**Objectives and Endpoints:**

| Objective | Endpoint |
|---|---|
| **Primary** | |
| • To compare the efficacy of daprodustat to placebo on mean change in Hgb levels | • Mean change in Hgb between baseline and the Evaluation Period (EP, mean over Week 24 to Week 28) |
| **Principal Secondary** | |
| • To compare the proportion of participants achieving increases in Hgb when treated with daprodustat versus placebo. | • % of participants having a Hgb increase of ≥1.0 g/dL to EP. |
| • To compare daprodustat to placebo for health related quality-of-life | • Mean Change in 36-item Short Form health survey (SF-36) Vitality domain, between baseline and Week 28 |
| **Safety** | |
| • To compare the safety and tolerability of daprodustat to placebo | • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest and adjudicated Major Adverse Cardiovascular Events (MACE) (composite of all-cause mortality, non-fatal MI and non-fatal stroke)<br>• Reasons for discontinuation of study treatment<br>• Absolute values and changes from baseline in laboratory parameters, blood pressure (BP) and heart rate (HR) |

**Overall Design:**

This is a 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center Phase 3 study in participants with anemia associated with CKD who are not on dialysis. This study will enroll participants with renal anemia who have a HemoCue Hgb 8.5 to 10.0 g/dL, inclusive, as measured by a point-of-care Hgb analyser (HemoCue). These participants will also have limited history of IV iron use and are rhEPO naïve prior to screening and randomization.

Study treatment doses for participants in both treatment arms will be titrated based upon HemoCue Hgb. Dose modifications for all participants will follow a protocol-specified dose adjustment algorithm to achieve and maintain Hgb within the target range of 11.0 to 12.0 g/dL, inclusive. Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both randomized treatment arms.

| **Protocol activity (visits ±1 week)**<br><br>(Note: All visit timings are relative to Day 1) | **Screening Week -4**[1] | **Screening Week -2** | **Treatment Period: Day 1 through Week 28** | | | | | | **Follow-up Visit (4 weeks post treatment)** |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Day 1** | **Week 2** | **Full study visit Week 4, 16** | **Abbreviated study visit Week 8, 12, 20, 24** | **Week 28** | **Unscheduled** | |
| Genetic Sample [14] | | | X | | | | | | |

1. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ECG, electrocardiogram; FSH, follicle stimulating hormone; FRP, Females of Reproductive Potential; WOCBP, woman of childbearing potential; hCG, human chorionic gonadotropin; UIBC, unsaturated iron binding capacity; hsCRP, high sensitivity C-reactive protein, serious adverse events (SAEs); ADPKD autosomal dominant polycystic kidney disease.If participants does not meet eligibility criteria during/after week -4, then week -2 visit should not be conducted.
2. Only history related to medical and hospitalization will be re-checked on Day 1 to confirm eligibility prior to randomization.
3. SBP/DBP, HR (single readings unless otherwise indicated)
4. ECG can be conducted at Week -2 visit or at Day 1 prior to randomization.
5. Ultrasound of the kidneys and adrenal glands must be performed prior to randomization. The screening period may be extended up to 2 weeks if needed. A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria provided the size and cyst category has been reported. If a more sensitive imaging study [e.g., magnetic resonance imaging (MRI), computed tomography (CT)] has been performed within this timeframe and a report is available, this may be used in place of the ultrasound. See Section 9.5.4.
6. Record historical and current anemia therapy in eCRF, if applicable.
7. See details on rescue in Section 7.7.2.
8. Repeat pregnancy test prior to study treatment re-administration if it is interrupted for >7 days and there was also a lapse in contraceptive use, regardless of the reason for the interruption. If a participant becomes post-menopausal (as defined in Section 12.4) during the study, pregnancy tests are no longer required.
9. Participant are eligible for randomization if the initial HemoCue Hgb assessment is from 8.5 to 10.0 g/dL. Repeat a HemoCue Hgb assessment using the same sample and use the average of the two values for randomization only if the initial assessment is from 10.1 to 10.3 g/dL, or if the initial assessment is from 8.2 to 8.4 g/dL. If the average Hgb is also from 10.1 to 10.3 or from 8.2 to 8.4 g/dL then another HemoCue Hgb assessment can be performed using a new blood sample on the Day 1 visit date. All HemoCue Hgb assessments, starting after Day 1 to end of treatment visit, should be conducted at the end of the study visit, only prior to study medication or rescue medication dispensation.
10. See details on hematology, clinical chemistry and other laboratory assessments in Section 9.5.5.
11. Ferritin, total iron and UIBC will be assessed at Week 16, but not at Week 4.
12. Participants will be provided a Visit Reminder Card (at Day 1) along with the verbal instruction to promptly inform site staff of any health changes. Health changes include new symptoms or medical problems (e.g., pregnancy, hospitalizations) and changes in medication .
13. Only SAEs assessed as related to study participation or a GSK product are collected at this visit. See Section 9.3.1 for additional details
14. 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.
15. France sites and participants with history of ADPKD only (to be performed at or after the week 28 study visit or as soon as clinically feasibile prior to the Follow-up visit (see Section 9.5.4) for additional details).
16. For Argentinian sites **only** and only in WOCB
17. New doses of study treatment will be provided to participants starting from Day 1 to week 24 visit as indicated by IRT System. Study treatment may be dispensed at week 2 or unscheduled visit only if indicated by IRT system, otherwise participants should continue on study treatment dispensed at prior study visit.

## Table 3 Schedule of Activities for Participants Permanently Discontinuing Study Treatment

| Protocol Activity (Note: All visit timings are relative to Day 1) | Early Treatment Discontinuation Visit (within 2 weeks of discontinuing study treatment) | Day 1 through Week 28 | | |
|---|---|---|---|---|
| | | Week 4, 16, 28 ± 2 weeks | Week 24 | Unscheduled |
| IRT system call | X | X | X | X |
| SBP/DBP, HR | X (Triplicate) | | | X |
| ECG | X | | | |
| Rescue medication [1, 2] | X | X | X | |
| Urine (serum if transitioned to dialysis) pregnancy test (WOCBP only) | X [7] | | | |
| HemoCue Hgb | X | X | X | X |
| Hematology[3] | X | X | Hgb Only | |
| Clinical chemistry[3] | X | X | | |
| Iron Panel | X | | | |
| Hospitalization[1] , transition to dialysis[1] | X | X | X | X |
| hsCRP | X | | | |
| Adverse event assessment | X | X | X | X |
| Review concomitant medications | X | X | X | X |
| Actigraphy [4] | X[9] | X | | |
| CKD-AQ [8] | X | X | | |
| PGI-S, PGI-C [8] | X | X | | |
| SF-36 [8] | X | X | | |
| EQ-5D-5L& EQ-VAS [6, 8] | X | X | | |
| WPAI-ANS-CPV [5, 8] | X | X | | |
| ADPKD participant only: Ultrasound | X[10] | | | |
| Healthcare resource utilization (participant-reported) | X | | | |

1. Record in eCRF, if applicable.
2. See details on rescue in Section 7.7.2.
3. See details on hematology and clinical chemistry in Section 9.5.5.
4. Actigraphy device could be worn for 7 days prior to the study visit indicated in Table 3 and as described in Section 9.7. Data will be downloaded at the Discontinuation Visit.
5. If local dialect or language is available.
6. Only in selected countries. See Section 12.8 (Appendix 8).

7. Additional pregnancy test required at subsequent visit. Must be at least 4 weeks after the end of randomized treatment.
8. Subjects who are unable to or require assistance to read must not complete the questionnaires.
9. If actigraphy device is available,participants should be instructed to wear actigraphy device for up to 7 days prior to early treatment discontinuation visit.
10 . Ultrasound of the kidneys will be performed within one month of discontinuing study treatment, or as soon as clinically feasible. See Section 9.5.4 for additional details.

| Objectives | Endpoints |
|---|---|
| | baseline in laboratory parameters, Blood Pressure (BP) and heart rate (HR) |
| **Secondary** | |
| • To compare daprodustat to placebo on additional Hgb endpoints | • N (%) responders, defined as mean Hgb within range.<br>• % time Hgb in range<br>• Mean change in Hgb from baseline. |
| • To compare daprodustat to placebo on the time to rescue | • Time to stopping study treatment due to meeting rescue criteria |
| • To compare daprodustat to placebo for improving symptoms of anemia of CKD | • Mean change from baseline by domain and overall symptom score on the Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ) symptom questionnaire |
| • To compare daprodustat to placebo on the severity and change in symptoms | • Change from baseline in PGI-S |
| • To compare daprodustat to placebo for improving health related quality-of-life | • Mean Change in individual items of the SF-36 Vitality Domain from baseline.<br>• Mean Change in SF-36 Physical Function domain from baseline. |
| • To compare daprodustat to placebo on improving work productivity and regular daily activity impairment | • N (%) of patients currently employed on the WPAI-ANS-CPV<br>• Change from baseline in percent and mean hours work time missed on the WPAI-ANS-CPVChange from baseline in percent impaired (equivalent) on the WPAI-ANS-CPV<br>• Change from baseline in overall percent work impairment (equivalent) on the WPAI-ANS-CPV<br>• Change from baseline in percent activity impairment on the WPAI-ANS-CPV |
| • To compare daprodustat to placebo on improving health status | • Change in EQ-5D-5L utility score from baseline.<br>• Change in EQ-VAS score from baseline. |
| • To compare daprodustat to placebo on BP | • Change from baseline in SBP, DBP, and MAP at week 28<br>• N (%) with at least one BP exacerbation event during the study |

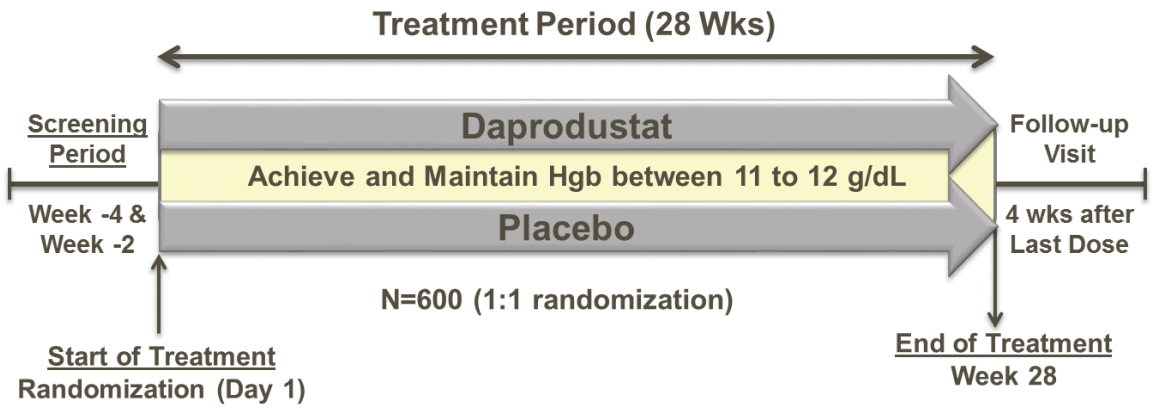
The total duration of study participation for each participant will be approximately 36 weeks.

Participants will be randomized 1:1 to receive either daprodustat or matching placebo tablets. Participants will not be provided with the results of their HemoCue Hgb assessment during their participation in the study.

Daprodustat and placebo doses for participants will be titrated based upon HemoCue Hgb. Dose modifications for these participants will follow a protocol-specified dose adjustment algorithm to achieve and maintain Hgb within the target range of 11.0 to 12.0 g/dL, inclusive. Dose changes will be made programmatically in a blinded fashion by the IRT system in order to ensure that investigators and participants stay blinded to the study treatment and the dose adjustments.

A rescue algorithm is provided to minimize participants having an inadequate response to the treatment for their anemia for an extended period of time and to enable rescue therapy to be provided to the participants based on local clinical practice. (Section 7.7.2)

**Figure 1 Study Schematic**




## 5.2. Number of Participants

Approximately 1200 participants with anemia associated with CKD who are not on dialysis will be screened to achieve approximately 600 randomized and to target approximately 540 evaluable participants for an estimated total of 270 evaluable participants with a 1:1 randomization per study treatment group.

## 5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the Follow-up visit, which takes place 4 weeks after the end of study treatment.

The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure shown in Table 1 of Schedule of Activities (SoA).

# 6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 6.1. Inclusion Criteria

Participants will be eligible for inclusion in this study only if all of the following criteria apply at **screening (Week -4 and Week -2)** and **randomization (Day 1)**, unless otherwise specified:

**Age**

1. ≥ 18 years of age at the time of signing the informed consent.

**Type of Participant and Disease Characteristics**

2. **CKD**: Have CKD, confirmed at screening: Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages 3, 4, or 5 defined by Estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009].
3. **Hgb**: Stable HemoCue Hgb from 8.5 to 10.5 at screening visit (Week -4) and from 8.5 to 10.0 g/dL at randomization (Day 1) (Section 9.1).
4. **IV Iron**: Participants may receive up to one IV iron dose within the 8 weeks prior to screening and NO IV iron use between screening visit and randomization (Day 1).
5. **Oral Iron**: If needed, participant may be on stable maintenance oral iron supplementation. There should be <50% change in overall dose and no change in type of iron prescribed doses in the 4 weeks prior to Day 1 randomization visit.

**Sex**

6. Male and female participants are eligible. A female participant is eligible to participate if she is not pregnant (see Section 12.4), not breastfeeding, and at least one of the following conditions applies:
    - Not a woman of childbearing potential (WOCBP) as defined in Section 12.4 (Appendix 4), or
    - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 4 weeks after the last dose of study treatment.

**Informed Consent**

7. Capable of giving signed informed consent as described in Section 12.2 Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be approximately 150 mL. This amount does not take into account the blood that can be collected at unscheduled visits.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- This section lists the procedures and parameters of each planned study assessment. Post randomization visits should be referenced back to the Randomization visit (Day 1). The allowable visit window is ±1 week. However, during the study, 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 Medical Monitor.
- Supplementary study conduct information is provided in the SRM. The SRM provides administrative and detailed technical information that does not impact participant safety.

## 9.1. 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 cardiovascular medical history/risk factors) will be assessed at screening (Week -4).
- A stable, HemoCue Hgb from 8.5 to 10.0 g/dL at Day 1 (randomization visit).
    - If the initial HemoCue Hg assessment is from 10.1 – 10.3 g/dL or from 8.2 to 8.4 g/dL, a repeat assessment should be conducted. The two Hemocue Hgb should be averaged and the average Hemocue Hgb value should be from 8.5 – 10.0 g/dL.

- If the average Hgb is also from 10.1 to 10.3 or from 8.2 to 8.4 g/dL then another HemoCue Hgb assessment can be performed using a new blood sample on the Day 1 visit date.
- Two values from one blood sample can be entered into the IRT system however only the first value or the average value will be used for randomization and dose modification algorithm. .

- Full details of screening (Week -4) and Day 1 assessments are provided in the Schedule of Activities.

## 9.2. Efficacy Assessments

- Planned time points for all Hgb efficacy assessments are listed in the Schedule of Activities (Section 2).
- 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 the Schedule of Activities.
- All HemoCue Hgb assessments after Day 1 visit to study completion should be conducted at the end of the study visit, prior to study medication or rescue medication administration.
  - All efforts should be made to conduct the Hemocue Hgb measurements in a separate area away from the participants.

## 9.3. Adverse Events

- The definitions of an AE or SAE can be found in Section 12.3 (Appendix 3).
- The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

### 9.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.

- All AEs will be collected from the start of study treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to GSK or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 12.4 (Appendix 3). The investigator will submit any updated SAE data to GSK within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.4 (Appendix 3).

### 9.3.2. 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 participant is the preferred method to inquire about AE occurrence.

### 9.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 9.3.6), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Section 12.4 (Appendix 4).

### 9.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to GSK of an SAE related to placebo or daprodustat is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 study treatment under clinical investigation. GSK will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For any cardiovascular events detailed in Section 9.3.5 and Section 9.3.6 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

### 9.3.7. 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):

- Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access
- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Worsening of hypertension
- Cardiomyopathy
- Pulmonary artery hypertension (see also Section 9.3.2)
- Cancer-related mortality or tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

The results of any investigation regarding adverse events of special interest should be recorded in the relevant sections of the participant's eCRF.

### 9.3.8. 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 or 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.

### 9.3.9. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until seven days after the last dose.
- If a pregnancy is reported, the investigator should inform Sponsor within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 12.5 (Appendix 5) .
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

## 9.4. Treatment of 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 hemodialysis (HD) or peritoneal dialysis (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 participant's clinical status. Additionally, participants should be monitored closely for CV events, increased heart rate and hematologic abnormalities.

## 9.5. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

### 9.5.1. Height and Weight

- Height and weight will be measured as specified in the SoA (Section 2). Weight should be measured with the participant wearing indoor daytime clothing with no shoes.

### 9.5.2. 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 SoA (Section 2)

- One measurement each of SBP, DBP and HR will be taken except at Day 1 and Week 28 (or Early Treatment Discontinuation visit) when SBP, DBP and HR will be measured in triplicate.
    - For measurements taken in triplicate, the readings can be averaged and the averaged value would be included in the eCRF.
- Measurements will be taken with participants in a seated position after at least a 5-minute rest period, and will be **before** collection of blood samples for laboratory testing, where applicable.

- For subjects transitioning to dialysis, SBP, DBP and HR will be measured pre and post-dialysis, whenever possible (e.g., in-center HD). Otherwise these assessments will be done between dialysis sessions.

### 9.5.3. Electrocardiograms

ECG measurements will be taken at the time points specified in the SoA (Section 2). Full 12-lead ECGs will be recorded with the participant in a supine position. HR, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcB will be calculated (machine-read or manually).

When an ECG is performed, two additional ECGs are required if the initial ECG indicates prolonged QTc (see Section 6.2) using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility (see Section 6.2). 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 ECG will be required to confirm eligibility. Additional details are provided in the SRM.

All ECGs will be performed **before** measurement of SBP, DBP and HR and collection of blood samples for laboratory testing.

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

### 9.5.4. Ultrasound

An ultrasound of the kidneys and adrenal glands will be performed prior to randomization. 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 a participant 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 6.2), 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.

For randomized participants with ADPKD:

- An ultrasound of the kidneys will be performed when participants permanently discontinue study treatment, preferably within one month of discontinuation of study treatment as soon as clinically feasible. This may occur during the study OR at the end of study. See Table 1 and Table 3 for details.
- As clinically feasible, an ultrasound should be performed PRIOR to the following:
    - Transition to dialysis
    - Bilateral nephrectomy

- Some of the central laboratory/analyte results which will not be reported to investigators, site staff and participants are Hgb, hematocrit, reticulocyte count, RBC count, etc. Additional details will be included in the SRM.

**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] | Sodium (serum) | AST | Carbon Dioxide (total) |
| | Potassium (serum) | ALT | Albumin |
| | Calcium (total and albumin-adjusted) | Inorganic phosphate | Urea (serum) |
| | Creatinine (serum) | Bilirubin (total and direct/indirect) | Chloride (serum) |
| | eGFR | | |
| **Iron parameters** | Iron (serum) | Ferritin | UIBC |
| | Hepcidin | TIBC | TSAT |
| **Lipid parameters** | Total cholesterol | LDL-C (direct) | HDL-C |
| **Other laboratory tests** | Urine/serum hCG pregnancy test [2,3] | FSH [4] | Estradiol [4] |
| | HemoCue Hgb | hsCRP | |

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; hCG, human chorionic gonadotropin; FSH, follicle-stimulating hormone.

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 6.
2. For women of childbearing potential only.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC, and for participants who transition to dialysis during the study.
4. Screening only. As needed for postmenopausal women when their menopausal status is in doubt. See Inclusion Criteria Section 6.1.

## 9.6. Patient Reported Outcomes

The patient-reported effect of daprodustat and placebo on symptoms, health related quality of life (HR-QoL), health status (e.g., utility) and work productivity and activity impairment will be assessed. Symptoms will be assessed using a symptoms questionnaire which is specific to anemia of Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ). Overall symptom severity will be assessed using the patient global impression of severity (PGI-S), and overall symptom change using the patient global impression of change (PGI-C). Quality of life will be measured via SF-36 and health status via the EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) and the EuroQol Visual

Analogue Scale (EQ-VAS). Work productivity and regular daily activity impairment will be measured via the Work Productivity and Activity Impairment Questionnaire for the specific health problem of anemia, Clinical Practice Version 2.0 (WPAI-ANS- CPV; V2.0).

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 participant is to complete these questionnaires will be provided in the SRM.

Patient reported outcomes questionnaires are to be administered at the beginning of the visits and the subjects should not be told the results of any diagnostic tests prior to completing the questionnaires. Adequate time must be allowed to complete all items on questionnaires, and if necessary, the subject must be encouraged to complete any missing items. So as to minimize the amount of missing data, the questionnaires should be completed by participants at a clinic visit, in the order specified: PGI-S, PGI-C, CKD-AQ, SF-36, EQ-5D-5L and EQ-VAS, then the WPAI-ANS- CPV. Additional instructions on how investigators and site staff will be trained to provide participants with instructions will be provided in the SRM.

### 9.6.1. Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ)

A novel symptom questionnaire – CKD-AQ has been developed to collect concepts of interest for the anemia of CKD population. Unlike the Functional Assessment of Cancer Therapy – Anemia (FACT-AN) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) which have not demonstrated content validity specific for the anemia of CKD population, the novel CKD-AQ instrument was developed to verify and ensure that concepts specific for anemia of CKD were captured and measured. It will measure both the frequency and/or severity in anemia of CKD concepts such as Weakness, Energy, Tiredness, Shortness of Breath, Exertion, Chest Pain, Memory, Concentration, Standing, Sleep and Distress over the past 7 days.

### 9.6.2. 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 participant'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 participant'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.

### 9.6.3. Health Related Quality of Life (SF-36)

The SF-36 acute version is a general health status questionnaire designed to elucidate the participant'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. The questionnaire contains 36 questions within these domains that ask the participant to recall how they felt during the past seven days.

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

EQ-5D-5L consists of 2 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 participant'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' at the time of completion. This information is used as a quantitative measure of health outcome as judged by individual participants.

### 9.6.5. Work Productivity and Activity Impairment (WPAI-ANS-CPV)

The WPAI-ANS-CPV is an anemia specific questionnaire designed as a self-reported quantitative assessment of social functioning related to work and regular daily activities. It contains two main concepts- work productivity impairment measured via absenteeism (time missed from work), presenteeism (impairment at work) and regular daily activity impairment. The questionnaire contains 6 questions and asks the patient to recall work and activity impairment over the past 7 days.

## 9.7. Actigraphy

Patients with anemia in CKD can experience decreased physical functioning and sleep disturbances [KDIGO, 2012]. Therefore, actigraphy assessment in this study will be conducted as a means to measure changes in the physical activity and sleep from a baseline measurement taken prior to Randomization (Day 1) to the end of study. The data collected may be used to conduct exploratory analyses of physical activity and sleep.

ActiGraph GT9X Link is being piloted in this study to capture and record high resolution human activity information by using a validated solid state 3-axis MEMS accelerometer and proprietary filtering algorithm to report daily movement associated with physical activity and sleep. This device will capture patterns of activity throughout the day and night.

Physical activity will be measured by subject activity metrics such as steps taken, physical activity intensity, and activity/sedentary bouts.

Sleep activity will be measured by subject sleep period metrics such as total sleep time, sleep latency and sleep efficiency.

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| | |
|---|---|
| HR | Heart rate |
| HR-QoL | Health Related Quality of Life |
| HRT | Hormone replacement therapy |
| hsCRP | High sensitivity C-reactive protein |
| KDIGO | Kidney Disease Improving Global Outcomes |
| KDOQI | Kidney Disease Outcomes Quality Initiative |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LDH | Lactate dehydrogenase |
| LDL-C (direct) | Directly measured Low density lipoprotein-C |
| MACE | Major adverse cardiovascular event |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| MRI | Magnetic resonance imaging |
| MSDS | Material Safety Data Sheet |
| NYHA | New York Heart Association |
| PD | Peritoneal dialysis |
| PGI-C | Patient Global Impression of Change |
| PGI-S | Patient Global Impression of Severity |
| PHI | Prolyl hydroxylase inhibitor |
| PK | Pharmacokinetic |
| PSRAE | Possible Suicidality Related Adverse Events |
| 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 |
| SD | Standard deviation |
| SF-36 | Short Form -36 |
| sPAP | Systolic pulmonary artery pressure |
| SRM | Study Reference Manual |
| TIBC | Total iron binding capacity |
| TSAT | Transferrin saturation |
| UIBC | Unsaturated iron binding capacity |
| U | Units |
| ULN | Upper limit of normal |
| WBC | White blood cells |

## 12.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.<br>• 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 study treatment. |

| **Events Meeting the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.<br>• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE. |

| **Events NOT Meeting the AE Definition** |
|---|
| • 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 participant's condition.<br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.<br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• 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. |

## Reporting of SAE to GSK

| **SAE Reporting to GSK via Electronic Data Collection Tool** |
|---|
| • The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.<br>• If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.<br>• The site will enter the SAE data into the electronic system as soon as it becomes available.<br>• The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.<br>• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.<br>• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.<br>• Contacts for SAE reporting can be found at the beginning of this protocol on the Medical Monitor Contact Information page. |

| |
|---|
| 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 |
| **Is associated with liver injury <u>and</u> impaired liver function defined as:**<br>• ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**<br>• ALT ≥ 3xULN and INR** > 1.5.<br>• 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.<br>• ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form. |

### 12.3.2. 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.<br>• The investigator will then record all relevant information regarding an AE/SAE in the eCRF<br>• It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE eCRF page.<br>• There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records prior to submission to GSK.<br>• 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.<br>• Participant-completed Patient Reported Outcomes questionnaires and the collection of AE data are independent components of the study. |

| | |
|---|---|
| **MONITORING:**<br><br>**<u>For bilirubin or INR criteria:</u>**<br><br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours**<br><br>• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline<br><br>• A specialist or hepatology consultation is recommended<br><br>**<u>For All other criteria:</u>**<br><br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours**<br><br>• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline | • Obtain complete blood count with differential to assess eosinophilia<br><br>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form<br><br>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.<br><br>• Record alcohol use on the liver event alcohol intake case report form<br><br>**<u>For bilirubin or INR criteria:</u>**<br><br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).<br><br>• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]).<br><br>• 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 participant 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 participants 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. 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 participant's

A rescue algorithm is provided to minimize participants having an inadequate response to treatment of their anemia after a fixed period of time and to enable rescue therapy to be provided to the participants based on local clinical practice.

A Clinical Events Committee (CEC) will adjudicate any event suspected to be a major adverse cardiovascular event (MACE).

**Number of Participants:**

Approximately 1200 participants will be screened to achieve approximately 600 randomized and approximately 540 evaluable participants for an estimated total of 270 evaluable participants per treatment arm.

**Treatment Groups and Duration:**

Participants will be randomized 1:1 to receive either daprodustat or matching placebo tablets, administered once daily.

This study includes a 4-week Screening period, a 28-week Treatment period, and a 4-week Follow-up period. The total duration of study participation for each participant will be approximately 36 weeks.

## Table 2 Schedule of Activities for Patient Reported Outcomes and Actigraphy

| **Protocol Activity (visits ±1 week)** (Note: All visit timings are relative to Day 1) | **Screening Week -4** | **Week -2** | **Treatment Period: Day 1 through Week 28** | | | | | | | | **Follow-up Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **Day 1** | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24** | **Week 28** | |
| Dispense Actigraphy Device | | X | | X | X | | | | X | | |
| Actigraphy (wearable)[1,5,6] | | | X | | X | X | | | | X | |
| Patient Global Impression of Severity (PGI-S)[2,3] | | X | X | | X | X | | | | X | |
| Patient Global Impression of Change (PGI-C)[2,3] | | | | | X | X | | | | X | |
| Symptoms of aCKD questionnaire2 | | X | X | | X | X | | | | X | |
| Short Form 36 (SF-36)[2,3] | | | X | | X | X | | | | X | |
| EuroQol 5 Dimension 5 Level Health Utility Index (EQ-5D-5L) and EuroQol Visual Analogue Scale (EQ-VAS) [2,3,4] | | | X | | X | X | | | | X | |
| Work Productivity and Activity Impairment Questionnaire (WPAI-ANS-CPV) [2,3] | | | X | | X | X | | | | X | |
| Healthcare resource utilization (participants-reported) | | | X | | X | X | | X | | X | |

1. Actigraphy device should be worn for 7 days prior to the study visits indicated in Table 2 and as described in Section 9.7. Data will be downloaded from device during the study visits indicated in Table 2.
2. Patient reported outcomes questionnaire should be completed as the first assessment, prior to conducting any other visit assessments (e.g. Adverse event assessment, HemoCue Hgb, etc.)
3. Subjects who are unable to or require assistance to read must not complete the questionnaires
4. Only in selected countries. See Section 12.8 (Appendix 8).
5. Sites can contact subjects to wear the actigraphy device 7 days prior to study visit.
6. All efforts should be made to encourage participation in this activity monitoring assessment. If a participant is unable to take part, the reason should be documented, and they may continue in the study.

# 3. INTRODUCTION

## 3.1. Study Rationale

Daprodustat (GSK1278863) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) currently being investigated as a treatment for anemia associated with chronic kidney disease (CKD) in both dialysis and non-dialysis participants with safety and efficacy having been demonstrated in clinical trials up to 24 weeks duration. Both pre-clinical and clinical data show that daprodustat-stimulated erythropoietin (EPO) production, increases erythropoiesis and thus elevates hemoglobin (Hgb) concentrations. These increases in Hgb are achieved with peak plasma EPO exposures substantially lower than those observed with recombinant human EPO (rhEPO). Data from completed clinical and preclinical studies are provided in the current Investigator Brochure [IB GlaxoSmithKline Document number RM2008/00267/07] and IB supplement(s).

Daprodustat has been evaluated as a treatment for anemia associated with CKD in non-dialysis participants. A Phase 2A clinical trial in non-dialysis participants with anemia associated with CKD demonstrated that fixed-dose daprodustat was better than placebo in increasing Hgb over 4 weeks [Holdstock, 2016].

Another Phase 2B, randomized, controlled 24-week parallel-group, multi-center study also evaluated daprodustat safety and efficacy in a non-dialysis population that were either naïve or previously treated with rhEPO [GlaxoSmithKline Document Number 2014N219818_00]. Titration of daprodustat demonstrated efficacy by achieving mean Hgb within target range with an adverse event rate consistent with the clinical events that generally occur in the CKD population.

Blood Hgb concentration, transferrin saturation and ferritin levels are the primary markers for evaluation of anemia in CKD patients. Initially, non-dialysis CKD patients receive iron therapy, to ensure that sufficient iron is available for erythropoiesis prior to initiating rhEPO therapy for anemia treatment. A one to three month trial of oral iron is generally recommended in rhEPO naïve patients with non-dialysis CKD [KDIGO, 2012). However, if poor compliance is seen with oral iron therapy due to lack of efficacy or gastrointestinal intolerance, IV iron may be administered in patients requiring iron repletion. rhEPO therapy is generally initiated in non-dialysis CKD patients once Hgb has dropped below 10 g/dL and benefits outweigh the risks associated with this therapy [KDIGO, 2012].Thus, the question arises whether initiation of treatment with a PHI, such as daprodustat, in the rhEPO naïve and iron sufficient population might result in Hgb benefits that are reflected as benefits in symptoms and quality of life.

This Phase 3 double blind study will be conducted to assess efficacy, safety and effects on quality-of-life of daprodustat compared to placebo. Study participants will be rhEPO naïve and had limited IV iron exposure at baseline. The purpose of this study is to evaluate the effect of daprodustat, on hemoglobin response and quality of life, compared to placebo over an extended period, i.e. 28 weeks, unlike the the previous study which evaluated the response over 4 weeks. The primary endpoint is Hgb superiority of daprodustat versus placebo, and a principal secondary endpoint includes measures of health related quality-of-life.

| Objectives | Endpoints |
|---|---|
| **Exploratory** | |
| • Further evaluations to compare daprodustat to placebo on Hgb variability | • % of time Hgb is above or below range.<br>• Number (%) of participants with mean Hgb above and below range.<br>• Number (%) of participants with a Hgb<7.5 g/dL<br>• Number (%) of participants with a >2 g/dL increase in Hgb within any 4 week period up to EP<br>• N (%) of participants with a Hgb value ≥ 13 g/dL during the treatment period<br>• Number of times Hgb ≥ 13 g/dL during the treatment period<br>• % of time Hgb ≥ 13 g/dL during the treatment period. |
| • Further evaluation to compare daprodustat to placebo on Hgb change. | • % of participants who achieved a Hgb increase of ≥1.0g/dL<br>• % of time Hgb increase of ≥ 1.0 g/dL from baseline<br>• % of participant having a Hgb increase of ≥ 1.0 g/dL at each post-baseline visit.<br>• % of participants who achieved and maintained a Hgb increase of ≥1.0g/dL between baseline and EP. |
| • To compare daprodustat to placebo on measures of iron status, rhEPO and Transfusion use | • Observed and change from baseline in hepcidin, ferritin, transferrin saturation, serum iron, total iron binding capacity (TIBC)<br>• Average monthly oral iron dose/participant (mg) to Week 28<br>• N (%) of participants who reduced oral iron supplementation from baseline<br>• N (%) of participants requiring IV iron each month.<br>• Average monthly IV iron dose/participant (mg) to Week 28<br>• Time to first IV iron, rhEPO and Transfusion use |

## 5.4. Scientific Rationale for Study Design

This study has a 28-week Treatment Period ending with a 4-week evaluation period from Week 24 to Week 28. At the Day 1 visit the subjects will be randomized to the daprodustat or placebo arm by the IRT system and the study treatment will be administered in a blinded manner. From Day 1 to Week 24 participant study treatment dosage will be adjusted, per the dosing algorithm (Section 7.2),in a blinded fashion, by the IRT system..

A placebo control will enable assessment of the magnitude of the daprodustat response and comparisons for safety data. Additionally, a placebo comparator allows for an assessment of the extent to which any improvement in symptoms and HRQoL observed in the daprodustat treatment group is due to the drug's effect.

The risk of drop-outs due to lack of treatment effect is estimated to also be low in this patient population since, prior clinical studies have indicated that non-dialysis, CKD patients can maintain, or even increase, their current level of Hgb value without requiring frequent interventional therapy with rhEPOs or IV iron for anemia [Skali, 2013].

Participants eligible for this study will be naïve to rhEPO therapies and have limited IV iron exposure at the time of screening and randomization, but may be receiving oral iron which will be allowed to continue during the course of the study. Participants may start treatment or change their dose of iron (oral, or IV if intolerable to oral) to maintain their iron levels during the study. Participants who experience worsening of their anemia during the study may receive rescue therapy based upon the protocol defined rescue algorithm. Therefore, the use of a placebo arm in this study does not represent the absence of any treatment for anemia, but rather placebo in addition to appropriate standard of care.

## 5.5. Dose Justification

Daprodustat starting doses were selected to enable the majority of study participants 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-participant variability in Hgb response to a given dose of daprodustat and the relatively narrow Hgb target range, individual dose adjustments of daprodustat are still expected during the first few months of treatment.

The daprodustat starting doses and dose steps (including the highest dose level, 16 mg) were based on dose exposure-response longitudinal modeling of Hgb data collected across the Phase 2 program.

In this study, the starting dose of daprodustat will be 2 or 4 mg based on baseline Hemocue Hgb, or a matching placebo dose, for all participants. The starting dose is estimated to increase steady-state Hgb on average by approximately 1g/dL. This starting dose is consistent with the dosing algorithm being evaluated in the Phase 3 study [GlaxoSmithKline Document Number 2015N230102_03] for non-dialysis dependent participants who are not currently receiving rhEPO therapy.

## 6.2. Exclusion Criteria

Participants will not be eligible for inclusion in this study if any of the following criteria apply at **screening (Week -4 and Week -2)** and **randomization (Day 1)**, unless otherwise specified:

**CKD Related Criteria**

1. **Dialysis:** On dialysis or clinical evidence of impending need to initiate dialysis within 180 days after randomization (Day 1).
2. **Kidney Transplant:** Planned living-related or living-unrelated kidney transplant within 28 weeks after randomization (Day 1).

**Anemia-Related Criteria**

3. **Transferrin saturation (TSAT)** <15% (Screening only)
4. **Ferritin** <50 ng/mL (Screening only)
5. **rhEPO or rhEPO analogues**: History of rhEPO or rhEPO analogue use within the 8 weeks prior to screening and rhEPO use between screening and randomization (Day 1).
6. **Transfusion**: History of transfusion within the 8 weeks prior to screening and transfusion between screening and randomization (Day 1).
7. **Aplasias:** History of bone marrow aplasia or pure red cell aplasia (PRCA)
8. **Other causes of anemia**: Megaloblastic anemia(untreated pernicious anemia and folate deficiency), thalassemia major, sickle cell disease or myelodysplastic syndrome
9. **Gastrointestinal (GI) bleeding:** Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding ≤ 8 weeks prior to screening through to randomization (Day 1)

**Concomitant medication and other study treatment-related criteria**

10. **Severe Allergic reaction**: History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product.
11. **Drugs and supplements:** Use of strong inhibitor of CYP2C8 (e.g.,gemfibrozil) or strong inducers of CYP2C8 (e.g., rifampin/rifampicin).
12. **Ferric Citrate:** Ferric citrate use within 4 weeks prior to randomization (Day 1)

**Prior Clinical Study Experience**

13. **Other interventional study participation:** Use of other investigational agent or device prior to screening through to randomization (Day 1).
    a. Note: at screening, this exclusion applies to use of the investigational agent within 30 days or within five half lives (whichever is longer).
14. **Prior treatment with daprodustat:** Any prior treatment with daprodustat for a treatment duration of >30 days.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from GSK will review and then file it along with the Investigator's Brochure[IB GlaxoSmithKline Document number RM2008/00267/07] and will notify the IRB/IEC, if appropriate according to local requirements.

### 9.3.5. Events Referred to the Clinical Events Committee (CEC)

Investigators should refer any event suspected to be one of the events below to the CEC for adjudication, 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 HF
- Thromboembolic events (vascular access thrombosis, deep vein thrombosis, 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 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 CEC Charter (available on request).

Source documentation required to support the adjudication of the events is described in the CEC site manual.

### 9.3.6. Other Cardiovascular (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 9.3.7 for further details).
- Valvulopathy
- Revascularization

- Kidney transplant.

- An additional ultrasound may be performed at any time during the study based on investigator's clinical judgment (e.g., deterioration of kidney function as measured by eGFR in the absence of other identifiable causes). Other imaging techniques (e.g., MRI) can be performed at the investigator's discretion.
- If an additional imaging study is performed, and the condition of the cystic disease in the kidney(s) has worsened more than expected given the clinical scenario, then **study treatment should be temporarily stopped**. Subsequently, if no other cause for the kidney function decline and/or cyst enlargement can be identified, study treatment should be permanently discontinued after consultation with the Medical Monitor.

### 9.5.5. Clinical Laboratory Assessments

- Refer to Table 8 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- 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.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Table 8, must be conducted in accordance with the laboratory manual and the SoA (Section 2). Laboratory assessments will be performed by a central laboratory with the exception of HemoCue Hgb and urine pregnancy tests which will be performed at the clinical site. The results of each HemoCue Hgb must be entered into the participant's eCRF.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

Prior to the participant leaving the study site at the screening visit, the participant must have been trained on how to position the device to their arm, how to charge the battery and check the battery status. These topics are all covered in the Participant Information Leaflet and further instructions regarding distribution, operation, retrieval of ActiGraph GT9X Link devices will be provided in the SRM.

All efforts should be made to encourage participation in this activity monitoring assessment. If a participant is unable to take part, the reason should be documented, and they may continue in the study.

The technical performance of the Actigraph device will also be closely monitored and assessed during the study and the Sponsor may elect to discontinue this assessment if device related difficulties are encountered.

## 9.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

## 9.9. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 12.5 (Appendix 5) for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in $Q^2$ Solutions Investigator Manual

## 9.10. Storage Biomarkers

Blood samples will not be stored for biomarker analysis in this study

## 9.11. Healthcare Resource Utilization and Economics

Healthcare resource utilization and health economic data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)

# 12. APPENDICES

## 12.1. Appendix 1: Abbreviations and Trademarks

### Abbreviations

| | |
|---|---|
| ADPKD | Autosomal dominant polycystic kidney disease |
| 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 |
| CKD-AQ | Chronic Kidney Disease - Anemia Questionnaire |
| CKD-EPI | Chronic kidney disease Epidemiology Collaboration |
| CNIL | Commission Nationale de I'Informatique et des Libertés |
| CPK | Creatine phosphokinase |
| CRA | Clinical Research Assistant |
| CTR | Clinical Trials Register |
| CT | Computed tomography |
| CV | Cardiovascular |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eGFR | Estimated glomerular filtration rate |
| EP | Evaluation period |
| EPO | Erythropoietin |
| EQ-5D-5L | EuroQol 5 Dimension 5 Level Health Utility Index |
| EQ-VAS | EuroQol Visual Analogue Scale |
| ESA | Erythropoetin-stimulating agent |
| FDA | Food and Drug Administration |
| FRP | Females of reproductive potential |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| GSK | GlaxoSmithKline |
| hCG | Human chorionic gonadotrophin |
| HD | Hemodialysis |
| HDL-c | High density lipoprotein-C |
| HDPE | High density polyethylene |
| Hgb | Hemoglobin |
| HIF | Hypoxia-inducible factor |

| | |
|---|---|
| WPAI-ANS-CPV | Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms Clinical Practice Version |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| NONE |

| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| ActiGraph GT9X Link |
| HemoCue |

### 12.3.1. 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:** |
|---|
| **Results in death** |
| **Is life-threatening**<br>• NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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. |
| **Requires hospitalization or prolongation of existing hospitalization**<br>• NOTE: In general, hospitalization signifies that the participant 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.<br>• Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **Results in disability/incapacity**<br>• NOTE:The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• 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 |
| **Is a congenital anomaly/birth defect** |
| **Other situations:**<br>• 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 participant 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.<br>• Examples of such events are invasive or malignant cancers, intensive treatment in |

### 12.3.3. 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 participant, 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 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 GSK. 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 GSK.**
- 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.

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.<br>OR<br>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 GSK **within 24 hours** of learning of the abnormality to discuss participant safety.<br>• Participant can continue randomized treatment<br>• Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline<br>• If at any time participant meets the liver chemistry stopping criteria, proceed as described above<br>• If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly.<br>• If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline. |

## References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute Liver failure. *Drug Metab Dispos* 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of hepatitis delta virus RNA in serum by consensus real-time PCR indicates different patterns of virological response to interferon therapy in chronically infected patients *J Clin Microbiol.* 2005;43(5):2363–2369.