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

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

Primary Efficacy Analysis

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

2. INTRODUCTION

2.1. Brief Background

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

2.2. Study Rationale

Based on its mechanism of action to stimulate erythropoiesis via inhibition of HIF-prolyl hydroxylase enzymes, CCI

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

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

- The stabilization period, defined as the period from Day 1 to Week 28 during which randomized treatment will be dose titrated to achieve the appropriate Hgb target.

- The evaluation period (EP), defined as the period from the end of the stabilization period (Week 28) to Week 52 (titrations may also occur during this treatment period), to assess safety and efficacy.

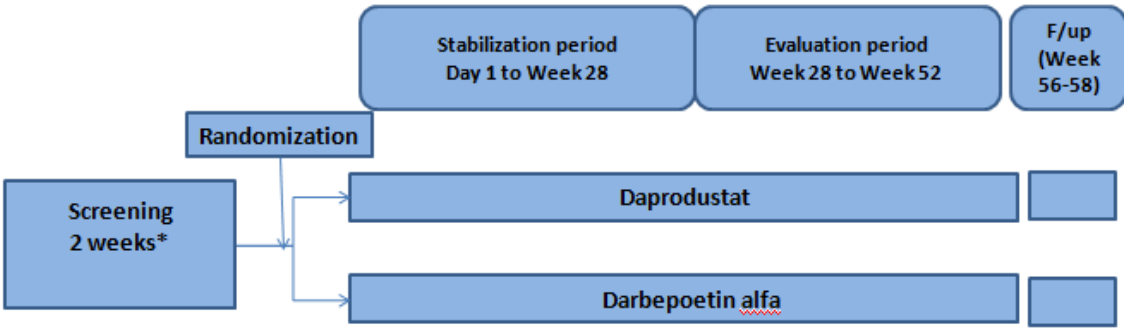
- Subjects will be stratified by dialysis type (hemodialysis [HD] or peritoneal dialysis [PD]) and by whether their dialysis start is planned or unplanned (urgent).

- Following stratification, subjects will be randomized 1:1 to receive daprodustat or rhEPO (darbepoetin alfa); all randomized treatments (Section 6.1) will be supplied by GSK.

- To ensure consistency of treatment across the study there are protocol-mandated algorithms for dose adjustments of daprodustat and rhEPO (Section 6.2), iron management (Section 6.10) and anemia rescue therapy (Section 6.11)

- An overview of the study design is provided in Figure 1.

Figure 1 Study Schematic



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

4.2. Type and Number of Subjects

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

- Planned: Subjects who are planning to start dialysis (HD **or** PD) within the next 6 weeks (from the day of screening).

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

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

4.4.2. Randomized Treatment Dose Adjustment Scheme

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

4.5. Benefit:Risk Assessment

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

4.5.1. Risk Assessment

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

4.5.2. Benefit Assessment

In clinical trials of up to 24 weeks in duration, in subjects with anemia associated with CKD, daprodustat has been shown to treat Hgb to target range. Daprodustat may present several important advantages over rhEPO and its analogs. It is an oral medication and does not require cold-chain storage as does rhEPO, thus increasing ease of use for patients and health care providers. After administration of daprodustat, data suggest that the increases in Hgb are achieved with EPO exposure lower than those observed with rhEPO. Treatment of anemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated supra-physiological increases in EPO exposure with rhEPO [Szczech, 2008];CCI

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.

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.

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

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

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

- For subjects on 3X/week HD: The designated study visit must not occur on the first dialysis session of the week. For example, if on a Monday-Wednesday-Friday schedule, the study visit should be on Wednesday or Friday.

- For subjects on 2X/week HD: The visit should occur during the session that is closest to the previous HD session. For example, if a subject receives dialysis on a Monday and Thursday, the study visit should be on the Thursday (2 days from the previous dialysis session) rather than the Monday (3 days from the previous dialysis session).

- For subjects on PD: study visits can occur on any day of the week.

Details regarding study-specific equipment are provided in Appendix 7.

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

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

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

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

7.3. Efficacy

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

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

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

7.4. Safety

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

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

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

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

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

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

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

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

7.4.2. Other CV Events

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

- Arrhythmias
- Pulmonary hypertension*
- Valvulopathy
- Revascularization

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

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

The definitions of an AE and SAE can be found in Appendix 8.

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

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

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

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

7.4.3.2. Method of Detecting AEs and SAEs

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

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

7.4.3.3. Follow-up of AEs and SAEs

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

7.4.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.4. Adverse Events of Special Interest

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

- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis

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

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

7.4.5. Possible Suicidality Related Adverse Events

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

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

7.4.6. Pregnancy

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

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

7.4.7. Height and Weight

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

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

7.4.8. Blood Pressure and Heart Rate

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

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

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

7.4.9. Electrocardiogram (ECG)

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

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

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

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

7.4.10. Ultrasound

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

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

Table 8 Protocol Required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count	*RBC indices:*	*WBC count with Differential*
	RBC count	MCV	Neutrophils
	Reticulocyte count	MCH	Lymphocytes
	Hgb	MCHC	Monocytes
	Hematocrit	RDW	Eosinophils
			Basophils
Clinical Chemistry[1]	ALT	AST	Bilirubin (total and direct/indirect)
	Potassium (serum)	Urea (serum)	Albumin (serum)
	Calcium (total and albumin-adjusted)	Inorganic phosphate	Creatinine (eGFR CKD-EPI)[4,5]
Iron parameters	Serum iron	Ferritin	UIBC
	Hepcidin	TSAT (calculated)	TIBC (calculated)
Lipid parameters	Total cholesterol	LDL-C (direct)	HDL-C
Other laboratory tests	Serum hCG pregnancy test[2]	Follicle stimulating hormone[3]	Estradiol[3]
	HemoCue Hgb	hsCRP	iPTH
	Stored sample (blood)	Vitamin B12	Folate

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

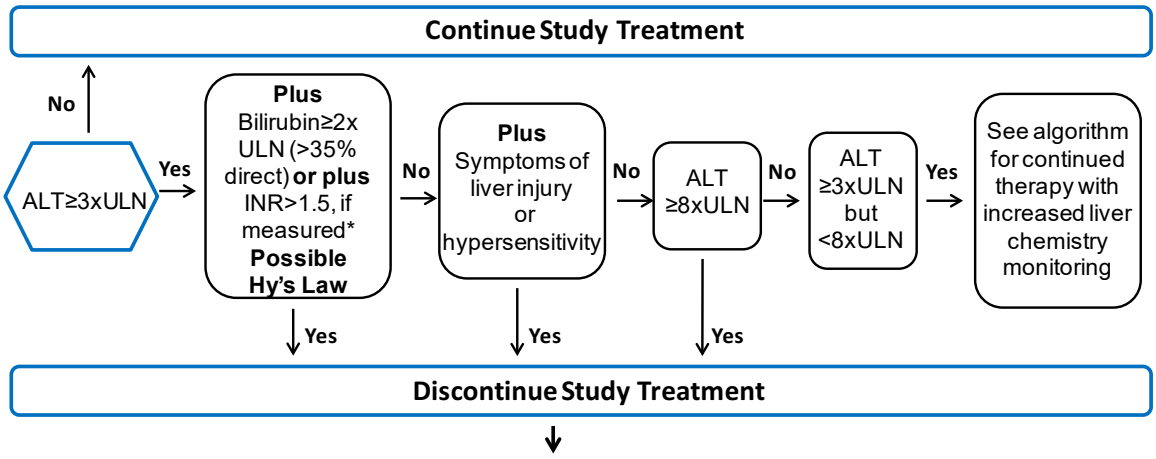
1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Appendix 6.
2. For females of reproductive potential only.
3. Screening only. As needed in postmenopausal women where their menopausal status is in doubt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

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

7.4.12. Liver Chemistry Stopping Criteria

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

Phase 3 Liver Chemistry Stopping and Increased Monitoring Algorithm

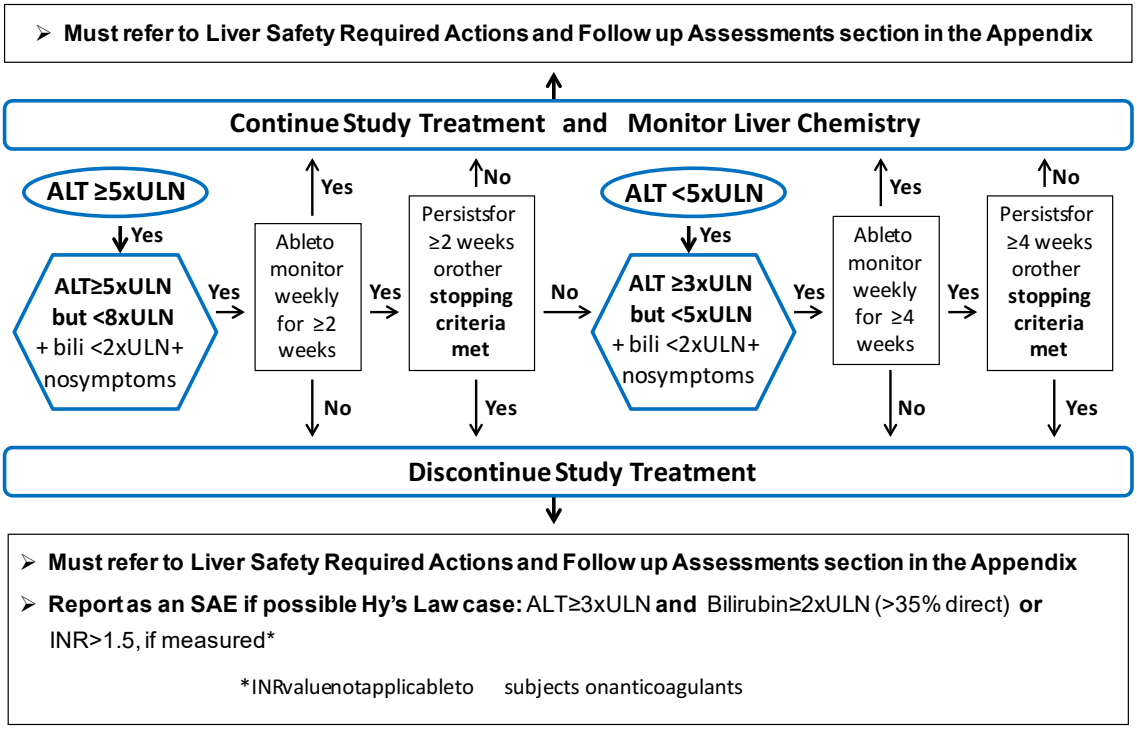


- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

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



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

*INR value not applicable to subjects on anticoagulants

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

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

The Patient Global Impression of Change (PGI-C) is a 1-item questionnaire designed to assess a subject's impression of symptom change of their anemia of CKD. It is measured on a 7-point Likert- type response scale (very much improved, moderately improved, minimally improved, no change, minimally worse, moderately worse, or very much worse) since they first started the study.

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

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

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

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

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

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

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

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

7.8. Storage Biomarkers

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

8. DATA MANAGEMENT

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Primary Hypotheses

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

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

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

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

- 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.

10.8.3. Steering Committees

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

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

10.8.4. National Leader Committee

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

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

Objectives	Endpoints
	and below the Hgb analysis range during EP and at the end of treatment • Number (%) of subjects with a Hgb <7.5 g/dL during the EP • Number of times Hgb < 7.5 g/dL during the EP • Number (%) of subjects with a >1 g/dL increase in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL increase in Hgb within any 4-week period from Week 4 to Week 52 • Number (%) of subjects with a >1g/dL decrease in Hgb over 2 weeks (assessed at Week 2 and Week 4) or a >2 g/dL decrease in Hgb within any 4-week period from Week 4 to Week 52 • N (%) of subjects with a Hgb value ≥ 12 g/dL during the EP • Number of times Hgb ≥ 12 g/dL during the EP • % of time Hgb ≥ 12 g/dL during the EP
To compare daprodustat to rhEPO on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, transferrin saturation, total iron, total iron binding capacity (TIBC) across all visits to end of treatment • Average quarterly TSAT • Average quarterly ferritin • Average quarterly IV iron dose/subject • N (%) of subject who met iron management criteria
To compare daprodustat to rhEPO on the need for RBC and whole blood transfusions	• Number (%) of subjects who receive at least one RBC or whole blood transfusion by Week 52 • Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years
To evaluate the dose adjustment schemes	• Assigned dose by visit and at Day 1, Week 28, Week 52 • Most recent dose prior to Week 28 and Week 52 • Number (%) of patients with 0, 1, 2, or >2 dose adjustments during the following periods: o Day 1 - <Week 28 o Week 28 - <Week 52 • Number of dose adjustments during the following periods: o Day 1 - <Week 28 o Week 28 - <Week 52 • Time dose held for Hgb ≥12 g/dL
To further compare daprodustat to rhEPO on BP	• Observed and change from baseline in SBP, DBP

study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 **hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24**-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue randomized treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of randomized treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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

12.8.2. Definition of Serious Adverse Events

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

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

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.8.3. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to PPD in lieu of completion of the PPD/GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by PPD. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to PPD. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be

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

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To compare daprodustat to rhEPO for Hgb efficacy (non-inferiority)	Mean change in Hgb between baseline and evaluation period (EP, mean over Weeks 28-52)
Principal Secondary (tested for superiority, adjusted for multiplicity)	
To compare daprodustat to rhEPO on the use of intravenous (IV) iron	1. Average monthly IV iron dose (mg)/subject from baseline to Week 52
Safety	
To compare the safety and tolerability of daprodustat to rhEPO	• Incidence and severity of AEs and SAEs including those AEs of special interest • Reasons for discontinuation of randomized treatment • Absolute values and changes from baseline in laboratory parameters, blood pressure, and heart rate

Secondary and exploratory objectives/endpoints are listed in Appendix 2.

4. STUDY DESIGN

4.1. Overall Design

- This is a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center study in subjects with anemia associated with CKD who are not regularly using routine erythropoiesis-stimulating agent (ESA) users and who are initiating dialysis.
- The study will comprise three study periods: a screening period (2 weeks*), a 52-week active treatment period, and a follow-up period (4-6 weeks) (Figure 1). Weeks 28-52 are defined as the efficacy evaluation period (EP) for the p*rima*ry efficacy comparison.

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

- A central randomization approach will be used to protect the trial from potential for selection bias due to the open-label design. All subjects will be treated to achieve and maintain an Hgb within a range of 10-11 g/dL.
- Limited ESA use is allowed around the time of dialysis initiation only (see Section 5.2 for definition of "limited use").
- The treatment period consists of:

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

4.3. Design Rationale

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

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

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

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

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

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

4.4. Dose Justification

Starting doses, dose steps, and elements of the dose adjustment scheme are provided in Section 6.2 and Appendix 3.

4.4.1. Daprodustat

Daprodustat starting doses are assigned based on Hgb at study entry, and were selected such that the target Hgb concentration would be reached after approximately one red blood cell lifespan of treatment (up to 90 days, pharmacodynamic steady-state). However, due to the between-subject variability in Hgb response to a given dose of daprodustat and the relatively narrow Hgb target range, individual dose adjustments of daprodustat are expected during the first few months of treatment. If an individual dose adjustment is made, subjects will increase or decrease the daprodustat dose through a series of dose steps, one dose step at a time. The highest dose of daprodustat in the dose adjustment scheme is 24 mg once daily.

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

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

5.1. Inclusion Criteria

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

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

5.2. Exclusion Criteria

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

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

Table 6 TIME AND EVENTS TABLE FOR SUBJECTS ON RANDOMIZED TREATMENT

Protocol activity (visits ±1 week, except Weeks 2 and 4 which are ±3 days)	Screening Week -2[1]	Randomization (Day 1)	Weeks 2, 6	Full study visit Weeks 4, 16, 28, 40	Abbreviated study visit Weeks 8, 12, 20, 24, 32, 36, 44, 48	Week 52	Unscheduled	Follow-up Weeks 56-58
Written informed consent[19]	X							
IRT system	X	X	X	X	X		X	X
Entry criteria	X	X						
History: medical, hospitalization, transfusion; demography, height	X							
Weight and estimated dry (target) weight	X	X	X	X	X	X	X	X
SBP/DBP[2], HR[2]	X	X[2] (triplicate)	X	X	X	X[2] (triplicate)	X	X
ECG[3]	X	X						
Ultrasound of kidneys and adrenal glands	X[4]							
Randomized treatment dispensing[16]		X		X	X		X[5,6]	
Randomized treatment compliance[16]			X	X	X	X	X[7]	
Iron therapy, transfusions (record in eCRF, if applicable)		X	X	X	X	X		X
Rescue medication (record in eCRF, if applicable)			X	X	X	X		X
Females only: estradiol & FSH (if required)	X							
Serum pregnancy test[8] (FRP only)	X	X		X	X[17]	X	X	X
HemoCue Hgb	X	X	X	X	X	X	X	
Hematology[9]	X	X		X	Hgb only	X	X	X
Clinical chemistry[9]	X	X		X		X	X	X
Ferritin, serum iron, UIBC	X[1]	X		X		X		X
Vitamin B12[1], folate	X							
Hepcidin		X		X		X		X

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

1. The screening period may be extended by an additional 4 weeks for subjects who require IV iron supplementation and/or vitamin B12 as outlined in Section 5.2. Ferritin, TSAT, and/or vitamin B12 must be re-assessed, where appropriate, following iron and/or B12 supplementation prior to randomization to meet entry criteria.
2. A single measurement each of SBP, DBP and HR will be taken, except at Day 1 and Week 52 where the measurements will be take in triplicate. Measurements will be taken post-dialysis for subjects receiving in-center dialysis. See Section 7.4.8 .
3. ECG assessment must be recorded pre-dialysis for dialysis subjects. ECG may be performed as early as at screening Week -2 and prior to randomization (Day1).
4. Ultrasound of the kidneys and adrenal glands must be performed prior to randomization. The screening period may be extended up to 4 weeks if needed. A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria, provided the size and cyst category has been reported. If a more sensitive imaging study [e.g., magnetic resonance imaging (MRI), computed tomography (CT)] has been performed within this timeframe and a report is available, this may be used in place of the ultrasound. See Section 7.4.10.
5. Additional visits to check Hgb and dispense randomized treatment are required under the circumstances described in Appendix 3. Hematology and chemistry samples are not required. For any unscheduled visit, compliance checking will be required when a dose of randomized treatment is changed.
6. Required only if dose is changed or randomized treatment is dispensed.
7. If dose does not change, then randomized treatment is returned to subject.
8. If a subject becomes post-menopausal (as defined in Appendix 5) during the study pregnancy tests are no longer required.
9. Testing panel in Table 8. Please note, creatinine and eGFR will only be tested and calculated at screening and randomization
10. A historical Kt/Vurea measurement within the last 12 weeks can be used. If a Kt/Vurea measurement is not available, then a urea reduction ratio (URR) measurement is acceptable.
11. PK sampling will be collected from all subjects randomized to the daprodustat arm at 1 of these 3 visits, Details in Section 7.5.
12. Informed consent for optional genetic research should be obtained before collecting a sample. To minimize potential study bias, the genetic sample should be collected on Day 1.
13. Subjects who are unable to or require assistance to read must not complete the questionnaires.
14. To be completed if available (e.g., translations may be not available in time in all countries).
15. Only SAEs assessed as related to study participation or a GSK product are collected during screening period
16. In circumstances where the new dose of randomized treatment cannot be dispensed on the day of the study visit, the new dose of randomized treatment can be dispensed at next HD treatment. For visits after Day 1, prior randomized treatment should be continued unless on dose hold, Hgb ≥12 g/dL. Compliance is deferred until randomized treatment is returned
17. For Argentina, ONLY: pregnancy testing will be performed every 4 weeks for FRP as required by local law
18. Biomarker samples will be stored for future analyses for all subjects, except if not permitted by IRB/EC or refused by subject.
19. Informed consent will be obtained prior to any study procedures.

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

7.4.11. Clinical Laboratory Assessments

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

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

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

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

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

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

7.4.12.1. Randomized Treatment Restart

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

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

The full liver safety drug restart guideline is provided in Appendix 6.

7.5. Pharmacokinetics (PK)

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

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

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

On the day of the scheduled PK visit:

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

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

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

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

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

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

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

9.2.2. Sample Size Sensitivity

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

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

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.

11. REFERENCES

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

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Objectives	Endpoints
and BP medication changes	and MAP by visit • Number of BP medications per subject by visit • Change from baseline in the number of BP medications per subject by visit • N (%) of subjects who had no change, an increase or a decrease in the dosage or number of BP medications from baseline by visit
To compare daprodustat to rhEPO on lipid parameters	• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)]
To further compare daprodustat to rhEPO on the symptom severity and change	• Change from Baseline at Wk 8,12, 28, & 52, by item on the CKD-AQ • Shift tables (Baseline to 8, 12, 28, & 52) in PGI-S • N(%) of patients within each PGI-C symptom change level at Wk 8, 12, 28, 52.
To further compare daprodustat to darbepoetin alfa on HRQoL and Utility score	• Change from baseline in Health Utility (EQ-5D-5L) score at Weeks 8,12, &28 • Change from baseline in EQ VAS at Weeks 8, 12, & 28
To evaluate graphical relationships between exposure parameters and selected efficacy endpoints	• Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. percent time in range during EP. • Scatter plots of average daprodustat dose during EP vs. percent time in range during EP. • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP vs. percent time in range during EP. • Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to 1 mg vs. change from baseline of Hgb during EP. • Scatter plots of average daprodustat dose during EP vs. change from baseline of Hgb during EP. •Scatter plots of daprodustat PK parameters (C_{tau} and C_{max}) dose normalized to average dose during EP vs. change from baseline of Hgb during EP.
To evaluate graphical relationships between daprodustat exposure and MACE and the composite endpoint of MACE+thromboembolic event+ hospitalization for heart failure	• Boxplots of daprodustat PK parameters (Ctau and Cmax) dose normalized to 1 mg by subjects with or without MACE or combined safety endpoint. • Boxplots of daprodustat PK parameters (Ctau and Cmax) dose normalized to dose at time of MACE or combined safety endpoint (or end of treatment if no endpoint) by subjects with or without MACE or combined safety endpoint.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue randomized treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.6.2. Liver Safety Drug Restart Guidelines

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

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

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

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

12.8.4. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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