed in a similar way as the primary, using analogous ANCOVA models with treatment and baseline as covariates.

The differences in proportion of subjects that increase/decrease their BP medication (number or dose) will be assessed using Fisher's Exact Test. The differences between treatment groups in the proportion of subjects that convert from dippers/non-dippers at baseline to non-dippers/dippers at end of sub-study will also be assessed using Fisher's Exact Test.

Plots of the mean 24 hour average values (two-sided 95% CIs) and mean changes from baseline in 24 hour average values (two-sided 95% CIs) for BP will be provided by treatment group.

Additional statistical considerations will be addressed in the RAP.

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12.13. Appendix 13: A Sub-study to Collect PK Samples in Dialysis Subjects with Anemia Associated with CKD

12.13.1. Rationale

The purpose of this sub-study is to collect PK samples in a subset of subjects (n=200) randomized to daprodustat in the main study to enable exploratory exposure-response and exposure-safety analyses.

12.13.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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 (C_{tau}) and C_{max}
Exploratory	
• 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.
• The evaluate graphical relationships between daprodustat exposure and MACE and the combined safety endpoint of MACE + thromboembolic event+ hospitalization for HF	• Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint. • Boxplots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to dose at time of MACE or combined safety endpoint (or end of treatment if no endpoint) by subjects with or without MACE or combined safety endpoint.

12.13.3. Study Design

This is a multicenter sub-study of daprodustat study 200807 (the main study). Approximately 200 subjects from centers in selected countries that are participating in the main study will be invited to participate in the PK sub-study.

12.13.4. Additional Inclusion Criteria

- Signed written informed consent prior to beginning sub-study-related procedures (subject must understand the aims, procedures, and possible consequences of the sub-study). Note: Consent to participate in the sub-study is separate from consent to participate in the main study.
- Subject must be receiving randomized daprodustat treatment in the main study.
- Only subject's receiving in center hemodialysis are eligible.

12.13.5. Study Assessments

Blood samples will be collected at any single study visit from the Week 4 through Week 52 visit (i.e., PK is collected at one visit only, based on convenience for the subject/site). Samples will be collected at the following times with respect to dosing of randomized treatment:

- Predose, 0.5h, 1h, 2h and 3h 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 the 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 main 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.

12.13.6. Sample Size

It is estimated that 150 sub-study subjects are required to have at least 80% power that the MACE rate in the sub-study is within 20% of the MACE rate in main study. To

account for missing or non-evaluable PK samples, approximately 200 subjects will be randomized. See Section 9.2.3 for more information about sample size adjustments.

Approximately 45% (n~65) of subjects in this sub-study would be expected to meet the combined safety endpoint (and n~85 subjects would not). Based on a between subject variability (CVb%) estimate for C_{max} and C_{tau} of up to 100% (as seen in a prior Phase 1 study in CKD and from population PK analysis), 65 subjects would be sufficient to have >80% power that the 95% CI around the geometric mean is within 0.6 to 1.4 times the estimate. This is considered sufficient precision for the descriptive analysis proposed.

12.13.7. PK/PD Analyses

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

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

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

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

Based on exploratory graphs (Section 12.13.2), and the efficacy and safety results from the main study, post-hoc exploratory exposure-response/safety modelling may be conducted, including exploratory graphics with metabolites. Further details will be provided in the RAP of the main study.

12.14. Appendix 14: Country Specific Requirements

12.14.1. French Administrative Considerations and Specifics Requirements

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

1. Concerning the « STUDY POPULATION»

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

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

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

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

3. Concerning the "STUDY CONDUCT CONSIDERATIONS"

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

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

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

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

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

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

  In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the

financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

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

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

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

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

4. Monitoring visits

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

5. Data entry into the eCRF

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

The Health Institution and the Investigator undertake:

1) That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.

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

6. CTR publication

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

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

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GLAXOSMITHKLINE to monitor and follow the implementation and the progress of the Study are declared with the Commission Nationale de l'Informatique et des Libertés (CNIL) by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GLAXOSMITHKLINE Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

12.14.2. Country-Specific Requirements for Czech Republic for Acceptable Contraceptive Methods

Purpose and Justification:

The purpose of this Czech Republic country-specific requirement is to specify acceptable contraceptive methods for use during participation in the study 200807. This is as a result of recent Czech Republic legislative requirements of CA directive KLH 22 dated 22Mar2016 for contraception methods.

Czech Republic Specific Contraception Requirements will apply in addition to the list of methods stated in Appendix 5:

Men and women able to have children and sexually active, must use acceptable methods of birth control 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).

- Methods of birth control include, one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide.

- Two barrier methods used in combination with spermicide, are considered as reliable contraception methods.

The study doctor will discuss with the subject the methods of birth control that should be used while he/she is in this study and will help the subject to select the methods that are appropriate for him/her.

12.15. Appendix 15: Protocol Changes

12.15.1. Changes Resulting from Protocol Amendment 1

This is an amendment to the original protocol dated 2016-JUN-09.

Amendment 1 applies only to Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Italy, Norway, Poland, Portugal, Romania, Spain, Sweden and the United Kingdom.

12.15.1.1. Summary of Changes

- Text added to clarify when the end of the study will occur.
- Removal of requirement to reduce ESA dose if Week -8 Hgb is >11.5 g/dL (study rationale and inclusion criteria).
- Additional guidance added to iron management criteria
- New exploratory objective to compare the effect of daprodustat to rhEPO on DGF after deceased donor kidney transplantation added.

12.15.1.2. List of Specific Changes

Section 4.1 Overall Design; new text; bullet point 6

- The end of the study will occur after the accumulation of 945 adjudicated first MACE and the last subject has completed their last required study visit (Section 7.1).

Section 4.3 Design Rationale; paragraph 1; sentence number 3

This study includes both a 4 week screening and a 4 week placebo run-in period prior to randomization (Day 1). The screening period permits eligibility based on laboratory assessments to be confirmed, while the run-in period will be used to establish compliance with placebo and study procedures in an attempt to minimize withdrawn consent post-randomization. ~~This 8-week period also provides an opportunity for ESA users whose screening Hgb is above the Hgb required at randomization (i.e., >11.5 to 12 g/dL) to have their ESA dose reduced (but not stopped) to allow the Hgb to decrease in order to potentially be eligible for randomization and to approach the Hgb target range (10 to 11g/dL).~~

Section 5.1 Inclusion Criteria; criteria number 3

3 Hgb concentration measured by HemoCue (range is inclusive):

	Hgb Range
Week -8	• Hgb 8 to 12 g/dL[1] (5 to 7.5 mmol/L) ~~If Hgb is >11.5 g/dL (7.1 mmol/L), decrease ESA dose aiming to achieve Hgb ≤ 11.5 g/dL by Day 1~~.

Section 6.11.1 Iron Management Criteria; paragraph 4; new text

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%.

Section 12.1 Appendix 1 Abbreviations and Trademarks; new abbreviation added

DGF	Delayed graft function

Section 12.2 Appendix 2: Secondary and Exploratory Objectives/ Endpoints; new exploratory objective added.

• To compare the effect of daprodustat to rhEPO on delayed graft function (DGF) after deceased donor kidney transplantation	• Number (%) of subjects experiencing DGF after deceased donor kidney transplantation (where DGF is defined as the use of dialysis within 7 days of the transplant) • Length of time that subjects experience DGF after deceased donor kidney transplantation

12.15.2. Changes Resulting from Protocol Amendment 2

This is an amendment to the original protocol dated 2016-JUN-09.

This amendment applies to all countries

12.15.2.1. Summary of Changes

- Changes from country-specific Amendment 1 applied to global amendment
- Country-specific requirements for France and Czech Republic added.
- Section and appendix relating to darbepoetin alfa pre-filled syringe incidents, malfunctions and user errors. Section deleted as darbepoetin alfa pre-filled syringes are not subject to device reporting requirements.
- Time and events Table 7 'Schedule of Assessments Year 1 to End of Study' modified. Main changes include new timepoints at Run-in (Week -4) and Week 2 for collection of information related to iron therapy; new timepoint at Week 52 for Kt/V_{urea} assessment; and transfusions and kidney transplant added to prompt completion of page in eCRF.
- Time and Events Table 8 'Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies' modified. Main changes are changes to the ABPM sub-study assessments including prompts for the end of the 44hour ABPM assessments and prompts for recording the times the subject awakens and goes to sleep during this 44 hour ABPM period.
- Time and events Table 9 'Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment' modified. Main changes include IRT system call removed at all visits except Early Treatment Discontinuation Visit and End of Study Visit; new timepoints for collection of information related to iron therapy, transfusions; and kidney transplant added to prompt completion of page in eCRF.
- Text added to clarify those randomized to rhEPO who transition from HD to PD will change from epoetin alfa to darbepoetin alfa.
- Text relating to the timing of dialysis in relation to the study visit has been amended. The original text 'For subjects receiving PD or home HD >3x/week, study visits must occur within 48 hours of their last dialysis session' was inaccurate as PD is daily treatment.
- For the negatively adjudicated events in 200807, the reporting process has been updated and the investigator-reported term (not the adjudicator-reported term) will be used.
- In addition to allowing a historical (last 6 months) kidney ultrasound to be used to assess entry criteria, a provision was added for a more sensitive imaging study (e.g., MRI, CT) to be used to assess entry criteria.
- Other changes include minor wording changes for clarity, updating of section numbering and cross referencing, formatting changes (for consistency) and administrative changes.

12.15.2.2. List of Specific Changes

Section 3 Objectives and Endpoints; first principal secondary endpoint; sub-bullet 2. Addition of the word symptomatic prior to deep vein thrombosis and pulmonary embolism.

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

Section 4.1 Overall Design; new text; bullet point 6. Text added to clarify when the end of the study will occur.

- **The end of the study will occur after the accumulation of 945 adjudicated first MACE and the last subject has completed their last required study visit (Section 7.1).**

Section 4.1 Overall Design; bullet point 8. Cross reference updated.

- To ensure subjects remain iron replete and to minimize the potential for iron overload during the study, the investigator will follow the iron management criteria (Section ~~6.12~~ **6.11.1**) from randomization through the end of the study treatment period.

Section 4.3 Design Rationale; paragraph 1; sentence number 3. Text deleted as requirement to reduce ESA dose if Week -8 Hgb is >11.5 g/dL removed.

This study includes both a 4 week screening and a 4 week placebo run-in period prior to randomization (Day 1). The screening period permits eligibility based on laboratory assessments to be confirmed, while the run-in period will be used to establish compliance with placebo and study procedures in an attempt to minimize withdrawn consent post-randomization. ~~This 8-week period also provides an opportunity for ESA users whose screening Hgb is above the Hgb required at randomization (i.e., >11.5 to 12 g/dL) to have their ESA dose reduced (but not stopped) to allow the Hgb to decrease in order to potentially be eligible for randomization and to approach the Hgb target range (10 to 11g/dL).~~

Section 5 Selection of Study Population and Withdrawal Criteria; paragraph 1. Text added for clarity.

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the randomized treatment is provided in the IB, IB

supplement(s) (if applicable)**, product labels for epoetin alfa and darbepoetin alfa** and other pertinent documents (e.g., Study Reference Manual (SRM), informed consent).

Section 5.1 Inclusion Criteria; criteria number 3. Text deleted as requirement to reduce ESA dose if Week -8 Hgb is >11.5 g/dL removed.

3 Hgb concentration measured by HemoCue (range is inclusive):

	Hgb Range
Week -8	• Hgb 8 to 12 g/dL[1] (5 to 7.5 mmol/L) ~~If Hgb is >11.5 g/dL (7.1 mmol/L), decrease ESA dose aiming to achieve Hgb ≤ 11.5 g/dL by Day 1~~.

Section 5.1 Inclusion Criteria; criteria number 7; paragraph 2. New text relating to country-specific amendment for France added.

Note: The country-specific requirements for France ONLY for the informed consent process are provided in Appendix 14 (see Section 12.14.1, Item 3 for details).

Section 5.1 Inclusion Criteria; criteria number 8. New criteria relating to country-specific amendment for France.

8 Other study eligibility criteria considerations: The country-specific requirements for France ONLY for inclusion in this study are provided in Appendix 14 (see Section 12.14.1, Item 1 for details).

Section 5.2 Exclusion Criteria; criteria number 18. New text added relating to the Czech Republic.

18 Females ONLY: Subject is pregnant [as confirmed by a positive serum human chorionic gonadotrophin (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 listed in the List of Highly Effective Methods for Avoiding Pregnancy in Appendix 5.

Note: See Section 12.14.2 for the country-specific requirements for the Czech Republic ONLY relating to acceptable contraceptive methods during participation in this study.

Section 6.2 Randomized Treatment Assignment; paragraph 1; sentence 2. Text deleted to avoid confusion. The randomization number is stored in the IRT database and will only be used at the very end of the study for the final data reconciliation. It is not ever used to identify the subject and not displayed on any notifications or reports.

~~Once a randomization number has been assigned by the IRT system, it must not be re-assigned.~~

Section 6.3.3 Daprodustat and rhEPO Dose Adjustment Algorithm; Paragraph 1; sentence 2. Words 'at least' added for clarity.

Dose adjustments (i.e., increase, decrease, maintain, or withheld if ≥12 g/dL) will be made programmatically for both the daprodustat and rhEPO arms by the IRT system to maintain Hgb concentrations within the range of 10-11 g/dL based on the HemoCue Hgb value measured **at least** every 4 weeks (Day 1 through Week 52) or **at least** every 12 weeks (post-Week 52 through end of treatment) disclosed to the IRT system by the investigator.

Section 6.11.1 Iron Management Criteria; paragraph 4. Additional guidance added to iron management criteria.

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%.

Section 6.12 Rescue Therapy; paragraph 2; sentence 2. New text added.

This rescue algorithm does not apply to subjects with a decrease in Hgb as a result of an acute or subacute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or vascular access). 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).

Section 6.12 Rescue Therapy; Table 6; Step 1 Initial Intervention; bullet point 3. Text added for clarity

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).**

Section 6.13 Subjects changing dialysis modality; paragraph 1; sentences 2 and 3. New text added to clarify those randomized to rhEPO who transition from HD to PD will change from epoetin alfa to darbepoetin alfa.

Subjects changing dialysis modality should not be withdrawn from the study, and should continue on the same randomized treatment (daprodustat or rhEPO). **Those subjects randomized to rhEPO who transition from PD to HD (in-center or home HD) will continue on darbepoetin alfa. However, subjects randomized to rhEPO who transition from HD to PD will switch from epoetin alfa to darbepoetin alfa at their next study visit (from Week 4 onwards). If this occurs from Week 52 onward, additional visits are required as outlined in Appendix 6.**

Section 7 Study Assessments and Procedures; bullet points 2 and 3 following paragraph 3. Text relating to the timing of dialysis in relation to study visit amended. Original text was inaccurate as PD is daily treatment.

- For subjects on PD or home HD ~~≥3x/week~~, study visits can occur on any day of the week.

- ~~For subjects receiving PD or home HD ≤3x/week, study visits must occur within 48 hours of their last dialysis session.~~

Section 7.1 Time and Events Table; Table 7 Schedule of Assessments Year 1 to End of Study; iron therapy, transfusions assessment line, new timepoints at Run-in (Week -4) and Week 2.

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			Day 1 through Week 52					
	Screen Week -8	Run-in Week -4	Day 1[13]	Week 2	Full study visit Week 4, 16, 28, 40	Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48	Week 52	Unscheduled[10]
Iron therapy, transfusions[3]	X	**X**	X	**X**	X	X	X	X

Section 7.1 Time and Events Table; Table 7 Schedule of Assessments Year 1 to End of Study; Kt/V_{urea} assessment line, new timepoint at Week 52 and footnote for Kt/V_{urea} (footnote 18) added

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			Day 1 through Week 52					
	Screen Week -8	Run-in Week -4	Day 1[13]	Week 2	Full study visit Week 4, 16, 28, 40	Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48	Week 52	Unscheduled[10]
Kt/V_{urea} **[18]**			X		X		**X**	

	Year 2				Year 3				Year 4							
Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	Week 64	Week 76	Week 88	Week 100	Week 112	Week 124	Week 136	Week 148	Week 160	Week 172	Week 184	Week 196	Week 208[14]	Unscheduled[10]	End of Study[15]	Follow-up (4-6 weeks after stopping randomized treatment)
Kt/V_{urea} **[18]**	X		X		X		X		X		X		X			

Section 7.1 Time and Events Table; Table 7 Schedule of Assessments Year 1 to End of Study; hospitalization line; kidney transplant added.

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			Day 1 through Week 52					
	Screen Week -8	Run-in Week -4	Day 1[13]	Week 2	Full study visit Week 4, 16, 28, 40	Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48	Week 52	Unscheduled[10]
Hospitalization [3] , **kidney transplant[3]**				X	X	X	X	X

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

Section 7.1 Time and Events Table; Table 7 Schedule of Assessments Year 1 to End of Study; footnote16.

16. Ultrasound of the kidneys and adrenal glands will be performed between the Week -4 and Day 1 visits. 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.

Section 7.1 Time and Events Table; Table 7 Schedule of Assessments Year 1 to End of Study; footnote17.

17 Treatment will be dispensed every 4**±1** weeks. IRT call will be required ~~every 4 weeks~~.

Section 7.1 Time and Events Table; Table 7 Schedule of Assessments Year 1 to End of Study; new footnote, footnote18.

18 A historical Kt/Vurea measurement within the last 12 weeks can be used. If a Kt/Vurea measurement is not available, then a urea reduction ratio (URR) measurement is acceptable.

Section 7.1 Time and Events Table; Table 8 Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies; VEO assessments; reference to footnote 5 added.

Protocol Activity (visits ±1 week) (Note: All visit timings are relative to Day 1)	**Screening**					**Day 1 through Week 208**								**Post-Week 52 through End of Study**
	Week -8	**Week -4**	**Day -21[1]**	**Day -14[1]**	**Day -12**	**Day 1**	**Week 4**	**Week 8 & 12**	**Week 16, 20 & 24**	**Week 28**	**Week 28 (End of week visit)**	**Week 52**	**Week 100, 148, 208**	**End of Study**
Patient Global Impression of Severity (PGI-S)[5]	X					X		X		X		X		
Patient Global Impression of Change (PGI-C)[5]								X		X		X		
Short Form 36 (SF-36)[5]						X		X		X		X		
EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) and EuroQol Visual Analogue Scale (EQ-VAS)[2, 5]						X		X		X		X	X	X

Section 7.1 Time and Events Table; Table 8 Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies; VEO assessments; new footnote added; footnote 5.

5 Subjects who are unable to or require assistance to read must not complete the questionnaires.

Section 7.1 Time and Events Table; Table 8 Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies; ABPM sub-study assessments. 44hr ABPM end, record awake and sleep times, and 44 urine collection prompts and timepoints added.

Protocol Activity (visits ±1 week) (Note: All visit timings are relative to Day 1)	Screening					Day 1 through Week 52							Post-Week 52 through End of Study	
	Week -8	Week -4	Day -21[1]	Day -14[1]	**Day -12**	Day 1	Week 4	Week 8 & 12	Week 16, 20 & 24	Week 28	**Week 28 (End of week visit)**	Week 52	Week 100, 148, 208	End of Study
ABPM sub-study(Appendix 12): Informed Consent		X												
Home BP monitoring**(twice daily for PRIOR 4 consecutive days)**			X				X	X	X	X				
44 hour ABPM **start**				X						X				
44 hour ABPM end					**X**						**X**			
Record awake and sleep times					**X**						**X**			
~~Pre- and post-dialysis weight~~				~~X~~[4]										

Section 7.1 Time and Events Table; Table 8 Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies; footnote 4 removed

4. ~~Additional to the timepoints specified in Table 7. Post-dialysis weight to be measure, before the ABPM device is attached.~~

Section 7.1 Time and Events Table; Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; IRT system call; IRT system call removed at all visits except Early Treatment Discontinuation Visit and End of Study Visit.

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)	Day 1 through Week 52[7]	
		Week 4, 16, 28, 40, 52 ± 2 weeks	Unscheduled
IRT system call	X	~~X~~	~~X~~

Protocol activity (visits ± 2 week) (Note: All visit timings are relative to Day 1)	Year 2[7]				Year 3[7]				Year 4[7]					Unscheduled	End of Study[8]
	Week 64	Week 76	Week 88	Week 100	Week 112	Week 124	Week 136	Week 148	Week 160	Week 172	Week 184	Week 196	Week 208		
IRT system call	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X

Section 7.1 Time and Events Table; Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; iron therapy, transfusions assessment line, new timepoints added at Weeks 4, 16, 28, 40, 52 and unscheduled visits.

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)	Day 1 through Week 52[7]	
		Week 4, 16, 28, 40, 52 ± 2 weeks	Unscheduled
Iron therapy, transfusions[1]	X	**X**	**X**

Section 7.1 Time and Events Table; Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; hospitalization line; kidney transplant added.

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)	Day 1 through Week 52[7]	
		Week 4, 16, 28, 40, 52 ± 2 weeks	Unscheduled
Hospitalization[1] , **kidney transplant[1]**	X	X	X

Protocol activity (visits ± 2 week) (Note: All visit timings are relative to Day 1)	Year 2[7]				Year 3[7]				Year 4[7]					Unscheduled	End of Study[8]
	Week 64	Week 76	Week 88	Week 100	Week 112	Week 124	Week 136	Week 148	Week 160	Week 172	Week 184	Week 196	Week 208		
Hospitalization[1], **kidney transplant[1]**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Section 7.1 Time and Events Table; Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; VEO assessments; reference to footnote 9 added.

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)	Day 1 through Week 52[7]	
		Week 4, 16, 28, 40, 52 ± 2 weeks	Unscheduled
PGI-S, PGI-C[4, 9]	X		
SF-36[4, 9]	X		
EQ-5D-5L& EQ-VAS[4, 5, 9]	X		

Section 7.1 Time and Events Table; Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; new footnote added; footnote 9.

9 Subjects who are unable to or require assistance to read must not complete the questionnaires.

Section 7.4 Safety; paragraph 2. ECG text deleted as the paragraph refers to safety endpoints. ECGs are not safety endpoints (baseline ECG is for entry criteria and annual ECG is for good patient care in a population with high CV risk.).

Safety endpoints will include monitoring of safety endpoint events including deaths (Section 7.4.1), other CV events (Section 7.4.2), AEs of special interest (Section 7.4.4), AEs, SAEs and AEs leading to discontinuation of randomized treatment, laboratory parameters, ~~electrocardiogram (ECG) parameters,~~ BP and HR.

Section 7.4.1.Events Referred to the Clinical Events Committee; final paragraph; sentence 2. Text updated to reflect that the reporting process has changed and the investigator-reported term (not the adjudicator-reported term) will be used.

Negatively adjudicated events will be reported as AEs or SAEs using the **investigator** ~~adjudicator~~-reported event term.

Section 7.4.3.Adverse Events (AE) and Serious Adverse Events (SAEs); paragraph 3; sentence 3. Text updated to reflect that the reporting process has changed and the investigator-reported term (not the adjudicator-reported term) will be used.

Negatively adjudicated events will be reported as AEs or SAEs using the **investigator** ~~adjudicator~~-reported event term.

Section 7.4.7 Darbepoetin Alfa Pre-filled Syringe Incidents, Malfunctions and User Errors. Section deleted as darbepoetin alfa pre-filled syringes are not subject to device reporting requirements.

~~Darbepoetin alfa pre-filled syringes are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with darbepoetin alfa pre-filled syringes.~~

~~The definition of an incident or malfunction can be found in Appendix 11. Detailed information on pre-filled syringe incidents, malfunctions and user errors will be collected on the Medical Device Incident Report Form – Darbepoetin Alfa Pre-filled Syringe.~~

~~Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 7.4.3 and Appendix 7 of the Protocol.~~

Section 7.4.9 Electrocardiograms (ECG); paragraph 4.Additional text added for clarity.

All ECGs will be performed before measurement of SBP, DBP, and HR **and before** collection of blood samples for laboratory testing, **where applicable (e.g., would not apply if ECG is performed post-HD).**

Section 7.4.10.Ultrasound, paragraph 2, sentence 2. New text to allow for the use of a more sensitive imaging study to assess entry criteria as an alternative to ultrasound.

A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria (see 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.**

Section 9.2.1 Sample Size Assumption; last paragraph. New text relating to country-specific amendment for France.

Note: The country-specific requirements for France ONLY for the sample size consideration are provided in Appendix 14 (see Section 12.14.1, Item 2 for details).

Section 9.4.2.1 Principal Secondary Analyses; bullet point 1 under paragraph 3. Addition of the word symptomatic prior to deep vein thrombosis and pulmonary embolism.

- MACE or a thromboembolic event (vascular access thrombosis, ~~a~~ **symptomatic** deep vein thrombosis or ~~a~~ **symptomatic** pulmonary embolism.

Section 10.8.2. Clinical Events Committee; paragraph 1. Addition of the word symptomatic prior to deep vein thrombosis and pulmonary embolism.

An external independent Clinical Events Committee blinded to treatment allocation will adjudicate all events reported during this study that constitute the co-primary CV safety endpoint of MACE [composite of all-cause mortality, non-fatal MI and non-fatal stroke], the principal CV secondary composite endpoints of MACE plus additional components including events of vascular access thrombosis, **symptomatic** deep vein thrombosis, **symptomatic** pulmonary embolism, CV mortality and hospitalization for HF.

Section 12.1 Appendix 1 Abbreviations and Trademarks. New abbreviations added and abbreviations not found in the protocol deleted.

ANSM	**L'Agence nationale de sécurité du médicament et des produits de santé**

~~CMO~~	~~Chief medical officer~~

CNIL	**Commission Nationale de I'Informatique et des Libertés**

CRA	**Clinical Research Assistant**

CTR	**Clinical Trials Register**

CT	**Computed tomography**

DGF	**Delayed graft function**

MRI	**Magnetic resonance imaging**

Section 12.2 Appendix 2: Secondary and Exploratory Objectives/ Endpoints; Objective 'To compare daprodustat to rhEPO on *additional CV safety endpoints'; endpoint bullet 3; death changed to mortality.*

• To compare daprodustat to rhEPO on additional CV safety endpoints	• CV ~~death~~ **mortality** or non-fatal MI[2]

Section 12.2 Appendix 2: Secondary and Exploratory Objectives/ Endpoints; Exploratory Objective 'To further compare daprodustat and rhEPO on Hgb variability'; endpoint bullet 4.

• To further compare daprodustat and rhEPO on Hgb variability	• Number (%) of subjects with a Hgb<7.5 g/dL

Section 12.2 Appendix 2: Secondary and Exploratory Objectives/ Endpoints. New exploratory objective added.

• **To compare the effect of daprodustat to rhEPO on delayed graft function (DGF) after deceased donor kidney transplantation**	• **Number (%) of subjects experiencing DGF after deceased donor kidney transplantation (where DGF is defined as the use of dialysis within 7 days of the transplant)** • **Length of time that subjects experience DGF after deceased donor kidney transplantation**

Section 12.5; Appendix 5 Female Eligibility Criteria; last paragraph before bullet 2. New text relating to country-specific amendment for Czech Republic

Note: See Section 12.14.2 for the country-specific requirements for the Czech Republic ONLY relating to acceptable contraceptive methods during participation in this study.

Section 12.6; Appendix 6: Randomized Treatment Dose Adjustment Scheme; line 9 column 3 of table; word visit added for clarity.

HemoCue Hgb (g/dL) at current study visit[1]	HemoCue Hgb change since last study visit[1]	Randomized Treatment Dose Adjustment[5]
≥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.**

Section 12.6; Appendix 6: Randomized Treatment Dose Adjustment Scheme; footnote 1; last bullet point.

- For subjects ~~transitioning to dialysis~~ **changing dialysis modality from HD to PD**: Visits every 4 weeks for 12 weeks.

Section 12.6; Appendix 6: Randomized Treatment Dose Adjustment Scheme; footnote 2; word visit added for clarity.

2. This rule applies to any mandated **visit** or unscheduled visit, provided it has been at least 2 weeks from the prior study visit.

Appendix 11 Definition of Darbepoetin Alfa Pre-filled Syringe Incidents. Section deleted as darbepoetin alfa pre-filled syringes are not subject to device reporting requirements.

~~**Definition:**~~

- ~~Incident – Any malfunction or deterioration in the characteristics and/or performance of the pre-filled syringe, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.~~
- ~~Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.~~

~~**It is sufficient that:**~~

- ~~an **incident** associated with a pre-filled syringe happened and~~
- ~~the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.~~

~~A serious deterioration in state of health can include:~~

- ~~life-threatening illness~~
- ~~permanent impairment of body function or permanent damage to a body structure~~

- ~~a condition necessitating medical or surgical intervention to prevent one of the above~~
- ~~fetal distress, fetal death or any congenital abnormality or birth defects~~

~~Examples of incidents~~

- ~~a patient, user, care giver or professional is injured as a result of failure or misuse of the pre-filled syringe~~
- ~~a patient's treatment is interrupted or compromised by failure of the pre-filled syringe~~
- ~~a patient's health deteriorates due to failure of the pre-filled syringe~~

Appendix 12; Section 12.12.3.3 Study Assessments; Week 28 Study Visit; sentence 3. Wording change for clarity.

The time and date of study medication administration, before and while ~~on~~ **wearing** the ABPM device, will be recorded

Appendix 14 Country Specific Requirements. Text deleted as country specific requirements added.

~~No county specific requirements exist~~

Appendix 14 Country Specific Requirements; new Section 12.14.1 French Administrative Considerations and Specifics Requirements

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

1. Concerning the « STUDY POPULATION»

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

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

Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"

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

9. Concerning the "STUDY CONDUCT CONSIDERATIONS"

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

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

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

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

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

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

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

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

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

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

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

10. Monitoring visits

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

11. Data entry into the eCRF

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

The Health Institution and the Investigator undertake:

1) That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the electronic eCRF of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
2) That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
3) That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
4) To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
5) That the Investigator and the staff of the investigator center enter the data of the electronic eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.
6) That the Investigator resolves and returns to GLAXOSMITHKLINE the data queries issued by GLAXOSMITHKLINE or a service provider designated by GLAXOSMITHKLINE within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GLAXOSMITHKLINE and/or a company designated by GLAXOSMITHKLINE.
7) To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.

8) To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

12. CTR publication

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

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

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GLAXOSMITHKLINE to monitor and follow the implementation and the progress of the Study are declared with the Commission Nationale de l'Informatique et des Libertés (CNIL) by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GLAXOSMITHKLINE Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

Appendix 15 Country Specific Requirements; new Section 12.15.2 Country-Specific Requirements for the Czech Republic; addition of text relating to acceptable contraceptive methods for the Czech Republic.

Purpose and Justification:

The purpose of this Czech Republic country-specific requirement is to specify acceptable contraceptive methods for use during participation in the study 200807. This is as a result of recent Czech Republic legislative requirements of CA directive KLH 22 dated 22Mar2016 for contraception methods.

Czech Republic Specific Contraception Requirements will apply in addition to the list of methods stated in Appendix 5:

Men and women able to have children and sexually active, must use acceptable methods of birth control 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).

- Methods of birth control include, one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide.

- Two barrier methods used in combination with spermicide, are considered as reliable contraception methods.

The study doctor will discuss with the subject the methods of birth control that should be used while he/she is in this study and will help the subject to select the methods that are appropriate for him/her.

12.15.3. Changes Resulting from Protocol Amendment 3

This is an amendment to the protocol amendment dated 2017-OCT-12.

This amendment applies to all countries.

12.15.3.1. Summary of Changes

- Added retest values for Hgb and TSAT to determine eligibility at Week -8.
- 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.
- Provided guidance for those receiving HD two times a week who are randomized to the epoetin alfa arm and require three times a week epoetin alfa dosing.
- 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 new darbepoetin alfa dose strengths (not available in all countries).
- Added direction regarding randomized treatment and study continuation for subjects who will be away from the research site for an extended period of time.
- Clarified timeframe for iron management criteria.
- Clarified "frequency of dialysis" inclusion criterion and valid study visit days by dialysis type.
- Clarified baseline dose for the purposes of the rescue algorithm for subjects switching from HD to PD who are randomized to rhEPO.
- Shortened visit window for the Week 2 and 4 visits and clarified visit window for Week -4 and Day 1 visits.
- Modified Time and Events Table 7 'Schedule of Assessments Year 1 to End of Study'. Main changes include addition of Informed Consent activity; revised footnotes to remove Kt/V and URR measurement for daily HHD and allowance of extended timing to do Day 1 ECG and to do ultrasound and/or additional testing; more clarity around randomized treatment dispensing and compliance, including provisions for deferring dose changes till the next HD treatment; removed capture of rescue medications from unscheduled and early termination visits as rescue evaluation is triggered at scheduled visits; added footnote to clarify biomarkers will be stored for future analyses except if not permitted by IRB/EC or refused by subject; addition of Argentina only pregnancy requirement; and removal of footnote at Week -4 visit for only collecting SAEs related to study participation or a GSK product as it did not apply.
- Modified Time and Events Table 8 'Schedule for Assessments for Patient Reported Outcomes, Genetics and Sub-studies' modified to add healthcare resource utilization data collection, to streamline ABPM assessments and to add timing for informed consent and additional eligible collection visits for PK sub-study.
- Modified Time and Events Table 9 "Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment" to remove capture of rescue

medications (rescue evaluation is triggered at on-treatment scheduled visits), to add healthcare resource utilization data collection, and to complete ABPM assessments.
- Added direction to see CEC Site Manual for full scope of reporting requirements.
- Add clarifications for PD subjects as to how weight, blood pressure, and laboratory assessments are to be done.
- Clarified timing of assessments relative to dialysis for SBP, DBP, HR and laboratory assessments.
- Added reminder for the ordering of assessments for blood pressure and that the over-read of the Day 1 ECG is required to confirm eligibility.
- Updated PRO section to add healthcare resource utilization data being collected for completeness and updated endpoint labels for EQ-5D-5L & EQ-VAS.
- Revised statistical section to change from two-sided testing at the 5% level to one-sided testing at the 2.5% level; correct the comparator for the Null and Alternative hypotheses; to change significance levels to p-values; to add a more complete description of the adjustments to statistical model; to update hyporesponder analyses; and to add additional text regarding the interim analysis process.
- Added exploratory endpoints around Hgb variability, iron parameters, transfusions, and dose adjustment scheme.
- Edited Risk Assessment information to align with version 8 of the Investigator's Brochure.
- Updated FSH level to confirm menopause.
- Provision for possible adjustment to the Dose Adjustment Algorithm triggers for Hgb values 7.5 g/dL to <9.5 g//dL based on the review of blinded instream aggregate Hgb data.
- Changes to ABPM sub-study to add atrial fibrillation/flutter screening, remove home BP monitoring, change from 44- to 24-hour APBM, change in time-point for assessment (from Week 28 to Week 16), and adjustments to objectives, endpoints and analysis.
- Clarified additional inclusion and added additional eligible visits to collect PK samples in PK sub-studies.
- Other changes include spelling corrections or minor wording changes for clarity, formatting changes (for consistency), a missing reference (epoetin alfa IV:SC conversion), and administrative changes.

12.15.3.2. List of Specific Changes

Cover page. Added back protocol "Short Title".

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

Section 1. Protocol Synopsis for Study 200807; Overall Design, 1st bullet and Section 12.1. Appendix 1: abbreviations. Corrected ESA abbreviation. Revised analysis provided.

- This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center, event-driven study in dialysis subjects with anemia associated with CKD who are currently treated with ~~erythropoietin~~**erythropoiesis**-stimulating agents (ESAs[1]).

ESA	~~Erthropoetin~~**Erythropoiesis**-stimulating agent

Section 1. Protocol Synopsis for Study 200807; Analysis 1st paragraph. Revised analysis provided.

The study's co-primary endpoints will **each** be tested for non-inferiority using a **one-sided** 2.5% significance level and **the relevant confidence bound from** a two-sided 95% confidence interval (CI) **(upper bound for MACE and lower bound for the Hgb co-primary endpoint)** ~~for each test~~.

Section 3 Objectives and Endpoints; safety endpoint. Changed "study treatment" to "randomized treatment" to more correctly describe endpoint.

Safety	
• To compare the safety and tolerability of daprodustat to rhEPO	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest[1] • Reasons for discontinuation of ~~study~~**randomized** treatment • Absolute values and changes from baseline in laboratory parameters, BP and heart rate (HR)

Section 4.1. Overall Design; 7th bullet. Clarified how stratification factors are considered prognostically important.

- Subjects will be stratified by dialysis type [HD* or PD], by region (see Appendix 3), and by participation in the ABPM sub-study. Dialysis type and region are ~~considered to be~~ stratification factors ~~that are~~**considered to be**-potentially prognostic**ally important, i.e., predictive** of study endpoints while participation in the ABPM sub-study is an administrative stratification factor intended solely to ensure a similar number of sub-study subjects in each of the two randomized groups.

Section 4.5.2. Benefit Assessment; 1st paragraph. Clarifited other ESAs.

In clinical trials of up to 24 weeks in duration, in subjects with anemia associated with CKD, daprodustat has been shown to treat Hgb to target range. Daprodustat may present several important advantages over rhEPO and ~~other ESAs~~ **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 increases in EPO exposure with rhEPO [Szczech, 200]; 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 #3. Added retest for Hgb values within the variability threshold for testing to determine Week -8 eligibility, with associated footnote (inserted new footnote 2).

	Hgb Range
Week -8	• Hgb 8 to 12 g/dL[1] (5 to 7.~~4~~5 mmol/L). • **If Hgb is 12.1 to 12.4 g/dL[2] (7.5-7.7 mmoL/L), up to two retests are allowed; the retest value must be between 8 to 11.5 g/dL (5 to 7.4 mmol/L).**
Day 1	• Hgb 8 to 11 g/dL (5 to 6.8 mmol/L) **and** receiving at least the minimum ESA dose[3]. • Hgb >11 g/dL to 11.5 g/dL (6.8 mmol/L to 7.1 mmol/L) **and** receiving greater than the minimum ESA dose[3].

1. Conversion from g/dL to g/L is 1:10, e.g., Hgb of 8 to 10 g/dL is equivalent to 80-100g/L.
2. **The first retest will use the original Week -8 blood sample. If this value is >12 g/dL, one additional retest can be performed using a new blood sample on the study visit day. The final retest value is entered into the IRT system. For in-center HD, retests will be pre-dialysis, in between dialysis sessions for HHD subjects at the study visits, and at the study visits for PD subjects, as per standard of care.**
3. Minimum ESA dose: epoetins (including biosimilars): 1500 units (U)/week intravenous (IV) or 1000 U/week SC; darbepoetin alfa: 20 μg/4 weeks SC/IV; methoxy PEG-epoetin: 30 μg/month SC/IV

Section 5.1. Inclusion Criteria; inclusion #5. Updated frequency of dialysis descriptions.

5. Frequency of Dialysis.

a. HD **(in-center)**: ≥2 times/week

b. PD: ~~Daily PD~~ ≥**5 times/week**

c. Home HD: ~~short daily or nocturnal (≥3x/week)~~ **≥2 times/week**

Section 5.1. Inclusion Criteria; inclusion #7. Clarified study visit this is confirmed.

7. Informed consent **(screening only):** capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

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

1. **Kidney transplant:** Planned living-related **or living-unrelated** kidney transplant within 52 weeks after study start (Day 1).

Section 5.2. Exclusion Criteria; exclusion #3. Added retest for TSAT values within the variability threshold for testing to determine Week -8 eligibility.

3. **Transferrin saturation (TSAT) (screening only):** ≤20%. **If TSAT is 18-20%, then a retest using a new blood sample can be obtained within 7 days of the final laboratory report; the final retest value must be >20% to confirm eligibility**.

Section 5.2. Exclusion Criteria; exclusion #5. Added Untreated.

5. **Other causes of anemia: Untreated** pernicious anemia, thalassemia major, sickle cell disease or myelodysplastic syndrome.

Section 5.2 Exclusion Criteria; exclusion #11. Clarified situation where exclusion does not apply.

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

Section 5.2. Exclusion Criteria; exclusion #16. Broadened exclusion to include participation in a study with an investigational agent or device.

16. ~~Prior investigational product exposure:~~ ~~Use of an investigational agent ≤30 days or within five half lives of the investigational agent (whichever is longer) prior to screening. Note: at screening, this exclusion applies to use of the investigational agent within 30 days or within five half lives (whichever is longer).~~ **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; revised bullet and new text. Removed "chronic" from prohibited medication use stopping criterion and added text to clarify that subjects may be reapproached about restarting randomized treatment.

- Need for ~~chronic (~~more than 14 days use~~)~~ of prohibited medication (Section 6.10.2)

Subjects may be reapproached about restarting randomized treatment in certain circumstances if the sponsor and the investigator agree.

Section 5.5.1. Procedures for Subject Follow-up; bullet 1. Deleted second sentence in first bullet.

- 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 6.1 Placebo Run-in and Randomized Treatment. Added footnote 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.

The term 'randomized treatment' is used throughout the protocol to describe either study treatment (i.e., daprodustat or darbepoetin alfa) received by the subject during the

treatment period as per the protocol design. **Randomized treatment will be provided by GSK[3].**

[3] 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.

Section 6.1 Placebo Run-in and Randomized Treatment. Added new EU-sourced darbepoetin alfa PFS strengths.

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 6.3.1. Daprodustat Dosing Information; Table 3, Added reference for epoetin IV to SC conversion (reference added to Reference list).

1. Standardized rhEPO IV dose (U/week) = 161/113 * (epoetin SC dose (units)) / (frequency) **[Beserab, 2002]**

Beserab A, Reyes C, Hornberger J. Meta-Analysis of Subcutaneous Versus Intravenous Epoetin in Maintenance Treatment of Anemia in Hemodialysis Patients. Am J of Kidney Dis 2002;40: 439-446.

Section 6.3.2. rhEPO Dosing Information. Added clarity how to dose three times a week study rhEPO to a subject on HD two times a week.

For subjects who are on HD two times a week and are randomized to the epoetin alfa arm <u>and</u> require three times a week epoetin alfa dosing, the weekly dose should be split as close to equally, using the study-allocated dose vials of epoetin alfa, across the two dialysis treatments.

Section 6.3.2. rhEPO Dosing Information; Tables 4 and 5. Clarified "every week" frequency to be "once a week".

Table 4 Epoetin Alfa Dose Steps

Total Weekly Dose	**Dose and Frequency**
1500	1500 U ~~every~~ **once a week**
2000	2000 U ~~every~~ **once a week**
3000	3000 U ~~every~~ **once a week**
4000	4000 U ~~every~~ **once a week**
5000	5000 U ~~every~~ **once a week**
6000	6000 U ~~every~~ **once a week**
8000	8000 U ~~every~~ **once a week**
10000	10000 U ~~every~~ **once a week**
12000	4000 U ~~3~~ **three** times a week
15000	5000 U ~~3~~ **three** times a week
18000	6000 U ~~3~~ **three** times a week
21000	7000 U ~~3~~ **three** times a week
24000	8000 U ~~3~~ **three** times a week
27000	9000 U ~~3~~ **three** times a week
30000	10000 U ~~3~~ **three** times a week
36000	12000 U ~~3~~ **three** times a week
42000	14000 U ~~3~~ **three** times a week
48000	16000 U ~~3~~ **three** times a week
60000	20000 U ~~3~~ **three** times a week

Table 5 Darbepoetin Alfa Dose Steps

Total 4-Weekly Dose	PFS Dose and Frequency
20 µg	20 µg every 4 weeks
30 µg	30 µg every 4 weeks
40 µg	40 µg every 4 weeks
60 µg	60 µg every 4 weeks
80 µg	80 µg every 4 weeks
100 µg	100 µg every 4 weeks
150 µg	150 µg every 4 weeks
200 µg	100 µg every 2 weeks
300 µg	150 µg every 2 weeks
400 µg	100 µg ~~every 1~~ once a week

Section 6.3.3. Daprodustat and rhEPO Dose Adjustment Algorithm; 2nd paragraph and new text. Added clarifier around dispensing of randomized treatment from Week 52 onwards and rationale for the possible adjustment to the Dose Adjustment Algorithm based on the review of blinded instream aggregate Hgb data.

From Week 52 onwards, additional study visits to check Hgb and dispense randomized treatment **(where directed by the IRT system)** will be required under the circumstances outlined in Appendix 6.

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 6 based on the review of blinded instream aggregate Hgb data.

Section 6.3.4. 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.

6.3.4. Randomized Treatment Temporary Interruption

Every effort must be made to continue randomized treatment and to complete study visits, where able; however, sites should contact PPD Remote Site Monitor-Local 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.**
- **HD or PD subjects receiving oral daprodustat or PD subjects receiving SC darbepoetin alfa who cannot return to the site for a period >5 weeks.**
- **HD subjects receiving IV rhEPO who cannot return to the site in time for the next scheduled dose.**

In exceptional circumstances, local 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 6.10.2. Prohibited Medications and Non-Drug Therapies; new text. Added clarification that no other investigational agents or devices are permitted during the study.

No other investigational agents or devices are permitted from study entry through completion of the study, with the exception of the randomized treatment administered for this study.

Section 6.11.1. Iron Management Criteria; paragraph 1. Added clarifier for when the criteria start and stop.

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 6.12. Rescue Criteria; paragraph 2. Minor clarification in wording to match wording in IRT system.

This rescue algorithm **does not** apply to subjects with a ~~decrease in~~ **low** Hgb as a result of an acute or subacute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or vascular access).

Section 6.12. Rescue Criteria; Table 6. Minor clarification for visits where rescue evaluation can be triggered and in title of Table 6.

Table 14 Rescue Algorithm for Anemia ~~Therapy~~**Management**

Evaluate Subject for Rescue if:

HemoCue Hgb remains <9 g/dL **(at a scheduled study visit, Week 4 onwards)** despite three[1] consecutive dose increases above the starting[2] or post-rescue[3] dose (where HemoCue Hgb is <9 g/dL prior to each dose increase) OR HemoCue Hgb is <7.5 g/dL despite a dose increase at the prior study visit.

Section 6.12. Rescue Criteria; footnotes. Inserted new footnote #2 to clarify baseline dose for the purposes of the rescue algorithm for subjects switching from HD to PD who are randomized to rhEPO and made a minor change in #3 (previously #2).

2.For subjects who have switched from HD to PD who are randomized to rhEPO, the baseline dose for the purposes of the rescue algorithm is the new darbepoetin alfa dose..

3.For subjects who previously ~~are~~were 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.

Section 6.13. Subjects Changing Dialysis Modality; 1st sentence. Clarification added on randomized treatment to receive if switching dialysis modality.

Subjects changing dialysis modality should not be withdrawn from the study, and ~~should~~**will** continue in ~~on~~ the same randomized treatment **arm** (daprodustat or rhEPO) **they were originally assigned**.

Section 7. Study Assessments and Procedures; 1st and 2nd bullets. Clarified valid study visit days.

- For subjects on 3-**5**x/week HD, the designated study visit must not occur on the first dialysis session of the week, **i.e., immediately following the longest interval between HD sessions**. For example, if on a Monday-Wednesday-Friday schedule, the study visit should be on Wednesday or Friday.

- For subjects on PD~~ or home HD~~, study visits can occur on any day of the week.

Section 7. Study Assessments and Procedures; new paragraph. Inserted new text to clarify the visit schedule for study visits through Day 1.

The Week -4 and Day 1 visits should be completed 4 weeks ±1 week after the last visit; however, the total duration of the Screening and Run-In periods (from Week -8 to Day 1) should be 8 weeks ±1 week (i.e., 7-9 weeks).

Section 7. Study Assessments and Procedures; paragraphs after bullets. Inserted new text to state the revised visit window for the Week 2 and 4 visits and made minor changes

to visit structure a separate paragraph as it applies to all study visits and corrected spelling of center.

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 8 onwards** is ±1 week.

In exceptional circumstances, minor changes to visit structure may be permitted after consultation with the PPD Medical Monitor.

Study assessments should preferably be done at dialysis centers; however, in some circumstances (i.e., where the dialysis ~~centre~~**center** and research site are not co-located) assessments can be performed at the research site.

Section 7.1. Table 7 Schedule of Assessments Year 1 to the End of the Study. Updated visit window text.

Protocol activity (visits ±1 week, **except Weeks 2 and 4 which are ±3 days)** All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**

Section 7.1. Time and Events Table; Table 7 Schedule of Assessments Year 1 to Week 52. Added Informed Consent activity and associated footnote (#22).

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
Informed Consent (main study)	**X[22]**							

22.Informed consent will be obtained prior to any study procedures.

Section 7.1. Table 7 Schedule of Assessments Year 1 to the End of the Study and Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment. Clarified name of IRT system transaction.

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
IRT system ~~call~~**transaction[17]**	X	X	X	X	X	X	X	X

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Year 2**				**Year 3**				**Year 4**					**Unscheduled[10, 12]**	**End of Study[15]**	**Follow-up (4-6 weeks after stopping randomized treatment)**
	Week 64	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208[14]**			

IRT system ~~call~~**transaction**[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)**	**Day 1 through Week 52**[7]	
		Week 4, 16, 28, 40, 52 ± 2 weeks	**Unscheduled**
IRT system ~~call~~**transaction**	X		

Section 7.1. Table 7 Schedule of Assessments Year 1 to the End of the Study and Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; Weight and SBP/DBP, HR. Updated text for PD subjects.

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1**[13]	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled**[10]
Weight (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; **at study visits per standard of care for** ~~and~~ PD ~~subjects~~) and EDW	X	X	X	X	X	X	X	X
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; **at study visits per standard of care for** ~~and~~ PD ~~subjects~~) (single readings unless otherwise indicated)	X	X	X (triplicate)	X	X	X	X (triplicate)	X

	Year 2				**Year 3**				**Year 4**							
Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Week 64**	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208**[14]	**Unscheduled**[10]	**End of Study**[15]	**Follow-up (4-6 weeks after stopping randomized treatment)**

Weight (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; **at study visits per standard of care for** ~~and~~ PD ~~subjects~~) and EDW	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects; between treatments for HHD; **at study visits per standard of care for** ~~and~~ PD ~~subjects~~) (single readings unless otherwise indicated)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (triplicate)	X

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)**	**Day 1 through Week 52[7]**	
		Week 4, 16, 28, 40, 52 ± 2 weeks	**Unscheduled**
SBP/DBP, HR (pre- and post-dialysis for in-center HD subjects**;** between treatments for HHD**; at study visits per standard of care for** ~~and~~ PD ~~subjects~~) (single readings unless otherwise indicated)	X (triplicate)	X	X

Section 7.1. Time and Events Table; Table 7 Schedule of Assessments Year 1 to Week 52. Added footnote #2 to Day 1 timepoint and updated wording of this footnote to provide flexibility around ECG timing.

Protocol activity (visits ±1 week**)** All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
ECG [2]			X[2]				X	

2. Day 1 ECG **may be performed as early as the Week -4 visit through the Day 1 visit on a dialysis day on a dialysis day (if 3 times/week dialysis, cannot be done on the first dialysis session of the week). If performed on Day 1, it** must be pre-dialysis **and over-read prior to randomization**. All other ECGs assessments may be recorded pre or post dialysis and require over-reading.

Section 7.1. Time and Events Table; Table 7 Schedule of Assessments Year 1 to Week 52. Updated footnote #16 to include a broadened window to conduct ultrasound and time to complete additional testing if required.

16. Ultrasound of the kidneys and adrenal glands will be performed ~~between the Week -4 and Day 1 visits~~ **as early as 6 weeks prior to the Day 1 visit. If results of kidney and adrenal ultrasound require follow-up testing, then the run-in period can be extended by 1 additional week.**

Section 7.1. Table 7 Schedule of Assessments Year 1 to the End of the Study. Clarified footnotes associated with Unscheduled visits and text and footnotes regarding randomized treatment dispensing and compliance; added flexibility for administering randomized treatment after the study visit day (new footnote #19).

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
Placebo run-in or randomized treatment dispensing **(start administration on day of dispensing)[19]**		X (placebo)	X	X[9~~11~~]	X	X	X	X[9~~11~~]
Placebo run-in or randomized treatment compliance[19]			X (placebo)	X[11]	X	X	X	X[11]

	Year 2				**Year 3**				**Year 4**							
Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Week 64**	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208[14]**	**Unscheduled[10,12]**	**End of Study[15]**	**Follow-up (4-6 weeks after stopping randomized treatment)**
Randomized treatment dispensing **(start administration on day of dispensing)[17,19]**	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9, ~~11, 12~~]		
Randomized treatment compliance[17,19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11, ~~12~~]	X	

10. If a subject lost their placebo run-in or randomized treatment, it is not necessary to perform the unscheduled visit assessments other ~~then~~ **than** dispensing placebo run-in or randomized treatment.
11. Required only if dose is changed or randomized treatment is dispensed ~~(year 2 onwards)~~. **Compliance checking will be required when a dose of randomized treatment is changed.**
12. Additional visits to check Hgb and dispense randomized treatment **(where directed by the IRT system)** are required under the circumstances described in Appendix 6. Hematology and chemistry samples are not required. ~~For any unscheduled visit, compliance checking will be required when a dose of randomized treatment is changed.~~

17. Treatment will be dispensed every 4±1 weeks; **an** IRT ~~call~~ **transaction** will be required; **perform randomized treatment compliance.**

19. In circumstances where the new dose of randomized treatment cannot be dispensed on the day of the study visit, the new dose of randomized treatment can be dispensed at next HD treatment. For visits after Day 1, prior randomized treatment should be continued unless on dose hold, Hgb ≥12 g/dL. Compliance is deferred until randomized treatment is returned.

Section 7.1. Table 7 Schedule of Assessments Year 1 to the End of the Study and Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment. Clarified Rescue Medication activity and removed X for unscheduled and Early Termination visits given rescue evaluation is only triggered at scheduled visits; for the latter, also removed footnote #2.

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
Rescue medication**(s) for Initial Intervention**[3,4]					X	X	X	~~X~~

	Year 2				**Year 3**				**Year 4**							
Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Week 64**	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208[14]**	**Unscheduled[10,12]**	**End of Study[15]**	**Follow-up (4-6 weeks after stopping randomized treatment)**
Rescue medication**(s) for Initial Intervention**[3,4]	X	X	X	X	X	X	X	X	X	X	X	X	X	~~X~~		

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)**	**Day 1 through Week 52[7]**	
		Week 4, 16, 28, 40, 52 ± 2 weeks	**Unscheduled**
~~Rescue medication[1,2]~~	~~X~~		

~~2. See details on rescue in Section 6.12.~~

Section 7.1. Table 7 Schedule of Assessments Year 1 to the End of the Study. Added pregnancy requirement (new footnote #20) for Argentina only as required by local law.

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
FRP only: Serum pregnancy test [5,20]		X	X		X		X	

	Year 2				**Year 3**				**Year 4**							
Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Week 64**	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208[14]**	**Unscheduled[10]**	**End of Study[15]**	**Follow-up (4-6 weeks after stopping randomized treatment)**
FRP only: serum pregnancy test[5,20]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

20. For Argentina ONLY: Pregnancy testing will be performed every 4 weeks for FRP as required by local law.

Section 7.1. Time and Events Table; Table 7 Schedule of Assessments Year 1 to Week 52. Added footnote #21 to permit omission of storage biomarker collection under certain circumstances.

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**
Storage biomarkers[21]			X		Wk 28		X	

21. Biomarker samples will be stored for future analyses for all subjects, except if not permitted by IRB/EC or refused by subject.

Section 7.1 Table 7 Schedule of Assessments Year 1 to the End of the Study and Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment Year 1 through End of Study. Removed footnote #8 from the Run-in Week -4 visit, as it did not apply, and changed MACE to clinical events to more accurately represent safety data collected (both tables).

Protocol activity (visits ±1 week) All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)			**Day 1 through Week 52**					
	Screen Week -8	**Run-in Week -4**	**Day 1[13]**	**Week 2**	**Full study visit Week 4, 16, 28, 40**	**Abbreviated study visit Week 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled[10]**

Non-serious AEs, SAEs, AEs of special interest, ~~MACE~~ **clinical events**	X[8]	X[8]	X	X	X	X	X	X

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

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)**	**Day 1 through Week 52[7]**	
		Week 4, 16, 28, 40, 52 ± 2 weeks	**Unscheduled**
Non-serious AEs, AEs of special interest, SAEs, ~~MACE~~**clinical events**	X	X	X

Protocol activity (visits ± 2 week) (Note: All visit timings are relative to Day 1)	**Year 2[7]**				**Year 3[7]**				**Year 4[7]**					**Unscheduled**	**End of Study[8]**
	Week 64	**Week 76**	**Week 88**	**Week 100**	**Week 112**	**Week 124**	**Week 136**	**Week 148**	**Week 160**	**Week 172**	**Week 184**	**Week 196**	**Week 208**		
Non-serious AEs, SAEs, AEs of special interest, ~~MACE~~**clinical events**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Section 7.1. Time and Events Table; Table 8 Schedule of Assessments for Patient Reported Outcomes, Genetics and Sub-studies. Added healthcare resource utilization for completeness. For ABPM sub-study, updated footnote #4 re: timing of informed consent, removed Home BP monitoring, added atrial fibrillation/flutter screening, and revised visit assessment timings and corresponding new footnote (#6). For PK sub-study, added Informed Consent timing and additional timepoints for PK sample collection. Reordered all footnotes.

Protocol Activity (visits ±1 week) (Note: All visit timings are relative to Day 1)	**Screening**					**Day 1 through Week ~~52~~208**								**~~Post-Week 52 through End of Study~~ End of Study**
	Week -8	Week -4	~~Day -21[1]~~	~~Day -14[1]~~	~~Day - 12~~	Day 1	Week 4	Week 8 & 12	Week 16, 20 & 24	Week 28	Week 32, 36, 40, 44, 48 ~~(End of week visit)~~	Week 52	Week 100, 148, 208	
Healthcare resource utilization (subject reported)							**X**	**X**	**X**	**X**		**X**	**X**	**X (& Follow up)**
ABPM sub-study (Appendix 12): Informed Consent	**X[4]**	X[4]												
~~Home BP monitoring(twice daily for PRIOR 4 consecutive days)~~			~~X~~				~~X~~	~~X~~	~~X~~	~~X~~				
Atrial fibrillation/flutter screening		X[5]												
4424 hour ABPM ~~start~~		X[6]		~~X~~					**X (Week 16)**	~~X~~				
~~44 hour ABPM end~~					~~X~~						~~X~~			
Record awake and sleep times		**X[7]**							X[7] **(Week 16)**		~~X~~			
PK sub-study (Appendix 13) **Informed Consent**						**X[8]**	**X[8]**	**X[8]**	**X[8]**	**X[8]**	**X[8]**	**X[8]**		
PK assessment							X[9]	X[9]	**X[9]**	**X[9]**	**X[9]**	**X[9]**		

1. Subjects who are unable to or require assistance to read must not complete the questionnaires.

2. Only in selected countries. See Appendix 3.

3. Informed consent for optional Genetic research should be obtained before collecting a sample. To minimize potential study bias, the genetic sample should be collected on Day 1.

4. Informed consent for ABPM sub-study can be obtained at Week -8 or at the Week -4 visit prior to conducting any ABPM sub-study assessments

5. Heart rate will be assessed prior to ABPM, subjects with irregular heart beat will undergo an ECG to assess if atrial fibrillation/flutter is present (see Section 12.12.3.3.)

6. Baseline ABPM will be performed at any mid-week dialysis visit starting at Week -4 until 1 week prior to randomization (Day 1); the device will be returned at the next visit, which ideally is no later than 1 week prior to randomization to allow for QC of the ABPM.
7. Subject will record sleep and awake times during the ABPM session.
8. Informed consent for PK sub-study can be obtained anytime from Day 1 (once the subjects is confirmed to have been randomized to daprodustat) till Week 52, i.e., last study visit where PK sampling can be obtained.
9. Blood samples will be collected at **any single study visit from the Week 4 through Week 52 visit** ~~the Week 4 OR Week 8 OR Week 12~~ (i.e., PK is collected at one visit only, based on convenience for the subject/site).
~~5. Subjects who are unable to or require assistance to read must not complete the questionnaires.~~

Section 7.1. Time and Events Table; Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; new rows. Added requirements for ABPM sub-study, including a footnote to clarify ABPM sub-study requirement to record sleep and wake time during the ABPM session.

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)**	**Day 1 through Week 52[7]**	
		Week 4, 16, 28, 40, 52 ± 2 weeks	**Unscheduled**
ABPM sub-study (Appendix 12**Appendix 12):** **24 hour ABPM**		**X (Week 16)**	
Record awake and sleep times		**X (Week 16)[2]**	

2. **Subject will record sleep and wake time during the ABPM session.**

Section 7.1. Time and Events Table; Table 9 Schedule of Assessments for Subjects Permanently Discontinuing Randomized Treatment; new row. Added healthcare resource utilization for completeness.

Protocol Activity All assessments pre-dialysis unless otherwise specified (Note: All visit timings are relative to Day 1)	**Early Treatment Discontinuation Visit (within 2 weeks of discontinuing randomized treatment)**	**Day 1 through Week 52**	
		Week 4, 16, 28, 40, 52 ± 2 weeks[7]	**Unscheduled**
Healthcare resource utilization (subject reported)	**X**		

Section 7.4.1. Events Referred to the Clinical Events Committee; 1st paragraph. Added reference to CEC Site Manual for scope of reporting requirements.

Investigators should refer any event suspected to be one **of** the ~~following~~ events **below** to the Clinical Events Committee for adjudication~~:~~**. See CEC Site Manual for full scope of reporting requirements.**

Section 7.4.1. Events Referred to the Clinical Events Committee; 2nd paragraph after bullets. Added clarity where to find description of source documentation required to support adjudication of events.

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

Section 7.4.4. Adverse Events of Special Interest; revised last sentence for clarity.

The results of any investigation should be recorded ~~in~~**on** the **AE page and** the relevant **AE of special interest page** of the subject's eCRF.

Section 7.4.7. Height and Weight; 3rd sentence; corrected spelling of center.

For in-**center**~~centre~~ HD subjects, weight will be measured pre and post-dialysis. For **HHD subjects, weight** will be done **at study visits** between **dialysis sessions. For PD subjects, this assessment will be done at study visits, as per standard of care.** ~~For HHD and PD subjects these assessments will be done 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.

For in-**center**~~centre~~ HD subjects, SBP, DBP and HR will be measured pre and post-dialysis. For HHD ~~and PD~~ subjects, these assessments will be done **at study visits** between **dialysis sessions. 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 (e.g., would not apply for post-HD measurement).

Section 7.4.9. Electrocardiogram (ECG); new text 2nd and 4th paragraphs. Additional clarity provided about Day 1 ECG requirements.

For ~~At~~ the Day 1 ~~visit when an~~ ECG ~~is performed~~, <u>two additional ECGs</u> are required if the initial ECG indicates prolonged QTc (see Section 5.2) using the automated or manually calculated QTcB value.

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; 1st and 2nd paragraph. Added new text to clarify the relative timing of laboratory assessments to dialysis and corrected spelling of center.

All protocol required laboratory assessments, as defined in Table 10, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Section 7.1). **Laboratory assessments will be done pre-dialysis for in-center HD subjects, in between dialysis sessions for HHD subjects at the study visits, 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/~~centre~~**center** number, and visit date.

Section 7.7. Patient Reported Outcomes; new text in 1st paragraph. Clarified healthcare resource utilization data to be collected.

In addition, healthcare resource utilization will be assessed including out-patient visits.

Section 7.7. Patient Reported Outcomes; new text in 2nd paragraph. Added provision for sponsor discussion if PRO assessments cannot be conducted.

All questionnaires used in this study have been translated and culturally adapted for 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. **If there are exceptional circumstances whereby the electronic PRO assessments cannot be conducted, the completion of these assessments will be discussed with the sponsor on a case-by-case basis.**

Section 7.7.3. Health Status (EQ-5D-5L & EQ-VAS); paragraph 2. Updated endpoint labels.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled '**the best health you can imagine**~~best imaginable health state~~' and '**the worst health you can imagine**~~worst imaginable health state~~**'**. This information is used as a quantitative measure of health outcome as judged by individual subjects.

Section 9. Statistical Considerations and Data Analyses; paragraph after table. Change from two-sided testing at the 5% level to one-sided testing at the 2.5% level.

The co-primary endpoints will each be tested using a **one-sided 2.**5% significance level and **the relevant confidence bound of the** ~~a~~ two-sided 95% CI **(upper bound for MACE and lower bound for the Hgb co-primary endpoint)**. The type I error rate will be strictly controlled at the **one-sided 2.**5% level across the co-primary analyses as both non-inferiority tests need to be met for the trial to be considered successful and for statistical analysis to proceed to evaluate MACE superiority and superiority for the principal secondary objectives/endpoints.

Section 9.1.1. CV Safety (MACE) Co-Primary Hypothesis; last paragraph. Added two-sided to 95% CIs.

Statistical significance of non-inferiority will be assessed at the ~~two~~**one**-sided **2.**5% level. A Cox-Proportional-Hazards-Regression model, adjusting for treatment and prognostic randomization stratification factors (region and current ESA use), will be used to estimate the hazard-ratio, its **two-sided** 95% CI and to generate the p-value for the non-inferiority test. Non-inferiority will be achieved if the upper limit of the two-sided 95% CI is below the margin of 1.20.

Section 9.1.2. Hgb efficacy Co-Primary Hypothesis; 3rd paragraph. Changed to one-sided 2.5% level and added two-sided to 95% CI.

Statistical significance of non-inferiority will be assessed at the ~~two~~**one**-sided **2.**5% level. An ANCOVA model including prognostic randomization stratification factors (dialysis type and region), baseline Hgb and treatment will be used to obtain a point estimate and the **two-sided** 95% CI for the treatment difference (daprodustat -rhEPO) and generate the p-value for the non-inferiority test

Section 9.2.1. Sample Size Assumptions; paragraph after bullets. Changed to one-sided 2.5% level and added two-sided to 95% CI.

The target of 945 adjudicated first MACE will permit a **two-sided** 95% CI of (0.880, 1.136) to describe the results for an observed hazard ratio of 1. The largest hazard ratio point estimate (**two-sided** 95% CI) that would meet the statistical criterion for non-inferiority is 1.056 (0.930, 1.200) and for superiority, the minimum observable effect would be a 12% relative risk reduction in favor of daprodustat, corresponding to a hazard ratio of 0.880.

Conditional on both co-primary endpoints achieving non-inferiority at the **one**-sided **2.**5% level, statistical testing will progress to evaluate MACE and the principal secondary endpoints for superiority.

Section 9.2.2. Sample Size Sensitivity; 1st paragraph. Corrected referencing.

The estimated (base case) 15% annual rhEPO MACE rate is based on a review of randomized clinical trials in dialysis (peginesatide EMERALD studies [Macdougall, 2013] and NHS study [Besarab, 1998]), observational data in dialysis patients (GSK report from the Dialysis Outcomes and Practice Patterns Study ~~(DOPPS)~~**[DOPPS, 2014]** and the USRDS 2013 annual report **[USRDS, 2013]**) and considering the planned regional distribution for recruitment.

Section 9.2.2. Sample Size Sensitivity; last paragraph. Added two-sided to 95% CI.

The planned study size far exceeds this requirement and provides more than 99% power for non-inferiority and a high level of precision to estimate the treatment effect (**two-sided** 95% CI half width of 0.128 g/dL, assuming 30% of subjects will be non-evaluable for efficacy). The largest (most negative) difference between arms that would meet the statistical criterion for non-inferiority would be -0.622 g/dL. If the **two-sided** 95% CI is

completely negative (i.e. lies fully within the range -0.75 to <0g/dL) non-inferiority would still be concluded.

Section 9.2.3. Sample Size Re-estimation or Adjustment; last sentence. Minor revisions.

GSK and the Executive Steering Committee will review blinded data periodically during the course of the study and should emerging data suggest that the overall event rate and/or the enrollment rate **(main study or sub-studies)** diverges significantly from protocol assumptions **either** the sample size **required** to achieve the event target **and/or the requirement for**~~with~~ a minimum of one year follow-up may be adjusted.

Section 9.4.1.1. Primary CV Safety Analysis (co-primary); 1st paragraph. Clarified two-sided 95% CI and one-sided p-value.

The statistical model is a Cox Proportional Hazards regression model, adjusting for treatment and the prognostic randomization stratification factors (dialysis type and region), to estimate the hazard ratio, **two-sided** 95% CI and **one-sided** p-value for the statistical non-inferiority test. Non-inferiority will be established if the upper limit of the two-sided 95% CI is less than the margin of 1.20. Cumulative time from randomization to first event or end of trial will be evaluated using Kaplan-Meier methodology and displayed graphically. Treatment comparisons from the Cox regression model will be presented as hazard ratios and **two-sided** 95% CIs and displayed on forest plots.

Section 9.4.1.2. Primary Efficacy Analysis (co-primary); 1st paragraph. Added two-sided 95% CI and one-sided p-value.

The ANCOVA model will include prognostic randomization stratification factors (dialysis type and region), 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.

Section 9.4.2.1. Principal Secondary Analyses; paragraphs 1 through 2. Revised to one-sided 2.5% level, statistical section, revised hypotheses to be tested, and changed darbepoetin alfa to rhEPO.

Conditional on the co-primary endpoints achieving at least non-inferiority at the ~~two~~**one-**sided **2.**5% level, statistical testing will progress to superiority for MACE and the principal secondary endpoints. The hypotheses to be tested for these endpoints are as follows:

- Null: daprodustat is ~~equal~~ **not superior** to **rhEPO** ~~darbepoetin alfa~~ (i.e. the hazard ratio is **greater than or equal to** 1.0 for time-to-event endpoints, or the mean difference is **greater than or equal to** 0 for continuous endpoints)
- Alternative: daprodustat is ~~not equal~~ **superior** to **rhEPO** ~~darbepoetin alfa~~ (i.e. the hazard ratio is ~~not equal~~ **less than** ~~to~~ 1.0 for time-to-event endpoints, or the mean difference is ~~not equal~~ **less than** l to 0 for continuous endpoints)

These tests will be multiplicity adjusted based on a family-wise Type I error rate set at the ~~two~~**one**-sided **2.**5% level, see Section 9.4.3 for further details.

Section 9.4.2.1. Principal Secondary Analyses; last paragraph. Changed significance levels to p-values and added two-sided to 95% CIs.

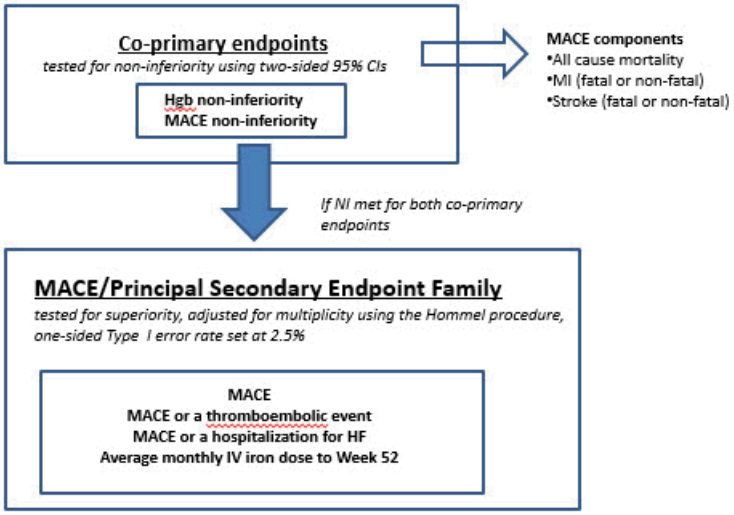
All analyses of secondary endpoints are of exploratory nature, summary statistics and nominal ~~two~~**one**-sided ~~5% significance levels~~ **p-values** will be used for any treatment comparisons.

Section 9.4.3. 2nd paragraph; revised to one-sided 2.5% level.

The procedure will be conducted based on a family-wise Type I error rate set at the ~~two~~**one**-sided **2.5**% level. Details of the Hommel procedure will be fully described in the RAP.

Section 9.4.3. Figure 2; updated figure to align with two-sided 95% CI and one-sided Type 1 error rate set at 2.5%.

Figure 2 Multiplicity controlled statistical testing plan



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

Statistical models will be adjusted for **the covariates used in the original analysis,** subgroup, treatment and treatment by subgroup interaction. Point estimates and **two-sided** 95% CIs will be estimated (presented on Forest Plots) and the subgroup by treatment interaction p-value calculated.

Section 9.4.4. Covariates and Subgroups of Interest; paragraphs 3-5. Updated hyporesponder analyses.

rhEPO hyporesponder subgroup definition: rhEPO hyporesponders will be identified either by the ESA Resistance Index (ERI) [HERO study, Johnson, 2015] or by treatment

at baseline with a very high dose of IV epoetin alpha. For each subject, baseline ERI will be calculated as the **dry** weight adjusted weekly **mean** ESA dose during the 8 week screening period divided by baseline Hgb concentration. Subjects with baseline ERI ≥2 U/kg/wk/g/L for epoetin-treated subjects; ≥0.008 μg/kg/wk/g/L for darbepoetin-treated subjects and ≥0.01 μg/kg/wk/g/L for methoxy-PEG-epoetin-treated subjects will be included in the pre-specified subgroup. In addition, subjects will be included if being treated at baseline with greater than or equal to the equivalent of 450 U/kg/week of IV epoetin alpha. This latter criterion covers subjects at higher body weight for which the ERI calculation is less accurate and is based on the NICE anemia guidelines of June 2015 [NICE, 2015]. **Sensitivity analyses will explore alternative subgroup definitions: an ERI cut-point of ≥1.5 (or equivalent depending on ESA treatment) or using baseline prior rhEPO dose above the top 20th percentile for the study population.**

rhEPO hyporesponder subgroup analysis plan: It is anticipated that approximately 10-15% of subjects may be classified as rhEPO hyporesponders according to this definition, thus resulting in a subgroup size of potentially 300-450 subjects. The subgroup efficacy analysis will follow the same structure as that defined for the full study, assessing the comparative treatment effect in mean Hgb change between baseline and EP in subjects **regardless of adherence to study treatment as well as in subjects** who adhere to randomized treatment and using the same non-inferiority margin of -0.75 g/dL. For at least 90% power to demonstrate non-inferiority, 86 evaluable rhEPO hyporesponders are required per arm. The statistical model (ANCOVA) will include terms for prognostic randomization stratification factors, baseline Hgb, treatment, hyporesponder subgroup and treatment by subgroup interaction. Point estimates and **two-sided** 95% CIs will be generated to describe the treatment effect separately for rhEPO hyporesponders and the complement set of rhEPO non-hyporesponders; non-inferiority would be established if the lower limit of the **two-sided** 95% CI is greater than -0.75 g/dL. **In addition, a nominal one-sided non-inferiority p-value and a nominal one-sided superiority p-value for the difference between the two groups will be generated.** ~~If non-inferiority is met for rhEPO hyporesponders, the analysis would proceed to determine whether daprodustat is more effective at achieving Hgb target levels compared to rhEPO with superiority established if the lower limit of the 95% CI exceeds 0 g/dL. Sensitivity analyses will explore alternative subgroup definitions either by raising the ERI cut-points to ≥2.5 and ≥3.0 (or equivalent depending on ESA treatment) or using baseline prior rhEPO dose above the top 20th percentile for the study population.~~

~~A formal comparative assessment of CV risk in this subgroup is not prospectively planned because, given the sample size,~~ **While** it is unlikely**, given the sample size,** that a sufficient number of adjudicated first MACE will occur to support a robust model-based analysis**, subgroup analyses are planned for the co-primary MACE and principal secondary CV endpoints. The statistical analysis model (Cox Proportional Hazards) will include terms for prognostic randomization stratification factors, treatment, hyporesponder subgroup and treatment by subgroup interaction. Point estimates and two-sided 95% CIs for the hazard ratio will be generated to describe the treatment effect separately for rhEPO hyporesponders and the complement set of rhEPO non-hyporesponders; non-inferiority would be established if the upper limit of the two-sided 95% CI is less than 1.20.** At a minimum, the incidence of

MACE, its components and the principal secondary CV endpoints will be descriptively summarized by treatment group.

~~Summary statistics for baseline characteristics and dosing experience will be generated and exploratory analyses conducted for secondary endpoints associated with Hgb, iron utilization, rescue (including transfusion), BP, symptoms and HR-QoL.~~

Section 9.4.5. Interim Analysis; 2nd paragraph. Added additional point for IDMC considerations regarding futility.

In addition to MACE, any decisions regarding futility will take into account data related to: 1) components of MACE, 2) endpoints describing BP, 3) efficacy in rhEPO hyporesponders, 4) other safety and efficacy data across the daprodustat clinical program**,** ~~and~~ 5) emerging data in the public domain pertaining to safety or efficacy of HIF-prolyl hydroxylase inhibitors, **and 6) any other data considered to be relevant by the IDMC**. The IDMC will make a recommendation to GSK **and the ESC chair as outlined in the IDMC charter** regarding whether the study should continue unchanged, be modified or be terminated.

Section 11. References. updated references; added two missing references (GSK DOPPS report and USRDS) and corrected year of publication of Hommel reference.

GSK Document Number WEUKBRE7146. Cardiovascular event rates, red blood cell transfusion rates, and anaemia management practices in CKD patients across 12 countries from the Dialysis Outcomes and Practice Patterns Study (DOPPS). 30-JUN-2014 (preliminary report).

Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* 19~~9~~**8**8; 75:383-386

U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 2013; Volume 2 (Chapter 5):263-270.

Section 12.1. Appendix 1: Abbreviations and Trademarks. Updated abbreviation list.

MCS	**Mental Component Score**
PASP	**Pulmonary Artery Systolic Pressure**
PCS	**Physical Component Score**
~~sPAP~~	~~Systolic pulmonary artery pressure~~

Section 12.2. Appendix 2: Secondary and Exploratory Objectives/ Endpoints; secondary and exploratory endpoints. Minor updates to secondary MACE and health outcome endpoints; exploratory objective and endpoint for blood transfusion; exploratory endpoints for Hgb variability, iron parameter, blood transfusion, and dose adjustment; and to footnote #2.

Secondary Objectives	Secondary Endpoints (tested for superiority1, no multiplicity

	adjustment)
• To compare daprodustat to rhEPO on additional CV safety endpoints	• ~~Individual MACE components[2] (~~All-cause mortality, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke[2]~~)~~ • MACE or hospitalization for HF2 (recurrent events analysis) • CV mortality or non-fatal MI[2] • All-cause hospitalization • All cause hospital re-admission within 30 days • MACE or hospitalization for HF or thromboembolic events2 • Hospitalization for HF2 • Thromboembolic events2
• To compare daprodustat to rhEPO on HRQoL and Utility score	• Mean change in SF-36 HRQOL scores (**Physical Component Score (**PCS**)**, **Mental Component Score (**MCS**)** and 8 health domains) between baseline and Weeks 8, 12, 28, 52, of particular interest are the changes from baseline in the vitality and physical functioning domains at Wk 28 and 52 • Change from baseline in Health Utility (EQ-5D-5L) score at Week 52 • Change from baseline in EQ VAS at Week 52
Exploratory Objectives	Exploratory Endpoints (statistical testing not planned)
• To further compare daprodustat and darbepoetin alfa on Hgb variability	• Hgb observed and change from baseline across all visits to end of treatment • % of time Hgb is above, within and below the range of 10-11.5 g/dL during EP and MP • Number (%) of subjects with mean Hgb above, within and below the Hgb analysis range during EP and at the end of treatment • Number (%) of subjects with a Hgb <7.5 g/dL **during the EP and MP** • **Number of times Hgb <7.5 g/dL during the EP and MP** • Number (%) of subjects with a >1g/dL increase in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL increase in Hgb within any 4 week period from Week 4 to Week 52 • **Number (%) of subjects with a >1g/dL decrease in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL decrease in Hgb within any 4 week period from Week 4 to Week 52** • N (%) of subjects with a Hgb value ≥ 12 g/dL during the EP and MP • Number of times Hgb ≥ 12 g/dL during the EP and MP • % of time Hgb ≥ 12 g/dL during the EP and MP
• To compare daprodustat to darbepoetin alfa on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, TSAT, total iron, TIBC across all visits to end of treatment • **Average quarterly ferritin** • **Average quarterly TSAT**

	• Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria • N (%) of subjects who reduced IV iron supplementation relative to baseline (defined as total iron (mg) over 4 weeks prior to randomization) ~~to~~**during** EP (defined as average monthly IV iron dose (mg) over Weeks 28 to 52)
• To compare daprodustat to darbepoetin alfa on the need for RBC **and whole blood** transfusions	• Number (%) of subjects who receive at least one RBC **or whole blood** transfusion**s** by Week 52 and by end of treatment • Number of RBC **and whole blood** transfusions per 100 patient years • Number of RBC **and whole blood** units per 100 patient years

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

2. Events adjudicated all ~~or in part~~.

Section 12.4. Appendix 4: Risk Assessment. Updates included throughout to align with version 8 of the Investigator's Brochure.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Daprodustat		
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion**/inflammation**, microthrombi, and tissue ischemia in a number of organs. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat. Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose steps, and dose adjustment scheme to optimize Hgb management.	• 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 Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb **(including rate of change)** is provided in Section 6.3 and Section 6.12. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Death, MI, stroke, ~~congestive HF~~heart failure, **thromboembolic events** ~~venous thromboembolism~~, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)	Marketed rhEPO **and its analogs**/~~ESAs~~ 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.** ~~Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.~~	• 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 Section 7.1. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study. • Planned formal interim analyses with stopping guidelines for evidence of increased CV risk as outlined in Section 9.4.5.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 ~~rodents~~rats, stomach erosions **were** observed with intravenous and oral administration of daprodustat. **Stomach erosions/ulcers also reported in rats with some marketed rhEPO/ and its analogs.**~~Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat).~~ 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.	• Suspected GI bleeding or significant symptoms consistent with erosion**s 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.
Cancer-related mortality and tumor progression and recurrence	Marketed rhEPO~~s~~ **and its analogs** ha~~ve~~ been associated with increased risk of cancer related morbidity and mortality when used in patients with cancer. 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 a 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**	• 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
	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 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.	
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 ~~mice and~~ dog**s**, up to ~~26 weeks~~**2 years** in rat**s and mice**, and up to 39 weeks in monkeys.	• 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
	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,** ~~T~~these hypoxia-induced PRVP changes ~~fall~~**were** within the range of PRVP ~~differences~~ **changes** noted among ~~non-~~**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 has no clinically significant effect on **transthoracic** echocardiographic~~ally~~ **(ECHO)** estimates~~d~~ of ~~systolic~~ pulmonary artery **systolic** pressure (~~s~~PA**S**P) 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**~~sPAP~~ in subjects not on dialysis for daprodustat. In hemodialysis subjects, mean absolute change from baseline in ~~sPAP~~**PASP** was similar for both treatment groups; however, there was a numeric imbalance (Daprodustat: 8 [7%]; Control 0) in subjects reaching the ~~sPAP~~**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 ~~sPAP~~**PASP** on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study treatment; and there was no dose relationship for subjects meeting the ~~sPAP~~**PASP** PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
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	• 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
	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.** ~~Small increases in cardiac troponin in 6 month rat study with daprodustat were consistent with the background finding of spontaneous rodent cardiomyopathy. There were no elevations observed in cardiac troponin in 9 month monkey study with daprodustat~~ 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 for daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
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. ~~No ocular abnormalities with daprodustat were seen in non-clinical studies of up to 13 weeks duration in mice and dogs, 26 weeks in rats, and 39 weeks in monkeys.~~ In clinical studies 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 30 mg administered three times weekly**. In studies up to 24 weeks duration at doses up to 25 mg, 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 with daprodustat. Following review of clinical data with daprodustat received to date, this has not been identified as a safety concern for daprodustat.	
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 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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.** Daprodustat is an inhibitor of CYP2C8: ~~*in vitro*, with an IC_{50} value of 21 µM.~~ **A clinical drug interaction study between 25mg and 100mg daprodustat with a CYP2C8 substrate (i.e., pioglitazone) showed that there is no PK interaction at these doses of daprodustat.** ~~Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with clopidogrel (a moderate CYP2C8~~	• Co-administration of daprodustat with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 6.10.2. • 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 6.3 and Appendix 6. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.10. • Hgb will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1. • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb is provided in Section 6.3 and Appendix 6. • 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
	~~inhibitor) leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution~~. ~~Co-administration of daprodustat with potent BCRP inhibitors has the potential to increase exposure of daprodustat.~~ ~~Use of BCRP inhibitors (mostly weak) was found to result in a small change in metabolite exposure (20% increase in AUC).~~ **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: ~~*in vitro*, with IC_{50} values of 6 µM and 11 µM, respectively.~~ A clinical drug interaction study between 25mg **and 100mg** daprodustat with ~~either a CYP2C8 substrate or~~ an OATP1B1/1B3 substrate **(rosuvastatin)** showed that there is no PK interaction at th**ese** dose**s** of daprodustat.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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, **heart failure~~, venous thromboembolism~~thromboembolic events**, thrombosis of vascular access, and for 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; death, MI, stroke, **heart failure,~~ venous thromboembolism~~ thromboembolic events**, thrombosis of vascular access; and for 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.

Section 12.4. Appendix 4: References. Added new references.

Brodie MJ, Mintzer S, Pack AM, Gidal Gary E, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: Cause for concern? *Epilepsia* 2013 54(1):11–27.

Ohnhaus EE, Breckenridge AM, Park BK. Urinary excretion of 6β-Hydroxycortisol and the Time Course Measurement of Enzyme Induction in Man. *Eur J Clin Pharmacol* 1989; 36: 39-46.

Section 12.5. Appendix 5: Female Eligibility Criteria; 1st bullet; clarification on timing for using highly effective contraceptive methods to avoid pregnancy.

Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP **from 30 days prior to the first dose of randomized treatment and until** ~~seven days after the last dose of randomized treatment and~~ **completion of the Follow-up visit (4-6 weeks after the end of randomized treatment)**;

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.

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 12.6. Appendix 6: Randomized Treatment Dose Adjustment Schemes; dose steps 2 and 3. Added provision for possible adjustment to the Dose Adjustment Algorithm, steps 2 and 3, based on the review of blinded instream aggregate Hgb data.

HemoCue Hgb (g/dL) at current study visit[1]	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[7]	Increase to the next higher dose step
7.5 to <9.5	Increasing[8]	Maintain dose

7.No change may be redefined as an increase of <0.5 g/dL based on the review of blinded instream aggregate Hgb data.

8.Increasing may be redefined as an increase of ≥0.5 g/dL based on the review of blinded instream aggregate Hgb data.

Section 12.6. Appendix 6: Randomized Treatment Dose Adjustment Schemes; footnote #1. Added clarifications regarding dispensing of randomized treatment and streamlined reasons for requiring additional study visits to check Hgb.

1. Study visit" refers to mandated study visits (every 4 weeks through Week 52; then every 12 weeks). From Week 52 onwards, additional study visits to check Hgb and dispense randomized treatment **(where directed by the IRT system)** are required under the following circumstances **(additional visits have a visit window of ±1 week)**:
   - **When Hgb at last study visit is outside of the target range, i.e., <10 or >11 g/dL: Visit 4 weeks later to assess for dose adjustment.**
   - ~~When the randomized treatment dose is interrupted: Visits every 4 weeks until study treatment is restarted.~~
   - When the dose of randomized treatment is changed or restarted in the previous 12 weeks **±1 week**: Visits every 4 weeks for 12 weeks.
   - ~~When Hgb at last study visit is ≥9.5 to <10 g/dL: Visit 4 weeks later to assess for dose adjustment.~~
   - ~~When Hgb at last study visit is >11-≤11.5 g/dL: Visit 4 weeks later to assess for dose adjustment.~~
   - When a medication that is a moderate CYP2C8 inhibitor (i.e., clopidogrel, teriflunomide, deferasirox) is started, stopped, or the dose is changed: Visits every 4 weeks for 12 weeks.
   - ~~When Hgb at the last study visit is <9 g/dL (includes those being evaluated for rescue): Visit 4 weeks later to assess for dose adjustment.~~.
   - When the investigator determines it clinically necessary to evaluate a subject sooner than 12 weeks later: Visit 4 weeks later to assess for dose adjustment.
   - For subjects changing dialysis modality from HD to PD: Visits every 4 weeks for 12 weeks.

Section 12.12. Appendix 12: A Sub-study of the Effect of Daprodustat Compared to rhEPO on BP in Hemodialysis Dependent Subjects with Anemia Associated with Chronic Kidney Disease who Switch from ESAs; revisions throughout. Changes to ABPM sub-study to add atrial fibrillation/flutter screening, remove home BP monitoring, change from 44- to 24-hour APBM, change in time-point for assessment (from Week 28 to Week 16), and adjustments to objectives, endpoints and analysis to account for design changes.

Introduction and Rationale: (paragraph 3)

This sub-study is intended to compare daprodustat to rhEPO on BP as assessed by ABPM in dialysis-dependent subjects with anemia associated with CKD who switch from ESAs. ~~Home BP monitoring will be used to establish baseline BP eligibility criteria and to compare the change in average BP between treatment groups as a secondary objective.~~

Objectives and Endpoints

Objectives	**Endpoints**
Primary	
8. To compare daprodustat to rhEPO for effect on SBP (superiority) by ABPM in subjects receiving maintenance hemodialysis in the ABPM ITT population	9. Change in ~~44~~**24** h**ou**r average SBP from baseline to ~~Week 28~~ **end of sub-study**[1] between treatment groups
Secondary	

Objectives	**Endpoints**
• To assess the effect of daprodustat and rhEPO independently within treatment group on SBP, DBP and mean arterial blood pressure (MAP) by ABPM in the ABPM ITT population	• Change in ~~44~~**24** h**ou**r average SBP from baseline to ~~Week 28~~ **end of sub-study[1]** within each treatment group • Change in ~~44~~**24** hour average DBP from baseline to ~~Week 28~~ **end of sub-study[1]** within each treatment group • Change in ~~44~~**24** hour average MAP from baseline to ~~Week 28~~ **end of sub-study[1]** within each treatment group
• To compare the effect of daprodustat to rhEPO on DBP and MAP by ABPM in the ABPM ITT population	• Change in ~~44~~**24** hour average DBP from baseline to Week ~~28~~ **end of sub-study[1]** between treatment groups • Change in ~~44~~**24** hour average MAP from baseline to ~~Week 28~~ **end of sub-study[1]** between treatment groups
• To compare the effect of daprodustat to rhEPO on BP parameters in the ABPM per-protocol population	• Change in: • ~~44~~**24** hour average SBP • ~~44~~**24** hour average DBP • ~~44~~**24** hour average mean arterial pressure from baseline to ~~Week 28~~ **end of sub-study[1]** between treatment groups
• To assess the effect of daprodustat and rhEPO on BP parameters in the ABPM per-protocol population	Change in: • ~~44~~**24** hour average SBP • ~~44~~**24** hour average DBP • ~~44~~**24** hour average mean arterial pressure from baseline to ~~Week 28~~ **end of sub-study[1]** within each treatment group
• To compare the percentage of subjects in each treatment group requiring a change in antihypertensive medications in the ABPM ITT population	• **Difference between treatment groups in percentage of subjects requiring no change in number or dosage of antihypertensive medications** • Difference between treatment groups in percentage of subjects requiring an increase in number or dosage of antihypertensive medications • Difference between treatment groups in percentage of subjects requiring a decrease in number or dosage of antihypertensive medications
~~• To compare the percentage of subjects in each treatment group requiring a change in antihypertensive medications in the ABPM per-protocol population~~	~~• Difference between treatment groups in percentage of subjects requiring an increase in dosage of antihypertensive medications~~ ~~• Difference between treatment groups in percentage of subjects requiring a decrease in dosage of antihypertensive medications~~
• To characterize the dipping pattern of sleeping BP in each treatment group in the ABPM ITT and ABPM per-protocol populations	• ~~44~~**24** hour BP profile as measured by ABPM, with subjects categorized according to their sleeping BP behaviors as: o dippers (normal) when the reduction in the

Objectives	Endpoints
	average SBP during the sleeping period was >10% to 20% of mean SBP during waking hours, ○ extreme dippers when this reduction was >20%, ○ non-dippers when the reduction was <10%, and ○ reverse dippers when the mean sleep SBP was higher than the awake SBP [Bakris, 2014]
• To compare the percentage of subjects that convert from non-dipper status to dipper status between treatment groups in the ABPM ITT and ABPM per-protocol populations	• Difference between treatment groups in percentage of subjects that convert from non-dipper status at baseline to dipper status at ~~Week 28~~ **end of sub-study**[1]
• To compare the percentage of subjects that convert from dipper status to non-dipper status between treatment groups in the ABPM ITT and ABPM per-protocol populations	• Difference between treatment groups in percentage of subjects that convert from dipper status at baseline to non-dipper status at ~~Week 28~~ **end of sub-study**[1]
~~• To compare the effect of treatment with daprodustat to rhEPO on change in average home BP between treatment groups in the ABPM ITT and ABPM per-protocol populations~~	~~• Change in SBP and DBP from baseline to Week 28 between treatment groups~~
• To compare the effect of treatment with daprodustat to rhEPO on ~~pulse~~ **heart rate** by ABPM in the ABPM ITT population	• Change from baseline to ~~Week 28~~ **end of sub-study**[1] in ~~44~~**24** hour average ~~pulse~~**heart rate** between treatment groups as measured by ABPM relative to time since administration of medication

1. **The end of the sub-study is defined as Week 16, or Week 28 for subjects completing the sub-study prior to Amendment 2.**

Study Design

This is a multicenter sub-study of the main ASCEND-D study. Subjects who qualify for the main study will be assessed for enrolment. Approximately ~~300~~**136** subjects from ~~60-90~~ centers in selected countries that are participating in the main study will be randomized.

Note: if the target number of randomized subjects in the ABPM sub-study is not achieved when the main study is fully enrolled, recruitment may be extended to allow randomization in the ABPM sub-study to complete. ~~Home BP monitoring will be done to establish baseline eligibility for subject participation and will continue through to Week 28 study visits.~~

ABPM Quality Control Criteria

Subjects will need to wear the ABPM device for two **24-hour** sessions during the study**: at a mid-week dialysis visit starting at Week -4 until 1 week** ~~at Day -14~~prior to randomization **(baseline ABPM)** and **then** at Week ~~28~~**16**. The ABPM device will be placed after assessments for the main study have been completed. ~~ABPM Quality Control (QC) criteria as defined in the Project Requirement Specification (PRS) for ABPM must be met.~~

Subjects will be expected to wear the ABPM device ~~twice~~for ~~44~~**24** hours **at** each session. The ABPM device will measure BP and ~~pulse~~**heart rate** every 30 minutes during both awake and asleep hours. The times the subject awakens and goes to sleep during this ~~44~~**24** hour period will be recorded.

For each session the ABPM Quality Control (QC) criteria as defined in the Project Requirement Specification (PRS) for ABPM must be met. If these criteria are not met the ABPM may be repeated (see Section 12.12.3.3).

Eligibility Criteria – Screening

Additional Inclusion Criteria

In addition to meeting entry criteria for the main study, a subject will be eligible for inclusion in this sub-study only if all of the following criteria apply.

1. Signed written informed consent prior to beginning sub-study-related procedures. **Note:** Consent to participate in this sub-study is separate from consent to participate in the main study, and ~~needs to~~**will** be signed **either at Week -8 or at** Week -4 **prior to ABPM assessments.**
2. Use of the same antihypertensive treatment for the 6 weeks prior to the Screening visit, through the entire Screening period and at randomization.
3. ~~Average home~~ SBP of ≤~~150~~**170** mmHg **based on the average of pre-dialysis clinic values obtained at** ~~as assessed starting Day 21~~**Week -8 and Week -4** ~~(prior to ABPM)~~ using the methodology described in the SRM.
4. Willing and able to wear ABPM device for ~~44~~**24** hours on two separate sessions.
5. Valid ABPM ~~measurements~~**at baseline [randomization (Day 1) only]**.
6. Dialysis schedule of three times per week.
7. **Average awake-time SBP of ≤150 mmHg as assessed by a valid baseline ABPM [randomization (Day 1) only].**

Additional Exclusion Criteria

A subject will not be eligible for inclusion in this sub-study if any of the following criteria apply:

1. Receiving peritoneal dialysis or home HD.

2. Subjects who are at high risk for loss to follow-up (e.g., subjects who are known to not regularly attend dialysis, subjects who may require frequent hospitalizations or vascular access interventions).
3. ~~Current or history~~**Evidence** of atrial fibrillation **or atrial flutter at time of baseline ABPM assessment (see Section 12.12.3.3).**
4. Oscillometer/sphygmomanometer cuff cannot accommodate their upper arm circumference.
5. BP cannot be measured in the arm opposite of current vascular access.
6. Subjects who experience, on average, >5% increase in weight above EDW between mid-week dialysis treatments between Week -48 and ~~Day –~~14 baseline ABPM reading. ~~(e.g., Monday to Wednesday or Wednesday to Friday if dialysis days are Monday, Wednesday, Friday).~~

Study Assessments

Week -4**8** Study Visit:

Subject's consent for ABPM is obtained (Note: if missed this may be obtained at Week -4 prior to ABPM assessments).

Week -4 Study Visit:

~~After the Week -4 main study assessments are completed and consent for participation in this ABPM sub-study is obtained, the subject will be given the home BP monitor and instructed on its use. Between Week -4 and Week -3, the subject must become familiar with obtaining twice daily home BP readings. Specific directions for measuring home BP will be provided in the SRM.~~

~~Screening Home Blood Pressure Monitoring~~

~~Starting at Day -21, the subject will obtain twice daily home BP readings for 4 consecutive days; initiation of home BP measurements will be on a mid-week dialysis day. For example, subjects on a Monday, Wednesday, Friday dialysis schedule, the first home BP recording must be obtained on a Wednesday morning. For subjects on a Tuesday, Thursday and Saturday dialysis schedule, the first home BP reading must be obtained on Thursday morning. Home BP results will be transmitted to the study center in real-time. Home BP readings should be obtained in the morning and evening (ideally spaced at least 8 hours apart), at least 1 hour after eating and not within 1 hour of awakening. These readings will establish BP eligibility for ABPM participation~~

~~Day -14 Study Visit:~~ *~~This clinic visit will be used to initiate~~* a**A** baseline ABPM reading *~~(prior to randomization and first dose of study medication)~~* ~~and~~ must ~~occur at the~~ **be initiated at a mid-week dialysis visit and may be performed following completion of the Week -4 study assessments or at a subsequent** mid-week dialysis visit **provided it occurs at least 1 week prior to randomization.**

Post-dialysis **and prior to ABPM, subjects will be assessed for the presence of atrial fibrillation/flutter as follows: subjects with an irregular heart beat detected during heart rate measurement will undergo an ECG and those with documented atrial fibrillation or atrial flutter will not be eligible for ABPM.**

~~t~~**T**he ABPM device will be placed on the arm opposite current vascular access, and will be removed ~~by study personnel at the next dialysis session (i.e., Day 12)~~**by the subject at home after a minimum of**~~, after 44~~ 24 hours of wear**; the device will be returned to the research staff at the next visit,** which ideally is no later than 1 week prior to randomization to allow for QC of the ABPM**.** See SRM for guidance on placement of ABPM device.

If the subject fails to meet the baseline ABPM QC criteria and agrees to repeat the ABPM procedure, then:

- **The baseline ABPM procedure can be repeated at the next mid-week dialysis visit.** ***Note: the atrial fibrillation/flutter assessment should be repeated prior to device placement.***
- **Day 1 (randomization) may be delayed.**
- **If the baseline ABPM fails the QC criteria after three attempts, then the subject will not be enrolled in this ABPM sub-study.**

Subjects will have their body weight measured and recorded in the eCRF both pre- and post-dialysis (see SRM for guidance on body weight measurement).

Day 1 **(~~r~~Randomization~~/next mid-week dialysis visit~~):**

If the ABPM measurements meet the QC criteria, the subject can be randomized.

~~If the subject fails to meet the baseline ABPM QC criteria and agrees to repeat the ABPM procedure, then:~~

- ~~The baseline ABPM procedure can be repeated once at the next mid-week dialysis visit.~~
- ~~Day 1 (randomization) may be delayed.~~
- ~~If the baseline ABPM fails the QC criteria a second time, then the subject will not be enrolled in this ABPM sub-study.~~

Subjects who either do not qualify for entry into the ABPM sub-study after failing QC criteria a ~~second~~third time or who do not desire to continue in the ABPM sub-study although they pass the QC criteria, should continue with randomization into the main study following the schedule of assessments as outlined in Table 7 of the main protocol if appropriate.

~~Week 4 through Week 28 Study Visits (*Home BP Monitoring Continues)*~~

~~Subjects should obtain home BP readings for the four days prior to each study visit between Week 4 and Week 28 as outlined in the SRM.~~

Week ~~28~~16 Study Visit:

At ~~the end of the main study Hgb stabilization period (i.e., at~~Week ~~28~~**16**, at the mid-week dialysis visit and after all main study assessments have been completed, the subject's pre- and post-dialysis weight will be measured and the EDW will be recorded.

The ABPM device will be placed on the subject's arm by site personnel~~ and the subject will wear the device for 44 hours until the next dialysis session~~**. After a minimum of 24 hours of wear, the device will be removed by the subject at home and returned to the research staff at the next visit.** The time and date of study medication administration, before and while wearing the ABPM device, will be recorded.

If the ABPM fails the QC criteria (same as baseline), up to two additional attempts may be made ~~in~~ **at** subsequent, mid-week dialysis visits. No further attempts are allowed. The subject will continue study visits in the main study as scheduled.

Permanent Discontinuation of Randomized Treatment

A subject who permanently discontinues randomized treatment prior to completing the ABPM sub-study should remain in the sub-study and complete the Week 16 ABPM assessment unless consent to participate in the ABPM sub-study is withdrawn (see also Section 5.5).

Estimated Dry Weight and Antihypertensive Medication Changes

It is preferred that no changes are made to EDW and antihypertensive medications while the subject is part of the sub-study.

If changes in EDW and/or antihypertensive medications are necessary, these must be documented in the eCRF along with the reasons. Subjects will remain in the sub-study regardless of any changes.

Withdrawal from ABPM Sub-Study

If a subject participating in this sub-study withdraws from the sub-study, the reason for the withdrawal must be recorded in the eCRF. The subject will remain in the main study unless the subject withdraws consent from the main study.

Sample Size and Power Calculations

The sample size of this sub-study has been designed based on the primary sub-study objective to demonstrate superiority in average SBP **change from baseline to end of sub-study** between arms (daprodustat versus rhEPO), measured by ABPM over a ~~44~~**24** hour assessment period. Assuming a **one-sided 2.**5% significance level, a true standard deviation for SBP change from baseline measured by ABPM of 11 mmHg [Peixoto, 2000], and up to a ~~30~~**20**% withdrawal rate from the sub-study, a sample size of ~~148~~**68** subjects per group (~~296~~**136** subjects in total) will provide greater than ~~90~~**80**% power to detect a -~~5~~**6** mmHg difference in treatment groups (i.e., achieve superiority). Under these

assumptions, superiority will be established if there is more than a ~~3~~**4.2** mmHg mean difference observed in favor of daprodustat.

Assuming a ~~20~~**40**% screen failure rate for the additional ABPM entry criteria, approximately ~~370~~**228** subjects that are eligible for the main study will need to be screened for the sub-study in order to randomize **approximately** ~~296~~**136 subjects. See Section 9.2.3 for more information about sample size adjustments.**

Unblinded ABPM data will be reviewed by the IDMC during the conduct of the trial as part of their data monitoring responsibilities. No formal interim analysis is planned.

Statistical Analysis

The primary sub-study estimand is to compare the treatment effect on change from baseline in 44**24** hour average SBP at ~~Week 28~~**end of sub-study**, in all randomized sub-study subjects. The statistical model for analysis will be an ANCOVA with terms for treatment and baseline 44**24** hour average SBP. This model will provide a point estimate and two-sided 95% CI for the treatment effect and a **one-sided** p-value for the superiority assessment. Superiority will be established if the p-value is <0.0**2**5. The primary analysis population will be the ABPM sub-study-ITT population defined as randomized subjects who were also entered into the ABPM sub-study.

Given the nature of ABPM measurement, a high degree of dropout unrelated to randomized treatment is anticipated. The potential high level of missing data poses a challenge in the interpretation of the primary ABPM sub-study analysis. The reason for missing ABPM data will be examined to explore the impact of missing data on the sub-study primary efficacy conclusions. If the majority (defined as >70%) of the missing data is due to either subject unwillingness to repeat the ABPM procedure or due to an un-evaluable reading, then data will be treated as missing at random and the primary analysis will be considered sufficient. Otherwise, a sensitivity analysis may be performed that will use multiple imputation from the active control arm to replace data from both treatment groups that was missing due to reasons other than subject unwillingness or un-evaluable readings. Further ~~sensitivity~~**supplementary** analyses may include an ABPM per-protocol population (PP) analysis, utilizing all ABPM-ITT subjects who are not major protocol violators or who did not change BP medications during the sub-study. Further details of sensitivity **and supplementary** analyses will be described in the RAP.

In order to contextualise the primary between-group comparison, a key secondary objective is to assess within-group changes from baseline over ~~28 weeks~~ **the sub-study**. Assessment of within-group changes will support interpretation of the primary analysis by identifying whether there was an absence of an increase in BP in one or both treatment groups. To that end, **two-sided** 95% confidence intervals will be calculated for change from baseline in each ABPM parameter separately for each treatment group. For either treatment group, a lack of adverse effect on the primary endpoint of average SBP at **and of sub-study** ~~Week 28~~ will be concluded if the upper 95% confidence limit is no more than 4 mmHg. This margin was chosen as it is less than the clinically meaningful change of 5 mmHg [Whelton, 2002] and it is half the historical increase in SBP observed with rhEPO [Krapf, 2009].

The mean and **two-sided** 95% CI will be estimated from the primary statistical model for within treatment arm SBP change from ~~B~~**b**aseline to ~~Week 28~~ **end of sub-study**.

The change from baseline ~~44~~**24** hour average DBP, mean arterial pressure and ~~pulse~~**heart rate** at ~~Week 28~~ **end of sub-study** will be assessed in a similar way as the primary, using analogous ANCOVA models with treatment and baseline as covariates.

The differences in proportion of subjects that increase/decrease their BP medication (number or dose) will be assessed using Fisher's Exact Test. The differences between treatment groups in the proportion of subjects that convert from dippers/non-dippers at baseline to non-dippers/dippers at ~~Week 28~~ **end of sub-study** will also be assessed using Fisher's Exact Test.

~~Changes from baseline in home BP measurements (SBP and DBP) at Week 28, utilizing all data collected at visits up to Week 28, will be analyzed using mixed model repeated measures (MMRM) with a model adjusting for treatment, baseline, time, treatment by baseline interaction, and treatment by time interaction.~~

Plots of the mean ~~44~~**24** hour average values (**two-sided** 95% CIs) and mean changes from baseline in 44**24** hour average values (**two-sided** 95% CIs) for BP will be provided by treatment group.

Additional statistical considerations will be addressed in the RAP.

Section 12.13.3. Appendix 14: A Sub-study to Collect PK Samples in Dialysis Subjects with Anemia Associated with CKD; study design – 1st paragraph; minor revisions.

This is a multicenter sub-study of daprodustat study 200807 (the main study). Approximately ~~40 to 50 centers~~ **200 subjects from centers in selected countries** that are participating in the main study will be invited to participate in the PK sub-study.

Section 12.13.4. Appendix 13: A Sub-study to Collect PK Samples in Dialysis Subjects with Anemia Associated with CKD; additional inclusion criteria – 2nd and 3rd bullets. Clarified 2nd inclusion criteria and corrected spelling of center in 3rd inclusion criteria.

- Subject must be **receiving** randomized ~~to receive~~ daprodustat **treatment** in the main study**.**
- Only subject's receiving in ~~centre~~**center** hemodialysis are eligible.

Section 12.13.5. Appendix 13 A Sub-study to Collect PK Samples in Dialysis Subjects with Anemia Associated with CKD; study assessments – 1st paragraph. Added additional eligible collection visits to collect PK samples in PK sub-studies.

Blood samples will be collected at **any single study visit from the** Week 4 **through Week 52**~~, Week 8, or Week 12~~ visit (i.e., PK is collected at one visit only, based on convenience for the subject/site).

Section 12.13.5. Appendix 13 A Sub-study to Collect PK Samples in Dialysis Subjects with Anemia Associated with CKD; study assessments – 2nd and 3rd bullets. Added clarifications around the PK visit, i.e., not being on dose hold and recording three prior doses.

- The dose taken in the clinic **should be from the same bottle(s) the subject has been using prior to the PK visit**, **and** 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 the 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 12.13.6. Appendix 13: A Sub-study to Collect PK Samples in Dialysis Subjects with Anemia Associated with CKD; sample size – 1st paragraph. Clarified sample size is an approximate.

~~The planned enrollment for this PK sub-study is 200 subjects.~~ It is estimated that 150 sub-study subjects are required to have at least 80% power that the MACE rate in the sub-study is within 20% of the MACE rate in main study. To account for missing or non-evaluable PK samples, **approximately** 200 subjects will be ~~enrolled~~**randomized**. **See Section 9.2.3 for more information about sample size adjustments.**

12.15.4. Changes Resulting from Protocol Amendment 4

This is an amendment to the protocol amendment dated 2020-JUL-30.

This amendment applies to all countries.

12.15.4.1. Summary of Changes

- Revised MACE NI margin in order to align the NI margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO.
- Revised target MACE as a result of the change to the non-inferiority margin.
- Updated the analysis of the hemoglobin co-primary endpoint based on FDA feedback.
- Updated terminology (i.e., use of 'supportive') to be consistent with ICH-E9 addendum.
- Multiplicity adjustment strategy updated from Hommel to Holm-Bonferroni based on FDA feedback.
- Added AESI of worsening of hypertension to footnote (included in IB, version 10).
- Edited Risk Assessment information to include worsening of hypertension.

- Updated pregnancy reporting timelines to align with revised Sponsor timings.

12.15.4.2. List of Specific Changes

Section 1. Overall Design, Revised MACE NI margin in order to align the NI margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO.

- The total duration of the study is dependent upon the accumulation of ~~945~~**664** adjudicated first MACE (i.e., it is event-driven) unless review of interim data by the Independent Data Monitoring Committee (IDMC) recommends bringing the study to an earlier close.

Section 1. Analysis, Revised MACE NI margin in order to align the NI margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO.

For CV safety, the primary question is whether daprodustat is non-inferior to rhEPO for adjudicated MACE. An Intent-to-Treat (ITT) analysis of time to the first occurrence of adjudicated MACE using a margin of 1.~~20~~**25** and a Cox Proportional Hazards regression model adjusting for treatment and prognostic randomization stratification factors (dialysis type and region), will be used.

For Hgb efficacy, the primary question is whether daprodustat is non-inferior to rhEPO for change from baseline in central laboratory Hgb. 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. An analysis of the ITT Population~~, comprising all subjects with a 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 prognostic randomization stratification factors (dialysis type and region), and factors for baseline Hgb and treatment.

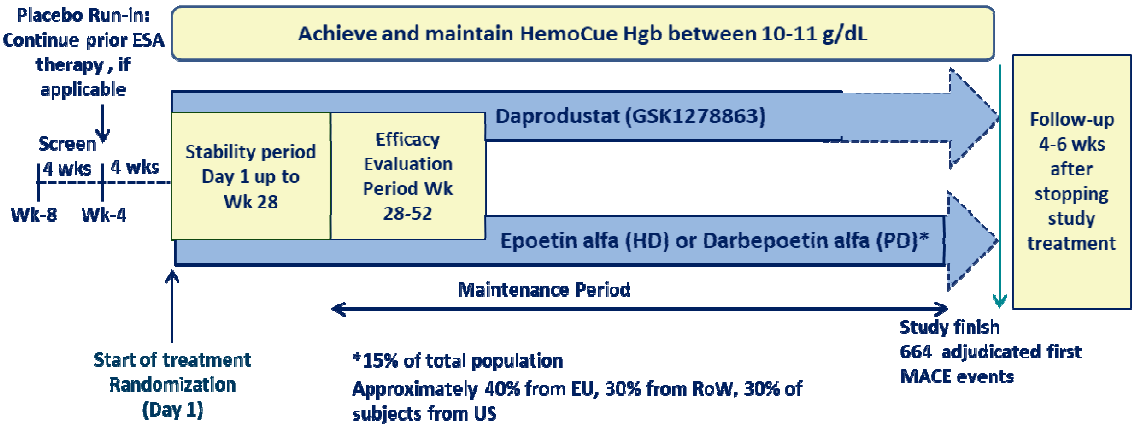
Section 3. Objective(s) and Endpoint(s), Added AESI of worsening of hypertension to footnote (included in IB, version 10).

2. Defined as thrombosis and/or tissue ischemia secondary to excessive erythropoiesis; **worsening of hypertension**; cardiomyopathy; pulmonary artery hypertension; cancer-related mortality and tumor progression and recurrence; esophageal and gastric erosions; proliferative retinopathy, macular edema, choroidal neovascularization; and exacerbation of rheumatoid arthritis

Section 4.1. Overall Design, Revised target MACE as a result of the change to the non-inferiority margin.

- The total duration of the study is dependent upon the accumulation of ~~945~~**664** adjudicated first MACE (i.e., it is event-driven) unless review of interim data by the Independent Data Monitoring Committee (IDMC) recommends bringing the study to an earlier close.
- The end of the study will occur after the accumulation of ~~954~~**664** adjudicated first MACE and the last subject has completed their last required study visit (Section 7.1).

Section 4.1. Overall Design, Streamlined schematic and revised target MACE as a result of the change to the non-inferiority margin.



Section 6.3.5. Randomized Treatment Discontinuation, Revised target MACE as a result of the change to the non-inferiority margin.

The sponsor will inform investigators when they should have subjects come in for an End of Study visit based on the projected occurrence of ~~945~~**664** first MACE.

Section 7.4.4. Adverse Events of Special Interest, Added AESI of worsening of hypertension to footnote (included in IB, version 10).

- **Worsening of hypertension**

Section 7.4.6. Pregnancy, Updated pregnancy reporting timelines to align with revised Sponsor timings.

If a pregnancy is reported then the investigator should inform PPD within **24 hours**~~2 weeks~~ of learning of the pregnancy and should follow the procedures outlined in Appendix 10.

Section 9.1.1. CV Safety (MACE) Co-Primary Hypothesis, Updates to non-inferiority margin and relative risk in order to align the non-inferiority margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO.

- **Null:** daprodustat is inferior to rhEPO, with at least a 2**5**~~0~~% increased relative risk of first MACE (i.e. the hazard ratio is ≥1.2**5**~~0~~)
- **Alternative:** daprodustat is non-inferior to rhEPO (i.e. the hazard ratio is <1.2**5**~~0~~)

The non-inferiority margin is pre-defined as the hazard ratio of 1.2**5**~~0~~; supported by a review of evidence reported in historical randomized trials of rhEPO in dialysis and ND CKD subjects and after consideration of the largest point estimate that, by design, would meet the statistical criterion for non-inferiority.

Statistical significance of non-inferiority will be assessed at the one-sided 2.5% level. A Cox-Proportional Hazards-Regression model, adjusting for treatment and prognostic randomization stratification factors (dialysis type and region), will be used to estimate the hazard-ratio, its two-sided 95% CI and to generate the p-value for the non-inferiority test. Non-inferiority will be achieved if the upper limit of the two-sided 95% CI is below the margin of 1.2**5**~~0~~.

Section 9.1.2. Hgb efficacy Co-Primary Hypothesis, Analysis of the hemoglobin co-primary endpoint was updated based on FDA feedback.

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

Section 9.2.1 Sample Size Assumptions, Revised target MACE, projected annual adjudicated first MACE rate and non-inferiority margin in order to align the non-inferiority margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO.

The size of this event driven trial is based on the co-primary CV safety objective and is determined by a fixed event target of **664**~~945~~ adjudicated first MACE. This provides approximately 90% power to establish non-inferiority assuming a true underlying 3% lower relative risk of MACE in favor of daprodustat compared to rhEPO (i.e., hazard ratio=0.97) and **82**~~80~~% power for non-inferiority under the assumption that the true

underlying risk of MACE is the same in both arms (i.e., hazard ratio=1.00). Other assumptions behind the sample size calculation include:

- Projected annual adjudicated first MACE rate of 1**1**~~5~~%. All-cause death is expected to be the most prevalent component, followed by non-fatal MI and then non-fatal stroke (projected break down of 60%, 30% and 10% respectively).
- Variance under the alternative hypothesis (i.e. hazard ratio=0.97)
- 1% annual lost to follow-up without vital status
- A two-sided 95% CI is used for analysis

The target of **664**~~945~~ adjudicated first MACE will permit a two-sided 95% CI of (0.**859**~~880~~, 1.**164**~~436~~) to describe the results for an observed hazard ratio of 1. The largest hazard ratio point estimate (two-sided 95% CI) that would meet the statistical criterion for non-inferiority is 1.0**74**~~56~~ (0.**922**~~930~~, 1.**250**~~200~~) and for superiority, the minimum observable effect would be a **14.1**~~12~~% relative risk reduction in favor of daprodustat, corresponding to a hazard ratio of 0.**859**~~880~~.

Conditional on both co-primary endpoints achieving non-inferiority at the one-sided 2.5% level, statistical testing will progress to evaluate MACE and the principal secondary endpoints for superiority. These tests will be multiplicity adjusted, details are provided in Section 9.4.3.

Based on an annual MACE rate of 11%, it is anticipated that ~~approximately 3000 dialysis subjects will be required to achieve~~ 664 adjudicated first MACE target **will be reached approximately** ~~after~~3.3 years from when the first subject is randomized. ~~Assuming the trial continues to its planned final analysis, and based on recruitment and event rate assumptions, enrolment is expected to complete within 1.4 years.~~ All subjects will have the opportunity for a minimum of 1 year exposure to treatment and thus the opportunity to complete the EP (Weeks 28 to 52). Exposure to daprodustat is expected to be in the region of **3,500**~~4,000~~ patient years with median patient follow-up expected to exceed 2 years.

Section 9.2.2. Sample Size Sensitivity, Updated based on blinded MACE accrual.

The estimated 11% annual MACE rate is based on a blinded summary of ASCEND-D data as of April 20, 2020. Table 11 illustrates the impact on power if the true underlying ~~The estimated (base case) 15% annual rhEPO MACE rate is based on a review of randomized clinical trials in dialysis (peginesatide EMERALD studies [Macdougall, 2013] and NHS study [Besarab, 1998]), observational data in dialysis patients (GSK report from the Dialysis Outcomes and Practice Patterns Study [DOPPS, 2014]and the USRDS 2013 annual report [USRDS, 2013]) and considering the planned regional distribution for recruitment. Table 11 illustrates the impact on timing of events if the true underlying annual MACE rate differs from 15% and Table 12 if the true underlying~~ treatment effect is not a hazard ratio of 0.97.

~~**Table 11 Sensitivity based on a different true underlying annual MACE rate**~~

~~**True annual first MACE rate**~~	~~**Time to accrue 945 first MACE**~~
~~12%~~	~~3.9y~~
~~14%~~	~~3.4y~~
~~**15% (base case)**~~	~~**3.3y**~~
~~16%~~	~~3.1y~~
~~18%~~	~~2.8y~~

Table 11~~2~~ Sensitivity Based on a Different True Underlying Treatment Effect

Underlying hazard ratio for MACE rate	**Power for non-inferiority**
0.90	~~>~~99%
0.95	9~~5~~%
0.97 (base case)	**90%**
1.00	8~~0~~%
1.03	**70~~65~~**%
1.05	**61~~54~~**%

Section 9.2.3. Sample Size Re-estimation or Adjustment, Updated to reflect no sample size re-estimation was performed.

At the time of this protocol amendment, the study was fully enrolled, and as such no sample size re-estimation was performed. ~~It is currently unknown whether the rhEPO MACE event rate based on the previous trials has changed due to modifications in rhEPO use following emergence of data demonstrating safety concerns with the use of rhEPO. GSK and the Executive Steering Committee will review blinded data periodically during the course of the study and should emerging data suggest that the overall event rate and/or enrolment rate (main study or sub-studies) diverges significantly from protocol assumptions either the sample size required to achieve the event target and/or the requirements for a minimum one year follow-up may be adjusted.~~

Section 9.3.1 Analysis Population, Updated terminology to be consistent with ICH-E9 addendum.

The primary population for the Hgb efficacy analyses will also be the ITT Population. ~~In order to assess the sensitivity of the primary efficacy analysis, an~~**A supportive** analysis **of the primary efficacy endpoint** 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.

Section 9.4.1.1. Primary CV Safety Analysis (co-primary), •Revised MACE NI margin in order to align the NI margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO and terminology updated to be consistent with ICH-E9 addendum.

Non-inferiority will be established if the upper limit of the two-sided 95% CI is less than the margin of 1.2**5**~~0~~.

Sensitivity **and Supportive** Analyses: ~~Sensitivity analyses~~**A sensitivity analysis** will be performed to address potential effects of drop outs and to evaluate the robustness of the co-primary MACE analysis. ~~These will include a~~**A sensitivity** "tipping point" analysis utilizing multiple imputation for randomized subjects who have withdrawn consent ~~or are lost to follow up~~**from the study will be performed, as well**~~; and~~ **as a supportive** "on-drug" analysis to evaluate the comparative treatment effect during the time that subjects remain on randomized treatment (plus a window of 28 days). Full details will be provided in the RAP.

Section 9.4.1.2. Primary Efficacy Analysis (co-primary), Analysis of the hemoglobin co-primary endpoint was updated based on FDA feedback.

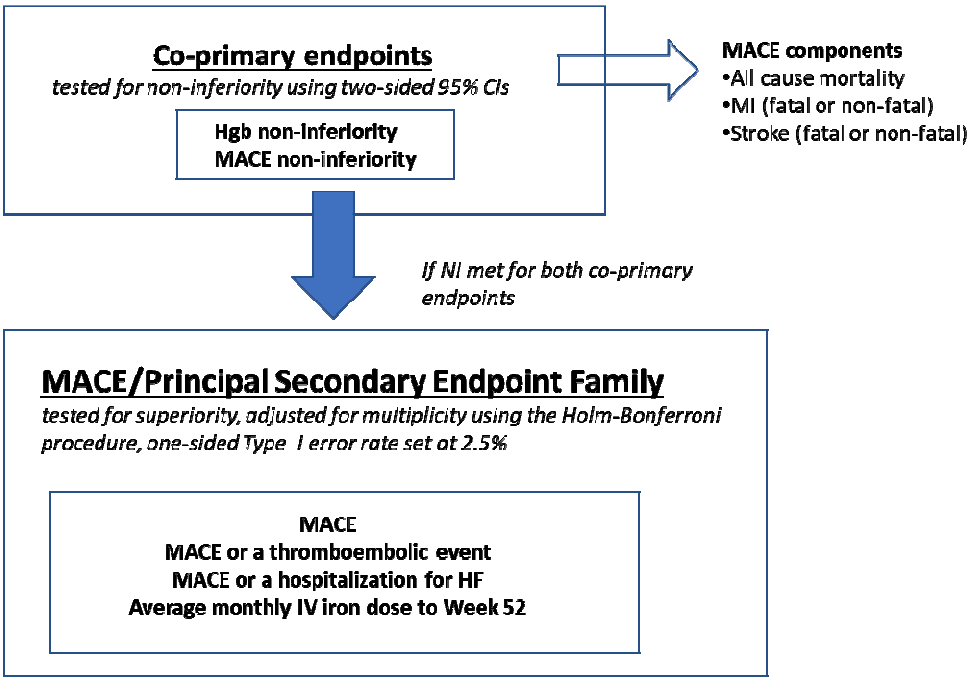
Mean change in Hgb between baseline and the EP (Weeks 28 to 52): The primary efficacy estimand is t**he effect of daprodustat relative to rhEPO on the change in Hgb from baseline to the average of all values in the EP, regardless of adherence to treatment including interruptions and discontinuation, the use of non-randomized ESA medication for any reason including rescue therapy, or the use of blood transfusions, in subjects on dialysis currently treated with an ESA with anemia secondary to CKD and assuming subjects do not die before the end of the EP.** ~~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 ANCOVA model. For each subject, 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 **and imputed** Hgb values between Weeks 28 to 52 inclusive regardless of adherence to randomized treatment. The ANCOVA model will include prognostic randomization stratification factors (dialysis type and region), 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~~ **Imputation will be used for missing Hgb data; further details will be provided in the RAP.**

Sensitivity **and Supportive** 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~~**supportive** 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~~**supportive** "tipping point" analysis as that described above for the primary analysis will be performed for this "on-drug" analysis. In addition, a per-protocol ~~sensitivity~~**supportive** analysis will estimate the treatment effect in subjects who strongly adhere to the protocol, and ~~sensitivity~~**supportive** analyses to explore a shorter EP (Weeks 28 to 36) will be performed for the co-primary effectiveness estimand and "on-drug"

efficacy estimand. Full details of all sensitivity **and supportive** analyses will be provided in the RAP.

Section 9.4.3. Multiplicity Strategy (text and figure), Multiplicity adjustment strategy updated based on FDA feedback. NOTE: update in figure is replacement of Hommel procedure with Holm-Bonferroni procedure).

Figure 2 illustrates the structure of the statistical testing plan. First, the co-primary endpoints will be evaluated for non-inferiority by comparing each two-sided 95% CI to the appropriate non-inferiority margin. Conditional on both co-primary endpoints achieving non-inferiority (i.e., passing the gatekeeper), the family of MACE and the principal secondary endpoints will be formally tested for superiority using the widely known ~~Hommel procedure [GSK Document Number WEUKBRE7146. Cardiovascular event rates, red blood cell transfusion rates, and anaemia management practices in CKD patients across 12 countries from the Dialysis Outcomes and Practice Patterns Study (DOPPS). 30 JUN 2014 (preliminary report). Hommel, 1988]~~ **Holm-Bonferroni procedure [Holm-Bonferroni, 1979]**. The procedure will be conducted based on a family-wise Type I error rate set at the one-sided 2.5% level. Details of the ~~Hommel~~ **Holm-Bonferroni** procedure will be fully described in the RAP.



Section 9.4.4. Covariates and Subgroups of Interest, Revised MACE NI margin in order to align the NI margin with similar studies that have already compared the effects of HIF-PHIs on MACE versus rhEPO.

Point estimates and two-sided 95% CIs for the hazard ratio will be generated to describe the treatment effect separately for rhEPO hyporesponders and the complement set of rhEPO non-hyporesponders; non-inferiority would be established if the upper limit of the two-sided 95% CI is less than 1.2~~0~~**5**.

References. Added Holm-Bonferroni reference as outlined in 9.4.3.

~~Besarab A, Bolton WK, Browne JK et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin *N Eng J Med* 1998; 339:584-590.~~

~~GSK Document Number WEUKBRE7146. Cardiovascular event rates, red blood cell transfusion rates, and anaemia management practices in CKD patients across 12 countries from the Dialysis Outcomes and Practice Patterns Study (DOPPS). 30-JUN-2014 (preliminary report).~~

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

~~Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika* 1988; 75:383-386Johnson DW, Pascoe EM, Badve SV et al. on behalf of the HERO Study Collaboration Group. A randomized, placebo-controlled trial of pentoxifylline on erythropoiesis-stimulating agent hyporesponsiveness in anemic patients with CKD: the Handling Erythropoietin Resistance With Oxpentifylline (HERO) trial. *Am J Kidney Dis*. 2015 65(1):49-57~~

~~Macdougall IC, Provenzano R, Sharma A, Spinowitz BS, Schmidt RJ, Pergola PE, *et al.* Peginesatide for anemia in patients with chronic kidney disease not receiving dialysis. *N Eng J Med* 2013 368:320-332~~

~~U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 2013; Volume 2 (Chapter 5):263-270.~~

Section 12.4. Appendix 4: Risk Assessment. Updated risk table to include the AESI of worsening of hypertension.

Worsening of hypertension	**In a dog cardiovascular study, single oral doses of daprodustat (up to 90 mg/kg) did not produce effects on blood pressure.** **Marketed rhEPO and its analogues have been associated with risks related to uncontrolled hypertension, including the need for initiation of or increases in antihypertensive therapy when used in patients with anemia of CKD (i.e. 25% Epogen, 27% Mircera, and 40% Aranesp treated patients with renal anemia required initiation or increase in their anti-hypertensive medications; hypertensive encephalopathy and seizures have been reported. The contribution of rhEPO-associated hypertension to the unfavourable effects on cardiovascular outcomes remains uncertain).** **Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]:** o **The majority (>90%) of subjects had a baseline history of hypertension.** o **No meaningful difference was seen between treatment groups in AEs (preferred term) of "hypertension" [29/688 (4%) daprodustat vs. 19/404**	• **Blood pressure will be closely monitored throughout the dosing period as outlined in the Time and Events Table Section 7.1.** • **Unblinded monitoring of safety data by an IDMC in-**

	(4%) rhEPO; 0.91 relative risk (RR) (95% confidence interval: 0.5, 1.67)] or "blood pressure increased" [16 (2%) daprodustat vs. 7 (2%) rhEPO; RR 1.22 (0.48,3.11)]. Results were not substantively different between non-dialysis and haemodialysis subjects. ○ **Although no clinically meaningful changes in blood pressure were observed, subjects in both treatment groups required increases in anti-HTN medications:** ○ **In the 24-week global phase 2b studies, 25/170 (15%) of ND subjects receiving daprodustat vs. 18/80 (14%) control and 22/177 (12%) of HD subjects receiving daprodustat vs. 2/39 (5%) control.** ○ **In the 52-week Japan phase 3 studies, 57/149 (38%) of ND subjects receiving daprodustat vs. 68/150 (45%) rhEPO and 51/136 (38%) of HD subjects receiving daprodustat vs. 66/135 (49%) for rhEPO.** ○ **The data received to date from completed clinical trials with daprodustat are insufficient to refute this risk.**	**stream throughout the study.**

Section 12.10. Appendix 10: Collection of Pregnancy Information, updated pregnancy reporting timelines to align with revised Sponsor timings.

- Information will be recorded on the appropriate form and submitted to PPD within **24 hours**~~2 weeks~~ of learning of a subject's pregnancy.