TITLE PAGE

Protocol Title: A 28-week, randomized, double-blind, placebo-controlled, parallelgroup, multi-center, study in recombinant human erythropoietin (rhEPO) naïve nondialysis participants with anemia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo.

Protocol Number: 205270/01

Short Title: **A**nemia **S**tudies in **C**KD: **E**rythropoiesis via a **N**ovel PHI **D**aprodustat in **N**on-Dialysis participants evaluating **H**emoglobin and **Q**uality of life (ASCEND-NHQ)

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 1	*23-Aug-2019*
Country Specific Protocol ITA-1	*02-Apr-2018*
Original Protocol	*22-Aug-2017*

Amendment Version 1 23-AUG-2019

Overall Rationale for Amendment: Amendment conducted to provide clarity regarding follow-up of participants with ADPKD and to incorporate new safety data provided in the Investigator's Brochure.

Section# and Name	Description of Change	Brief Rationale
Section 2: Schedule of Activities, Table 1	Added footnote #17 to state when study treatment should be dispensed.	Footnote was added to clarify when study treatment is dispensed at study visits through the IRT system.
Section 2: Schedule of Activities, Table 1	Revised footnote #9 to permit a HemoCue Hgb retest with a new blood sample	A re-test provides an opportunity for participants and sites to avoid the inappropriate screen-failures due to technical issues with the initial sample collection and analysis via the HemoCue device.
Section 2: Schedule of Activities, Table 1	Revised footnote #12 to clarify the purpose of the participant reminder card	To clarify the purpose of the participant reminder card.
Section 2: Schedule of Activities, Table 1	Edited footnote #15 to add necessary ultrasound assessments for ADPKD participants at end of treatment	All participants with ADPKD will require an ultrasound within one month of study treatment discontinuation or as soon as clinically feasible as mandated by Dear Investigator Letter (DIL, dated 14 Dec 2018)
Section 2: Schedule of Activities for Patient Reported Outcomes and Actigraphy,	Added row to conduct assessment regarding healthcare resource utilization	Clarified timepoints for collection of the healthcare resource utilization data for all

Section# and Name	Description of Change	Brief Rationale
Table 2 and Schedule of Activities for Participants Permanently Discontinuing Study Treatment, Table 3	reported by participants at each visit starting with Day 1 (randomization visit) and after study treatment discontinuation	participants in the study.
Section 2: Schedule of Activities for Participants Permanently Discontinuing Study Treatment, Table 3	Added renal ultrasound for ADPKD participants upon discontinuation of study treatment.	Per the DIL, renal ultrasound is mandated for all participants with history of ADPKD who have discontinued study treatment.
Section 3.3.1 Risk Assessment	Updated risk assessment table with language related to Investigator Brochure update.	Edited Risk Assessment information to align with version 10 of the Investigator's Brochure.
Section 4. Objectives and Endpoints	Added secondary and exploratory endpoints and objectives related to BP exacerbations and concomitant medications	New objectives and endpoints were added to evaluate the effect of study treatment on BP.
Section 4. Objectives and Endpoints	Revised secondary endpoints for work productivity and regular daily activity impairment to quantify participant employment status and remove mean hours captured on WPAI-ANS-CPV	Endpoints were revised to align with the type of data captured in WPAI-ANS-CPV questionnaire.
Section 4. Objectives and Endpoints	Amended exploratory objectives for Hgb change to evaluate participants achieving a Hgb increase of ≥1.0g/dL instead of ≥1.2g/dL	Exploratory objective amended to fix the administrative error (typo) from the initial protocol.
Section 4. Objectives and Endpoints	Updated the exploratory objective to capture time to first rhEPO and Transfusion use.	Objective and endpoints were updated to additionally analyse the use of rhEPO and Transfusion in the study.
Section 6.1 Inclusion Criteria #5	Edited inclusion crtierion #5 to provide clarity for requirements of compliance with oral iron	Inclusion criterion to provide further clarity on appropriate compliance with type and dose

Section# and Name	Description of Change	Brief Rationale
	dosing prior to Day 1, and removed the need for stable iron dose prior to screening.	of oral iron prior to randomization.
Section 6.2 Exclusion Criteria #13	Edited exclusion criterion #13 edited to include use of investigational device	Broadened exclusion to include participation in a study with an investigational agent or device
Section 6.2 Exclusion Criteria #22	Added exclusion criterion #22 for uncontrolled hypertension	Additional criterion added to exclude participants with uncontrolled hypertension as worsening of hypertension has been added to the list of AESI for daprodustat per IB Version 10
Table 6. Study Treatment Dosing Algorithm	Instructions to repeat and average HemoCue Hgb assessment for Hgb <8.5 g/dL	Language added to align with the IRT system programming.
Section 8.1 Discontinuation of Study Treatment	Added information regarding discontinuation of study treatment in participants with ADPKD.	Study treatment must be discontinued in participants with ADPKD who experience greater than expected worsening of kidney function and/or cyst enlargement with no other cause or clinical scenario identified.
Section 8.2 Withdrawal from the Study	Added language related to alternative methods of follow-up	To align with the ICF and provide information regarding additional methods of follow-up for participants unwilling to perform study clinic visits.
Section 8.3 Lost to Follow Up	Added language regarding alternative methods of follow-up for participants potentially lost to follow up.	To provide further guidance on evaluation of participant status after the participant is lost to follow up.
Section 9.1 Screening and Critical Baseline Assessments	Added language regarding retests with a new blood sample and entering HemoCue Hgb values into the IRT system	To ensure sites they may retest Hgb with a new blood sample for the day 1 visit. Additional clarification provided regarding data entry criteria to capture HemoCue Hgb values

Section# and Name	Description of Change	Brief Rationale
		in the IRT system.
Section 9.3.7 Adverse Events of Special Interest	Added “worsening of hypertension” as an additional adverse event of special interest	AESI list of was updated to align with the changes in the Risk Assessment table and the IB version 10.
Section 9.5.4 Ultrasound	Added guidance on conducting ultrasound for participants with ADPKD based on different clinical scenarios in the study.	Added text related to requirements for ADPKD participants as mandated by the DIL (dated 14 Dec 2018)
Section 12.7, Appendix 7: Country specific requirement	Changes made to provide guidance regarding the conduct of the study at French site only.	Updated French Administrative Considerations and Specifics Requirements based on an updated template
Entire protocol	Minor editorial and document formatting revisions	Minor, therefore have not been summarized.

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1. SYNOPSIS

Protocol Title: A 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, study in rhEPO naïve non-dialysis participants with anemia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo.

Short Title: **A**nemia **S**tudies in **C**KD: **E**rythropoiesis via a **N**ovel PHI **D**aprodustat in **N**on-Dialysis participants evaluating **H**emoglobin and **Q**uality of life (ASCEND-NHQ)

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.

Blood hemoglobin (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 therapy with recombinant human erythropoietin (rhEPO) for anemia. A one to three month trial of oral iron is generally recommended in rhEPO naïve patients with non-dialysis CKD. 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 at which stage benefits outweigh the risks associated with this therapy. 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 28 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 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) • Reasons for discontinuation of study treatment • 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.

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.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of Activities

Protocol activity (visits ±1 week) (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**	
Informed Consent	X								
Assess eligibility	X		X						
IRT system call	X	X	X	X[17]	X	X	X	X[17]	X
Birth Year (demography)	X								
History: medical, hospitalization, height, weight		X	X[2]						
SBP/DBP and HR [3]		X	X (triplicate)	X	X		X(triplicate)	X	X
ECG		X[4]					X		
Ultrasound of kidney and adrenal glands (if able to be visualized)		X[5]					X[15]		
Anemia therapy[6]	X		X		X	X	X	X	X
Rescue medication [7]					X	X	X	X	
Review concomitant medications		X	X	X	X	X	X	X	X
Females only: estradiol and FSH (if required and only for women whose menopausal status is unclear)		X							
FRP only: urine pregnancy test[8]		X	X		X	X[16]	X		X
HemoCue Hgb	X		X (Duplicate)[9]	X	X	X	X	X	
Hematology [10]	X		X		X	Hgb only	X	X	X
Clinical chemistry [10]	X		X		X		X	X	X
Iron Panel [10]	X		X		X[11]		X	X	X
Hepcidin			X		X		X		
Lipids (non-fasting)			X				X		
hsCRP			X				X		
Distribution of participant reminder tool[12]			X						
Adverse Event Assessment	X[13]	X[13]	X	X	X	X	X	X	X

Protocol activity (visits ±1 week) (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 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.

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.

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.

3.2. Background

Anemia is a common complication of CKD. The cause of anemia in this population is multi-factorial, including relative or absolute deficiency of EPO, reduced iron availability related to chronic inflammation or acute infection, and gastrointestinal blood loss. Anemia is further exacerbated by shortened erythrocyte survival that is associated with the uremic milieu and declining kidney function.

Current treatments for anemia associated with CKD include supplemental iron therapy (IV or oral), the use of rhEPO, and blood transfusions. While existing therapies are useful and effective in treating anemia, they each have significant limitations.

Thus, an unmet need exists for a safer alternative for treatment of anemia associated with CKD. 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.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of daprodustat may be found in the daprodustat IB and IB supplements (if applicable).

Specific information regarding warnings, precautions, contraindications, adverse events (AEs), and other pertinent information on the randomized treatment is provided in the IB, IB supplement(s) (if applicable) and other pertinent documents (e.g., Study Reference Manual [SRM], informed consent).

3.3.1. Risk Assessment

The potential risks of clinical significance including AEs of special interest (Section 9.3.7), and the mitigation strategies for this protocol taking into account the results of completed clinical and nonclinical studies with daprodustat, are outlined below.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Daprodustat		
Excessive erythropoiesis leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis (Hgb/Hct > upper limit normal) attributed to daprodustat was associated with vascular congestion, microthrombi, and tissue ischemia in a number of organs. In the phase 2 proof of concept study, a high incidence of discontinuation due to hemoglobin stopping criteria (Hgb > 13.5 g/dL or Hgb increased > 1 g/dL over any 2-week period) was observed. In non-dialysis participants administered 10 mg, 25 mg, 50 mg or 100 mg of daprodustat daily, a total of 21 of 61 participants (34%) met these criteria. In hemodialysis-dependent participants administered either 10 mg or 25 mg of daprodustat daily, a total of 8 of 31 participants (26%) met these criteria.Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose steps, and dose adjustment scheme to optimize Hgb management. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: Few participants experienced a possible thrombosis related adverse event in the setting of excessive erythropoiesis [3/688 (0.5%) participants on daprodustat vs. 0/404 on rhEPO]. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat when dose is managed appropriately according to target Hgb. However, experience with daprodustat is currently insufficient to fully characterize this risk.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 6.1 • Hgb will be closely monitored throughout the dosing period as outlined in the SoA Table Section 2. • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb (including rate of change) is provided in Section 7.2 and Section 8.1. • Instream monitoring of safety data by internal safety review team.
Worsening of hypertension	In a dog cardiovascular study, single oral doses of daprodustat (up to 90 mg/kg) did not produce effects on blood pressure. Marketed rhEPO and its analogues have been associated with risks related to uncontrolled hypertension, including the need for initiation of	• Specific eligibility criteria related to current uncontrolled hypertension are outlined in Section 6.2 • Blood pressure will be closely monitored

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	or increases in antihypertensive therapy when used in patients with anemia of CKD (i.e. 25% Epogen, 27% Mircera, and 40% Aranesp treated patients with renal anemia required initiation or increase in their anti-hypertensive medications; hypertensive encephalopathy and seizures have been reported. The contribution of rhEPO-associated hypertension to the unfavourable effects on cardiovascular outcomes remains uncertain). Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: ○ The majority (>90%) of participants had a baseline history of hypertension. ○ No meaningful difference was seen between treatment groups in AEs (preferred term) of "hypertension" [29/688 (4%) daprodustat vs. 19/404 (4%) rhEPO; 0.91 relative risk (RR) (95% confidence interval: 0.5, 1.67)] or "blood pressure increased" [16 (2%) daprodustat vs. 7 (2%) rhEPO; RR 1.22 (0.48,3.11)]. Results were not substantively different between non-dialysis and haemodialysis participants. ○ Although no clinically meaningful changes in blood pressure were observed, participants in both treatment groups required increases in anti-HTN medications: ○ In the 24-week global phase 2b studies, 25/170 (15%) of ND participants receiving daprodustat vs. 18/80 (14%) control and 22/177 (12%) of HD participants receiving daprodustat vs. 2/39 (5%) control. ○ In the 52-week Japan phase 3 studies, 57/149 (38%) of ND participants receiving daprodustat vs. 68/150 (45%) rhEPO and 51/136 (38%) of HD participants	throughout the dosing period as outlined in the Schedule of Activities (Section 2) • Instream monitoring of safety data by internal safety review team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	receiving daprodustat vs. 66/135 (49%) for rhEPO. The data received to date from completed clinical trials with daprodustat are insufficient to refute this risk.	
Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)	Marketed rhEPO/ Erythropoetin-stimulating agent (ESAs) have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD. Clinical studies with marketed rhEPO/analogs have suggested "higher" target hemoglobin, rate of hemoglobin rise of greater than 1 g/dL in any 2-week period, and/or higher doses may contribute to these risks. In non-clinical studies conducted to date, not observed at tolerated doses when hemoglobin/hematocrit within normal range for species. Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in the overall incidence of this AESI: [39/688 (5.5%) daprodustat vs. 25/404 (6%) rhEPO; 0.92 relative risk (95% confidence interval: 0.55, 1.53)]. Within this composite AESI, the most frequent event types were heart failure (at least 12 events daprodustat vs. at least 13 events rhEPO) and thrombosis (at least 14 events daprodustat vs. at least 8 event rhEPO); and a numerical imbalance was noted in events of myocardial ischemia (at least 7 events daprodustat vs. at least 1 event rhEPO). The small number of events makes it difficult to draw any firm conclusions. The clinical data received to date from completed clinical trials with daprodustat are insufficient to substantiate or refute this risk.	• Specific eligibility criteria related to CV risk are outlined in Section 6.2. • Hgb will be closely monitored throughout the dosing period as outlined in the SoA (Section 2). • Instream monitoring of safety data by internal safety review team.
Esophageal and gastric erosions	In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ ulcers with hemorrhage were observed with	• Suspected GI bleeding or significant symptoms consistent with erosion or ulcers should be investigated diagnostically (i.e. endoscopic

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	daprodustat. In rodents stomach erosions were observed with intravenous and oral administration of daprodustat. Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat). In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported adverse event, however causal association has not been established. Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in reports of this AESI [17 (2.7%) daprodustat vs. 10 (2.3%) rhEPO; 1.16 relative risk (95% confidence interval: 0.52, 2.58)]. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	examination) as clinically warranted. • Instream monitoring of safety data by internal safety review team.
Cancer-related mortality and tumor progression and recurrence	Marketed rhEPOs has been associated with increased risk of cancer related morbidity and mortality when used in patients with cancer. Administration of 60mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. There were no daprodustat-related neoplastic findings in a 2-year rat oral carcinogenicity study. In clinical studies conducted to date, administration of daprodustat has been associated with: <u>Once daily administration:</u>	• Specific eligibility criteria related to personal history of malignancy or participants with complex kidney cyst are outlined in Section 6.2. • Stopping criteria for participants with treatment emergent malignancy are outlined in Section 8.1 • Instream monitoring of safety data by internal safety review team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• In studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations, at doses ranging from 10 to 150 mg. • In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentrations were variable but similar relative to control. <u>Three times weekly administration:</u> • In studies up to 4 weeks duration at doses of 10 to 30 mg: o Dose dependent increases in plasma VEGF and EPO concentrations were observed. o Pre-dose concentrations of EPO and VEGF were near or below baseline indicating no accumulation of EPO or VEGF after three times weekly dosing. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in the occurrence of this AESI: [8/688 (1.1%) daprodustat vs. 4/404 (0.9%) rhEPO; 1.14 relative risk (95% confidence interval: 0.31, 4.28)]. Clinical experience to date is not yet sufficient to substantiate or refute this as a safety concern for daprodustat.	
Pulmonary artery hypertension (PAH)	A role for HIF-regulated pathways in the pathophysiology of PAH has been suggested based on well established effects of acute and chronic hypoxia in man on the pulmonary vasculature (vasoconstriction), and by findings in patients with naturally occurring mutations that result in decreased HIF degradation [Smith, 2006; Formenti, 2011]. There have been no histopathologic findings suggestive of PAH in pre-clinical safety studies with daprodustat (up to 13 weeks duration in	• Instream monitoring of safety data by internal safety review team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	mice and dogs, up to 26 weeks in rats, and up to 39 weeks in monkeys. Acute hypoxic challenge (rats): Daprodustat produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. These hypoxia-induced PRVP changes fall within the range of PRVP differences noted among non-treated rats. Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with daprodustat 5mg or 100mg had no clinically significant effect on transthoracic echocardiographic (ECHO) estimates of systolic pulmonary artery pressure (sPAP) under either normoxic or hypoxic conditions. ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in sPAP in participants not on dialysis for daprodustat. In hemodialysis participants, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (Daprodustat: 8 [7%]; Control 0) in participants reaching the sPAP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 participants with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study treatment; and there was no dose relationship for participants meeting the sPAP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat. • A post-hoc analysis was performed using a definition of PAH often cited in the literature [Navaneethan, 2016]. participants with sPAP >35 mmHg and/or tricuspid regurgitation maximum jet velocity (TRV) >2.5 m/s were considered as having	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	PAH. Regardless of baseline status of PAH, there was no clinically meaningful difference in the proportion of participants with on-treatment PAH between the two treatment groups: ○ Participants with PAH at baseline: 35/113 (31%) vs. 21/54 (39%) (ND) and 37/115 (32%) vs. 7/21 (33%) (HD), daprodustat vs. control, respectively. ○ Participants without PAH at baseline: 25/113 (22%) vs. 12/54 (22%) (ND) and 22/115 (19%) vs. 6/21 (29%) (HD), daprodustat vs. control, respectively. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: Four (0.5%) non-serious AEs in the daprodustat group vs 0 in rhEPO. • Review of participant level information did not suggest adverse treatment effect: 2 participants from phase2b that met protocol specified stopping criteria on scheduled ECHO had non-serious AEs of 'pulmonary arterial pressure increased' and 2 participants from Japan Phase 3 had non-serious AE 'pulmonary hypertension' in setting of concurrent serious AEs of acute pulmonary embolus and mitral regurgitation (respectively) identified during hospitalization for coronary angiography. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Cardiomyopathy	Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized. With lifetime exposure to daprodustat in a 2-year rat oral carcinogenicity study, an exacerbation of rat spontaneous, progressive cardiomyopathy (PCM)(focal myofiber degeneration/necrosis with	• Instream monitoring of safety data by internal safety review team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	inflammatory infiltrates) was observed at doses of 0.8 mg/kg/day and above, although total incidence and severity distribution within any daprodustat-group were within historical control ranges. This is consistent with an equivocal threshold for exacerbation of spontaneous, progressive cardiomyopathy at 0.8 mg/kg/day which is also the threshold dose for observing increased Hct values in inndividual rats.. Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization. ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in LVEF for daprodustat. Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in reports of this AESI [1 (0.1%) daprodustat vs. 1 (0.2%) rhEPO; 0.64 relative risk (95% confidence interval: 0.02, 18.07)]. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Proliferative retinopathy, macular edema, choroidal neovascularization	Increases in local (ocular) VEGF production with retinal neovascularization and macular edema observed in diabetic retinopathy and to choroidal leakage, edema and neovascularization seen in age-related macular degeneration [Campochiaro, 2006]. Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. No ocular abnormalities with daprodustat were seen in non-clinical studies of up to 13 weeks duration in mice and dogs, 26 weeks in rats,	• Instream monitoring of safety data by internal safety review team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and 39 weeks in monkeys. In clinical studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg administered once daily and from 10 to 30mg administered three times weekly In studies up to 24 weeks duration at doses up to 25mg, changes in VEGF plasma concentrations were variable but similar relative to control. Ophthalmologic assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization with daprodustat. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in reports of this AESI [9 (2.9%) daprodustat vs. 6 (2.5%) rhEPO; 1.19 relative risk; (95% confidence interval: 0.42, 3.43)]. Following review of clinical data with daprodustat received to date, this has not been identified as a safety concern for daprodustat.	
Exacerbation of rheumatoid arthritis	In inflamed rheumatic joints, activation of HIF- related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra, 2010; Muz, 2009]. No abnormalities seen in non-clinical studies conducted to date for daprodustat. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between	• Instream monitoring of safety data by internal safety review team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	treatment groups in reports of this AESI [2 (0.3%) daprodustat vs. 1 (0.2%) rhEPO; 1.20 relative risk; (95% confidence interval: 0.07, 20.87) and the incidence of musculoskeletal AEs was generally lower in the daprodustat treatment group]. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Drug-drug interactions	Daprodustat is a substrate of CYP2C8: Co-administration of daprodustat with a strong CYP2C8 inhibitor (gemfibrozil) increased the Cmax and AUC of daprodustat, 4- and 19-fold, respectively, while co-administration of a weak inhibitor (trimethoprim) increased the Cmax and AUC of daprodustat by 1.3- and 1.5-fold, respectively. Although CYP2C8 induction studies were not performed, co-administration of daprodustat with an inducer of CYP2C8 may decrease the exposure of daprodustat. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with a moderate CYP2C8 inhibitor (clopidogrel), leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Daprodustat is an inhibitor of CYP2C8 *in vitro,* with an IC_{50} value of 21 µM. Population PK analysis from Phase 2 studies suggested that while BCRP inhibitors were a covariate for daprodustat CL/F (8.6% lower clearance) the predicted change in exposure was not considered to be of clinical relevance. Co-administration of daprodustat with BCRP inhibitors [e.g., cyclosporine, HIV antivirals (atazanavir, lopinavir, ritonavir, tipranavir), lapatanib and curcumin]] is not expected to produce clinically relevant increases in daprodustat exposure Daprodustat is an inhibitor of OATP1B1/1B3 *in vitro,* with IC_{50} values	• Co-administration of daprodustat with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 7.8.2. • Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 7.8 and Section 7.2. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 7.8 • Hgb will be closely monitored throughout the dosing period as outlined in the SoA in Section 2. • Specific guidance for dose adjustment, dose interruption, or discontinuation of daprodustat based on achieved Hgb is provided in Section 7.2 and Section 8.1. • Instream monitoring of safety data by internal

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of 6 µM and 11 µM, respectively. A clinical drug interaction study between 25mg and 100mg daprodustat with either a CYP2C8 substrate or an OATP1B1/1B3 substrate showed no PK interaction at these doses of daprodustat.	safety review team.
Cyst progression in patients with autosomal dominant polycystic kidney disease (ADPKD)	Published data provide in vivo evidence for a potential role of HIF-1a in the growth of polycystic kidneys; Hif-1a deletion was sufficient to significantly mitigate a progressive polycystic phenotype in an ADPKD mouse model, while conversely pharmacologic HIF-1a stabilization was sufficient to convert a mild polycystic disease into a severely aggravated phenotype with marked loss of renal function. However, the dose of FG-2216 (a PHI) used resulted in a significant erythropoietic response as reflected by ≥10% relative increases in hematocrit over the course of the study (Kraus, 2018; Hofherr, 2018). A review of the non-clinical data from toxicity studies conducted with daprodustat does not indicate an exacerbation in incidence or severity of kidney cysts in daprodustat-treated animals in comparison to controls. However, the wild type animals used in these toxicity studies have a very low background incidence of renal cysts and are not comparable to the mice used in the Kraus article (Kraus, 2018) which are an inducible kidney epithelium-specific Pkd1-deletion model. There is limited experience with daprodustat in participants with ADPKD in completed clinical trials. In the Japan phase 3 study in non-dialysis participants, there were 5 participants with ADPKD (all CKD stage 5) in each treatment group. Mean baseline eGFR was 10 mL/min/1.73m2 in the daprodustat participants vs. 16 mL/min/1.73m2 in the rhEPO participants. The mean (SD) percent change from baseline at Week 52 in eGFR was: -18% (8) vs. -21% (14) in daprodustat vs. rhEPO, respectively. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Kidney function will be monitored throughout the study as outlined in SoA Section 2. • Ultrasounds will be performed as outlined in Section 9.5.4. • Monitoring of emerging safety data by an internal safety review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
Randomization to Placebo arm	Potential to receive no therapy due to the placebo-controlled design of the study can cause participants to be ineffectively treated for anemia associated with CKD.	• A rescue algorithm is provided to minimize participants having an inadequate response to the treatment for their anemia as outlined in Section 7.7.2 • Instream monitoring of safety data by internal safety review team

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3.3.2. Benefit Assessment

Generally, participants with non-dialysis dependent CKD undergo clinical assessment of anemia only every few months. This study may be beneficial to study participants by allowing participants access to anemia management and CKD care. Study participants will benefit from routine medical visits to the site and easy access to clinical facilities geared towards treatment of anemia in CKD. Study participants will also benefit from potentially obtaining a treatment for anemia in the form of an oral tablet which increases the 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 rhEPOs. 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.

3.3.3. 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 in non-dialysis CKD participants, daprodustat treats Hgb to target range, with a safety profile consistent with the patient population. Furthermore, this protocol employs precautions to mitigate known and potential risks to randomized participants (Section 3.3.1). 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.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
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 inclusive)
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 from baseline to EP.
• To compare daprodustat to placebo for health related quality-of-life	• Mean Change in SF-36 Vitality domain between baseline and Week 28
Safety	
• To compare the safety and tolerability of daprodustat to placebo	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest and adjudicated MACE (composite of all-cause mortality, non-fatal MI and non-fatal stroke) • Reasons for discontinuation of study treatment • Absolute values and changes from

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. • % time Hgb in range • 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. • 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 • 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 • Change from baseline in overall percent work impairment (equivalent) on the WPAI-ANS-CPV • 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. • 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 • N (%) with at least one BP exacerbation event during the study

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

Objectives	Endpoints
	• Summary of frequency and dose of IV iron
• To compare daprodustat to placebo on renal function	• Estimated Glomerular Filtration Rate (eGFR) observed and change from baseline • Serum creatinine observed and change from baseline • N (%) transitioning to dialysis
• Evaluate the dose adjustment schemes	• Assigned dose by visit • Most recent dose prior to Week 24, Week 28 and End of Treatment • Maximum achieved dose • Number (%) of participants with 0, 1, 2 or >2 dose adjustment • Mean number of dose adjustments • Time dose held for Hgb≥13 g/dL
• To compare daprodustat to placebo on BP medication changes	• N (%) of subjects who had no change, an increase or a decrease in the number of BP medications from baseline to week 28 or final visit for non-completers
• To compare daprodustat to placebo on the severity and change in symptoms	• N(%) of participants within each PGI-C symptom change.
• To compare daprodustat to placebo for improving physical activity (actigraphy)	• Change in percent and mean number of hours of daily activity from baseline. • Change in percent sleep efficiency from baseline.

5. STUDY DESIGN

5.1. 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 chronic kidney disease (CKD) who are not on dialysis. This study will enroll anemic participants who have a HemoCue Hgb 8.5 to 10.0 g/dL, inclusive. These participants will have limited history of IV iron and be rhEPO naïve prior to screening and randomization.

This study includes a 4-week screening period, a 28-week treatment period, and a 4-week follow-up period (Figure 1).

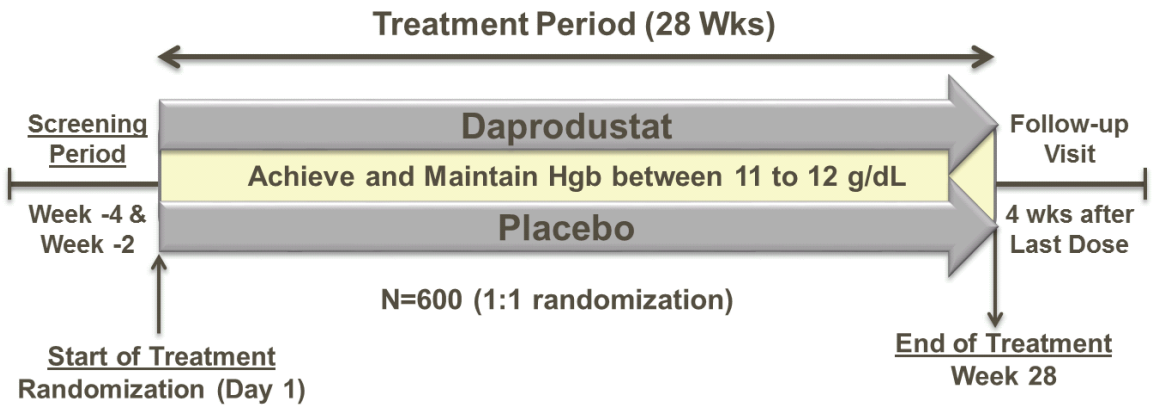
The total duration of study participation for each participant will be approximately 36 weeks.

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).

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. 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.

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.

Cardiovascular Disease-Related Criteria (see also other cardiovascular exclusion criteria #22)

15. **MI or acute coronary syndrome:** within the 8 weeks prior to screening through to randomization. (Day 1)
16. **Stroke or transient ischemic attack:** within the 8 weeks prior to screening through to randomization. (Day 1)
17. **Heart failure:** Chronic Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system
18. **QTcB (Day 1):** QTcB >500 msec or QTcB >530 msec in participants with bundle branch block. There is no QTc exclusion for participants with a predominantly paced rhythm.

Other Disease Related Criteria

19. **Liver Disease-Related Criteria**:
    - Alanine transaminase (ALT) >2x upper limit of normal (ULN) at screening (Week -4).
    - Bilirubin >1.5xULN at screening (Week -4). NOTE: Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.
    - Current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including asymptomatic gallstones, chronic hepatitis B or C, or Gilbert's syndrome) is acceptable if participant otherwise meets entry criteria.
20. **Malignancy**: History of malignancy within the 2 years prior to screening through to randomization (Day 1), or currently receiving treatment for cancer, or complex kidney cyst (e.g. Bosniak Category II F, III or IV) > 3cm. Note: The only exception is localized squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥8 weeks prior to screening.

Other Exclusion

21. **Other Conditions:** Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study.

Other cardiovascular exclusion criteria

22. **Current uncontrolled hypertension:** Current uncontrolled hypertension as determined by the investigator

6.3. Lifestyle Restrictions

There are no lifestyle restrictions required for this study. Any restrictions of concomitant medications and non-drug therapies are described in Section 7.6.1.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Participants that fail screening are eligible to be rescreened up to two additional times as soon as the investigator assesses they may meet study entry criteria. If participants are rescreened, they must sign a new informed consent form. Rescreened participants will also be assigned a new participant number, while maintaining the link to the participant number used for the initial screening.

7. TREATMENTS

Study treatment is defined as daprodustat or matching placebo, intended to be administered to a study participant according to the study protocol. Once daily oral daprodustat starting doses or matching placebo are assigned based on the HemoCue Hgb concentration at randomization (Day 1) (Table 4).

Table 4 Daprodustat Starting Dose

Baseline (Day 1) Hgb (g/dL)	Daprodustat Starting Dose (mg, once daily)
8.5 to <9	4
9 to 10	2

7.1. Treatments Administered

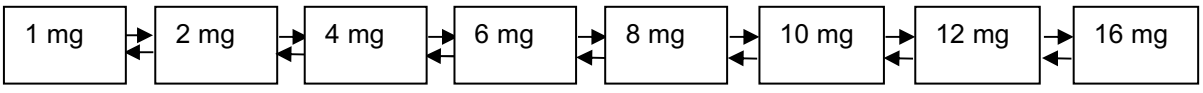
Participants randomized on Day 1 to either daprodustat or placebo will receive 3 bottles, and will take one tablet from each bottle at each dose. The study treatments to be administered in this study are described in Table 5.

Table 5 Description of Daprodustat and Matching Placebo Tablets

Study Treatment Name:	Daprodustat (GSK1278863)	Placebo
Dosage formulation:	film-coated tablet	film-coated tablet
Unit dose strength(s)/Dosage level(s):	Unit dose strength: 7mm tablet: 1mg, 2mg, 4mg 9mm tablet: 6mg, 8mg, 10mg Dosage levels: 1, 2, 4, 6, 8, 10, 12, 16 mg	Unit dose strength: Matching 7mm and 9mm tablets Dosage levels: Matching 1, 2, 4, 6, 8, 10, 12, 16 mg
Route of Administration	oral	oral
Dosing instructions:	3 Tablets are to be taken daily with water. Tablets can be taken without regard to food.	3 Tablets are to be taken daily with water. Tablets can be taken without regard to food.
Packaging and Labeling	Study Treatment will be provided in white, opaque high density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will be labeled as required per country requirement.	Study Treatment will be provided in white, opaque high density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will be labeled as required per country requirement.
Manufacturer	GlaxoSmithKline	GlaxoSmithKline

7.2. Dose Modification

The available dose steps of daprodustat and placebo are outlined below. Dose adjustments (increase or decrease by one dose step, maintain, or withheld if ≥13 g/dL) will be made programmatically for both the daprodustat arm and the matching placebo arm by the IRT system to increase and maintain hemoglobin within the target range based on the HemoCue Hgb value measured at least every 4 weeks. Those receiving the highest dose of daprodustat ,or dose matched placebo, who require a dose increase will maintain the same dose, while those receiving the lowest dose of daprodustat, or matching placebo, that require a dose decrease will receive placebo until such time as when study treatment can be restarted according to Table 6.



Dose adjustment decisions will be based on individual participant HemoCue Hgb response. The decision to proceed to the next dose (either an increase or a decrease) or maintain current dose will be conducted as follows:

Table 6 Study treatment dosing algorithm

HemoCue Hgb (g/dL) at current study visit[1]	HemoCue Hgb change since last study visit[1]	Study Treatment Dose Adjustment[6]
<8.5[2]	Any change	Repeat Hgb and average values, if confirmed [8],Increase dose to next higher step AND evaluate for rescue criteria [7]
8.5 to <10.5	Hgb increase <0.5 g/dL or any Hgb decrease or No change	Increase dose to next higher step
8.5 to <10.5	Increase by ≥0.5 and ≤2 g/dL	Maintain dose
≥10.5 to ≤12.5	Any change ≤2 g/dL[4]	Maintain dose
≥10.5 to <11.0 at 2 consecutive visits	Decreasing or No change	Increase to the next higher dose step
>12.0 to ≤12.5 at 2 consecutive visits	Increasing or No change	Decrease to the next lower dose step
>12.5 to <13	Decreasing	Maintain dose
> 12.5 to <13	Increasing or No change	Decrease to the next lower dose step
≥13.0 [3]	Any change [5]	Repeat Hgb and average values [8]; if confirmed, temporarily hold the dose and re-check Hgb at next study visit [1]; restart at one dose step lower when Hgb <12.0 g/dL and provided it has been at least 2 weeks from the prior study visit.
Any	>2 g/dL increase over 4 weeks (>1 g/dL increase over 2 weeks [2,5])	Repeat Hgb and average values [8]; if confirmed, decrease to the next lower dose step
Any	>2 g/dL decrease over 4 weeks (>1 g/dL decrease over 2 weeks [2,5])	Repeat Hgb and average values [8], if confirmed, increase to the next higher dose step [7]

1. "Study visit" refers to scheduled visits as outlined in SoA.
2. This rule applies to any scheduled or unscheduled visit, provided it has been at least 2 weeks from the prior study visit.
3. This rule applies to any scheduled or unscheduled visit
4. Any change is defined as an increase, decrease or no change of ≤ 2g/dL, from prior study visit, when Hgb is ≥10.5 or <12.5 g/dL.
5. This rule applies to Week 2 visits as well.
6. Those receiving the highest dose of study treatment who require a dose increase will maintain the same dose, while those receiving the lowest dose of study treatment that require a dose decrease will have doses withheld.
7. If HemoCue Hgb <8.5 g/dL, then also consider participant for rescue criteria per protocol Section 7.7.2.
8. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample) and take average.

7.3. Method of Treatment Assignment

- Subjects will be stratified by region (Section 12.8 Appendix 8). Region at study entry is considered a stratification factor that is potentially prognostic of study endpoints. Following stratification all participants will be centrally randomized in a 1:1 fashion to receive either oral daprodustat or oral placebo.

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

- Study treatment will be dispensed at the study visits summarized in the SoA (Section 2).

- Returned study treatment should not be re-dispensed to the participants.

7.4. Blinding

This will be a double-blind study. The participant, investigator, site staff, and GSK study team are all blinded to the assigned study treatment.

The IRT will be programmed with blind-breaking instructions. The investigator may unblind a participant's study treatment assignment in case of an emergency or in the event of a serious medical condition when knowledge of the study treatment assignment is essential for the appropriate clinical management or welfare of the participant. In case of lack of efficacy, a participant should receive rescue therapy as per protocol Section 7.7.2, but the study treatment assignment should not be unblinded except in case of an emergency or serious medical condition as previously described. GSK must be notified before the blind is broken, unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, GSK must be notified within 24 hours after the blind is broken. The investigator should not reveal the participant's unblinded treatment assignment to GSK, unless that information is important for the safety of participants currently in the study. The date and reason that the blind was broken must be recorded in the source documentation and eCRF.

A participant may continue in the study if their treatment assignment blind is broken by the investigator. However the study treatment will be discontinued and the participant will be followed until the end of study on standard of care.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4.1. Additional Considerations to Maintain the Blind

This study is double-blinded, such that the sponsor, investigator and participant will all be blinded to the study treatment assignment. Participants will not be provided with the

results of the HemoCue Hgb assessment during their pariticipation in the study. Subjects should be provided with the understanding to also not obtain Hgb information from local labs prior to study visits. Additionally, Investigators, site staff and participants will also be blinded to some of the central laboratory results during the study.

7.5. Preparation/Handling/Storage/Accountability

No preparation of study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
    - Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
    - A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

Given participants self-administer study treatment(s) at home, compliance with blinded study treatment will be assessed through querying the participant during the site visits and documented in the source documents and eCRF. A record of the number of bottles of study treatment and the number of tablets from each bottle dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or treatmentinteruptions will also be recorded in the eCRF.

7.6.1. Study Treatment Extended Interruption

Sites should contact GSK if a subject will be away temporarily from the research site for >5 weeks during their participation in the study, in order to discuss options for continuing randomized treatment and completing study visits. Every effort must be made to continue randomized treatment; however if a subject will be off the study treatment, sites should

consult with GSK in order to determine if the subjects should be withdrawn from treatment and brought in for a treatment discontinuation visit.

7.7. Standard of Care

During the study (from screening), investigators are expected to monitor the participant's overall clinical status to ensure standards of care are met to enable consistency of practice with Kidney Disease Improving Global Outcomes [KDIGO, 2012]guidelines or local equivalent (e.g, phosphate and albumin).

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

7.7.1. Iron Management Criteria

Investigators should make every effort to maintain participants' serum TSAT ≥15% and ferritin ≥ 50 ng/mL from randomization (Day 1) to end of study. The investigator will follow the iron management criteria from randomization (Day 1) through end of study for all participants receiving study treatment.

Iron therapy will be administered, starting with oral iron, if ferritin is <50 ng/mL and/or TSAT is <15%, to reestablish participant's screening (Week -4) iron parameters. Participants that are on oral iron at randomization may change their dose of oral iron in order to maintain their TSAT and ferritin levels as stated above. IV iron can be administered to participants who are intolerant to oral iron, otherwise IV iron should only be administered to participants being evaluated for rescue criteria (Section 7.7.2), please see the SRM for additional IV Iron administration requirements. Iron parameters will be assessed at scheduled study visits outlined in the SoA. Iron therapy may be discontinued once screening ferritin and TSAT levels are reached

- Only results for ferritin and TSAT measured by Q2 (central lab) should be used to inform if iron therapy is required.

7.7.2. Rescue Criteria

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 consistency in the application of rescue therapy across the study. Details are provided in Table 7.

This rescue algorithm **does not** apply to participants with low Hgb as a result of an acute or subacute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or vascular access). In these cases, treatment should be directed to the specific cause and randomized treatment will be continued at the current dose (unless Hgb is ≥13 g/dL which requires a dose hold).

Table 7 Rescue Algorithm for Anemia Management

Evaluate Participant for Rescue starting from Week 4 if: • HemoCue Hgb is <7.5g/dL, or • HemoCue Hgb is <8.5g/dL and participant is symptomatic[1], or • HemoCue Hgb is <8.5 g/dL on three consecutive visits	
Step 1: **Initial Intervention**	Initial intervention depends on the participant's iron status: • If participant has TSAT < 15% and/or Ferritin < 50 ng/mL from a prior study visit, then o continue with study treatment, and o intervene with iron therapy: Single dose of IV iron up to 1000 mg (in addition to the iron management criteria) At the next study visit in 4 ±1 weeks, recheck HemoCue Hgb. If HemoCue Hgb value continues to meet the evaluation criteria for rescue, then Proceed to Step 2. • If participant has TSAT ≥15% and Ferritin ≥ 50ng/mL, proceed to step 2.
Step 2: **Rescue**	**Randomized treatment should be permanently discontinued (but participant should remain in study to monitor Hgb) and the participant should be rescued according to local clinical practice:** • If HemoCue Hgb remains <8.5 g/dL despite Initial Intervention (Step 1) based on the average of two HemoCue Hgb values [2] • Rescue can be considered IV iron, rhEPOs and/or Transfusions.

1. Symptoms should be related to anemia of CKD. Further information regarding collecting this data will be stated in the SRM.
2. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample); take average of 2 values.

The study site will supply any rescue medication that will be obtained locally.

Although the use of rescue medications is allowable, if the participant meets rescue criteria, the use of rescue medications should be delayed, if possible, for at least 4 weeks following the initial administration of study treatment at randomization. The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF

7.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- route of administration

For any therapy related to anemia and hypertension, including iron, the following additional information should also be captured:

- Dosage information including:
    - Dose and frequency
    - Formulation
    - Reason for addition or termination
    - Change in dose and reason for change in dose

The use of rescue medications is discussed in Section 7.7.2.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 7.8.2, all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Co-administration of daprodustat with moderate CYP2C8 inhibitors (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should subsequently be monitored at each visit for the following 12 weeks.

7.8.2. Prohibited Medications and Non-Drug Therapies

Use of any of the following prescription drugs from screening (Week -4) until 7 days after the last dose of randomized treatment is prohibited and will constitute a protocol violation.

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

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

7.9. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study. The investigator is responsible for ensuring that consideration has been given to post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Every effort should be made to keep participants in the study including those who permanently stop randomized treatment. A participant may permanently discontinue randomized treatment at any time at his/her own request, or at the discretion of the investigator for safety, or compliance reasons. However, treatment should not be discontinued due to an inadequate hemoglobin response to the study treatment, by the investigator, since in such instances the study treatment dosing algorithm (Table 6) or the rescue criteria (Section 7.7.2) should be followed.
A participant must permanently discontinue study treatment for the following reasons, and should continue attending study visits as outlined in the SoA for participants that discontinued study treatment (Section 12.2 Appendix 2):

- Participant receives a kidney transplant
- Participant initiates dialysis
- Participant meets the criteria to receive rescue therapy (Section 7.7.2).
- Participant becomes pregnant or intends to become pregnant during the study.
- Liver chemistry abnormalities exceed the threshold criteria (Section 8.1.1).
- Diagnosis of cancer (new or recurrent), with the exception of localized squamous cell or basal cell carcinoma of the skin.
- Need for more than 14 days of prohibited medication (Section 7.8.2).
- **ADPKD participants only**: following further imaging , condition of the cystic disease in the kidney(s) has worsened more than expected given the clinical scenario and no other cause for the kidney function decline and/or cyst enlargement can be identified (Section 9.5.4).

In all cases, the reason for study treatment discontinuation and the date of the last dose will be recorded in the participant's eCRF.

8.1.1. Liver Chemistry Stopping Criteria

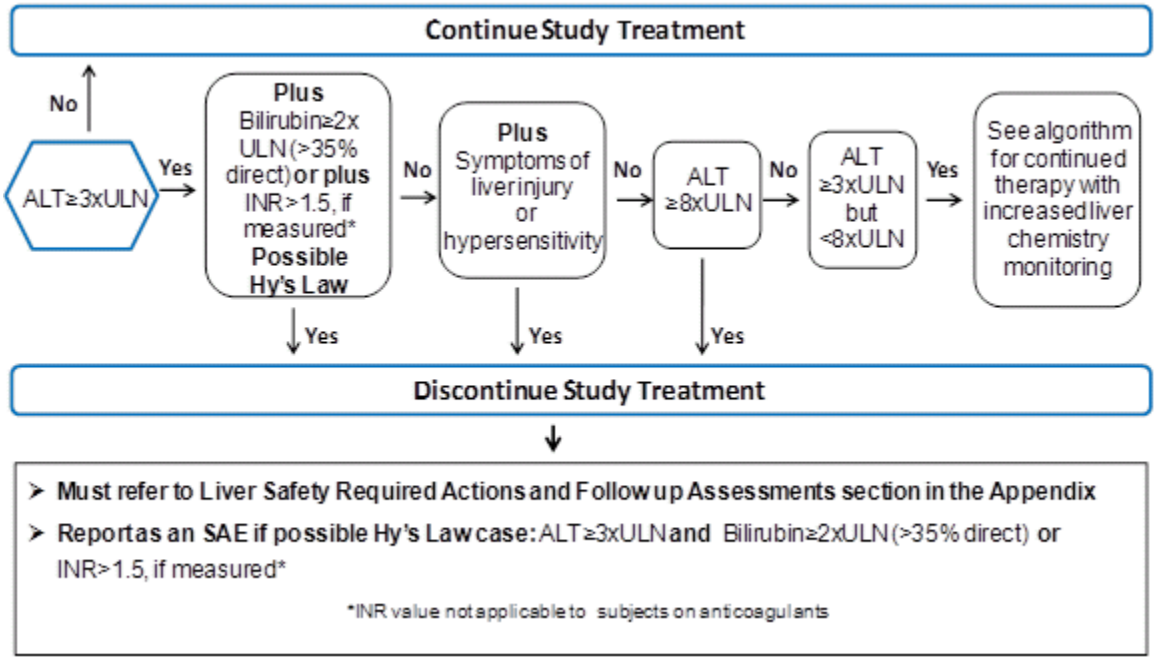
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study treatment for abnormal liver tests is required when:

- A participant meets one of the conditions outlined in the algorithm

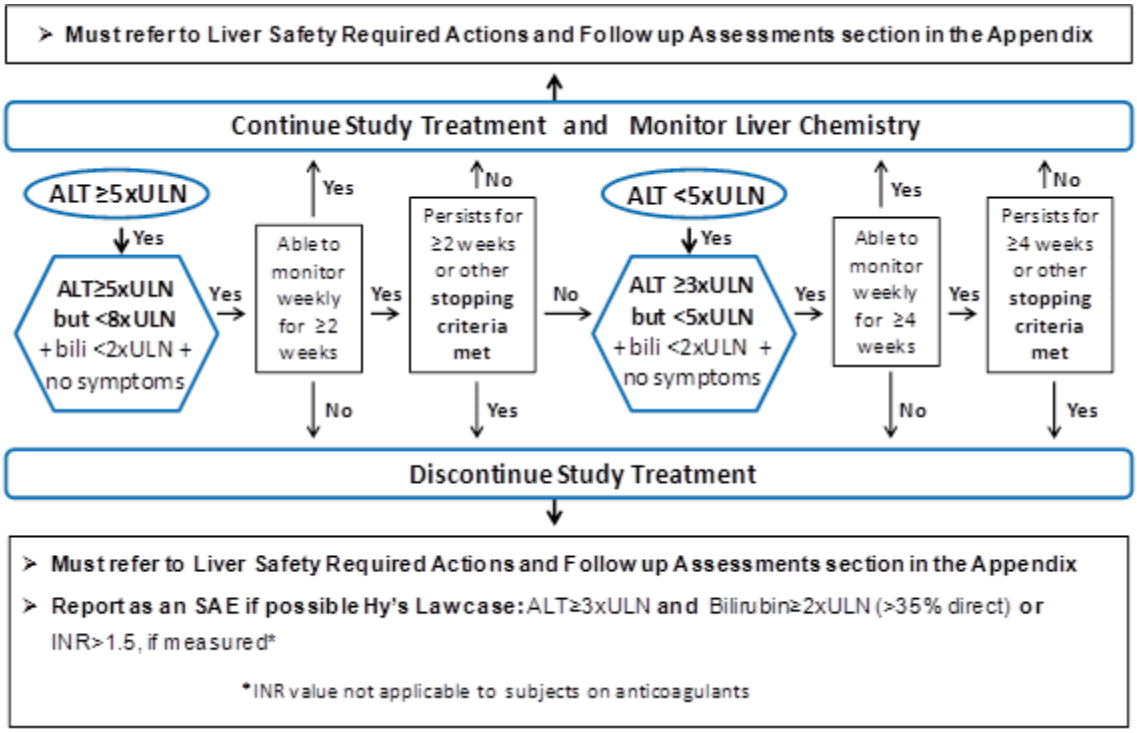
- In the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.6 (Appendix 6).

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.6 (Appendix 6).

8.2. Withdrawal from the Study

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

Withdrawal of consent from the study is expected to be a rare occurrence. If a participant expresses a wish to withdraw consent from the study, the investigator will review the following contact options with the participant.

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

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

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

In rare cases if a participant has been discontinued from the study without discussing all possible alternatives for follow-up the investigator may contact the participants to discuss all of the alternative methods of follow-up described above.

Participants may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Refer to the SoA (Section 2) for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- Investigators should make every effort to contact participants who are deemed lost to follow-up and who have not withdrawn consent to follow-up contact . The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, medical records review, third-part follow-up and/ora certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns.

- 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.

- 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

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

- 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.

- 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.

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)

- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).
- Pharmacy utilization focused on anemia associated with CKD only, including rhEPO rescue, IV iron (use or rescue), blood pressure medications, and cholesterol lowering agents

9.12. Patient Feedback Survey

An optional smartphone App or website will be available during the study. Participants may be asked for feedback on their experience during the study, in the form of anonymized App or web based surveys. The purpose of this survey is for GSK to learn about participant experience in the study and possibly make future GSK trials more participant friendly and better focused on participant's needs.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Primary Hypothesis

The primary Hgb efficacy objective will assess the estimand defined as the comparative treatment effect in mean Hgb change between baseline and evaluation peorid (EP, i.e., week 24 to week 28 inclusive) in all randomized participants; defined as those who remain in follow-up throughout the period of stabilization and have at least one Hgb assessment during the EP regardless of adherence to study treatment. The analysis will test whether daprodustat is superior to placebo according to the following statistical hypotheses:

- **Null:** The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-placebo), is less than or equal to 0 g/dL.
- **Alternative:** The difference in mean change in Hgb between baseline and EP between treatment arms (daprodustat-placebo), is greater than to 0 g/dL.

Statistical significance will be assessed at the one-sided 2.5% level. An analysis of covariance (ANCOVA) model including the randomization stratification factor, baseline hemoglobin and treatment will be used to obtain a point estimate and the two-sided 95% CI for the treatment difference (daprodustat-placebo) and generate the one-sided p-value for the superiority test. Superiority will be established if the one-sided p-value is less than 0.025.

10.2. Sample Size Determination

10.2.1. Sample Size Assumptions

The sample size of this study has been primarily determined in order to achieve sufficient power for the principal secondary endpoint SF-36 vitality sub-score, since the anticipated effect size of this endpoint is less than that for the primary endpoint.

Approximately 600 participants are planned to be randomized (300 per arm) to receive daprodustat or placebo, who will be treated to achieve and maintain Hgb between 11 and 12 g/dL. Under the assumption that up to 10% of participants will withdraw from the study before Week 24 (start of EP), 600 randomized participants will result in at least 540 evaluable participants.

For the primary endpoint, the expected difference in mean Hgb change from baseline and the EP, between arms, is 1.0 g/dL and the anticipated between participant standard deviation (SD) is 1.5 g/dL, based on historical rhEPO trials and daprodustat clinical trial experience to date. The planned study size provides more than 99% power for superiority. In addition, it is anticipated that the smallest difference in mean Hgb change between arms that would meet the statistical criterion for superiority would be 0.25 g/dL.

For the first principal secondary endpoint of % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP, 540 evaluable participants provides >90% power to detect a 20% difference between daprodustat and placebo, assuming 30% of placebo arm participants will have a Hgb increase of ≥1.0 g/dL. In that case the smallest difference between daprodustat and placebo that would meet the statistical criterion for superiority would be 8%.

For the second principal secondary endpoint of mean change in SF-36 vitality sub-score between baseline and week 28, 540 evaluable participants provides for 79% power to detect a difference between arms under the assumption of a between treatment effect of 5 points in favor of daprodustat and a within-group standard deviation of 21 points. Prior research has determined that anemia is associated with a difference of 5.4 points from baseline for SF-36 vitality scores (Bjorner, 2007). It is expected that the smallest difference between arms that would meet the statistical criterion for superiority in this principal secondary endpoint is 3.5 points.

10.2.2. Sample Size Sensitivity

Since the sample size is primarily determined by the principal secondary endpoint SF-36 vitality sub-score, the following table illustrates the impact on power for that endpoint based on alternative assumptions for the between participant SD and the number of evaluable participants.

Between Participant SF-36 Vitality Sub-score SD	Number of Evaluable Participants			
	300	400	500	540
19	62%	75%	84%	86%
20	58%	70%	80%	83%
21	54%	66%	76%	79%
22	50%	62%	72%	75%
23	47%	58%	68%	71%

10.2.3. Sample Size Re-Estimation or Adjustment

The assumptions used to determine the planned sample size may be reassessed, if during the course of the study, information becomes available external to the trial that is informative with respect to clinically meaningful difference or variability estimates for the QoL principal secondary endpoint. If considered appropriate the planned sample size may be re-calculated and implemented via a protocol amendment as necessary. It is anticipated that the maximum sample size for the study will not exceed 800 patients.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

The primary population for Hgb efficacy analyses will be the All Randomized Intent-to-Treat (ITT) Population. Participants will be analyzed according to the treatment to which they were randomized.

For analyses of quality of life endpoints, the All Randomized (ITT) Population will also be used. Participants will be analyzed according to the treatment to which they were randomized.

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

Additional populations may be defined in the Reporting and Analysis Plan (RAP).

10.4. Key Elements of Analysis Plan

10.4.1. Primary Analyses

Mean change in Hgb between baseline and EP (week 24 to week 28 inclusive): The primary efficacy estimand is to compare the effect of treatment for the evaluation of mean change from baseline in Hgb during the 4 week EP in all ITT participants with at least one Hgb during the EP. The ITT analysis of this endpoint will include all on and off treatment Hgb values of the ITT population, including values taken after rescue and IP discontinuation. The analysis will use an ANCOVA model. For each participant, the baseline Hgb will be the value obtained on Day 1, prior to taking randomized treatment, and Hgb during EP will be determined by calculating the mean of all available Hgb values between week 24 to week 28 inclusive regardless of the use of rescue medication

or adherence to randomized treatment. The ANCOVA model will include the randomization stratification factor, baseline Hgb and treatment. It will provide a point estimate and two-sided 95% CI for the treatment effect, together with the one-sided p-value. There will be no imputation for missing data.

Sensitivity Analysis: A sensitivity analysis that considers an "on-drug" efficacy estimand will be conducted. In this analysis, only Hgb values measured while the participant was taking randomized study medication will be included. Missing Hgb values will be imputed based on the reasons of missing. Full details will be provided in the RAP.

10.4.2. Secondary Analyses

10.4.2.1. Principal Secondary Efficacy Analyses

Conditional on the primary endpoint achieving superiority at the one-sided 2.5% level, statistical testing will progress to the principal secondary endpoints which will evaluate superiority using a one-sided 2.5% significance level.

For the first principal secondary endpoint of % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP, a Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment, baseline Hgb, and the prognostic randomization stratification factor, will be used to make comparisons between the treatment groups. An "effectiveness" estimand will be used in the analysis to include all on and off treatment Hgb values of the ITT populations, including values taken after rescue and IP discontinuation.

For the second principal secondary endpoint of mean change in SF-36 vitality sub-score between baseline and Week 28, an ANCOVA model will be used to compare the difference in this endpoint between arms, including factors for baseline score, treatment and the randomization stratification factor. An "efficacy" estimand will be used in the analysis in which we include only on-treatment values and exclude measures taken after IP disc/rescue medication. For this endpoint, an alternative approach may be conducted that includes the development of a prior distribution for the effects of placebo based on external data to be combined with the data from this trial in a Bayesian framework in order to make inference on the effects of daprodustat. If such an approach is undertaken it will be fully described in the RAP prior to the breaking of the study blind.

In addition, descriptive statistics for each individual item within the SF-36 vitality sub-score will be generated. Of particular interest are the items assessing if patients have a lot of energy, feel tired, and feel worn out. These concepts have been found to be important and relevant concepts in this population[Martin, 2011] .

Additional secondary/exploratory endpoints are listed in Section 4.

10.4.2.2. Safety Analyses

Safety data, including all AEs (i.e., non-serious, serious and AEs of special interest), laboratory data, vital signs, concomitant medications and meeting protocol defined

stopping criteria (e.g., liver chemistry) will be descriptively summarized by treatment arm. Reasons for stopping randomized treatment and for early study withdrawal will also be summarized by treatment group and time to stopping treatment or study will be presented graphically and assessed. Full details of all safety data reporting will be described in the RAP.

10.4.3. Multiplicity Strategy

The primary endpoint will be tested first for superiority using a one-sided 2.5% significance level. Conditional on achieving statistical significance, the first principal secondary endpoint will be tested for superiority using a one-sided 2.5% significance level. Finally, conditional on achieving statistical significance of both the primary endpoint, and the first principal secondary endpoint, the second principal secondary endpoint will be tested for superiority using a one-sided 2.5% significance level. This three-step hierarchical strategy will preserve the study-wise Type I error rate at a one-sided 2.5% level.

The additional secondary/exploratory endpoints as listed in Section 4 are of exploratory nature,and if tested, will not be adjusted for multiplicity. Summary statistics and nominal one-sided 2.5% significance levels will be used to describe the results of these treatment comparisons.

10.4.4. Covariates and Subgroups of Interest

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

Category	Subgroups
Age	<65 years, ≥65 years - <75, ≥75 years
Gender	Female, Male
Race group	American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race
Ethnicity	Hispanic, non-Hispanic
Region	per Section 12.8 (Appendix 8).
BMI	<30, ≥30
Weight	< 75kg, ≥75kg
Baseline Hgb	8.5 - <9 g/dL, 9 – 10 g/dL
Serum Iron levels	TSATs ≥20% and Ferritins ≥100 ng/mL, others
IV Iron Therapy	Yes, or No
hsCRP	Tertile analysis
Diabetic	Yes or No

10.4.5. Interim Analyses

An interim analysis to assess futility may be performed if the rate of the enrolment is considerably slower than expected. This analysis will only consist of the principal secondary endpoint of QoL SF-36 vitality sub-score, due to its considerably larger sample-size requirement for a powered analysis compared to the primary endpoint. The primary endpoint of mean change in Hgb between baseline and EP, and the principal secondary endpoint of % of participants having a Hgb increase of ≥1.0 g/dL from baseline at EPwill not be included in this interim analysis. The potential outcomes of this analysis include the continuation of the study with no change and the stopping of the enrolment. It is planned that the interim analysis will only be performed once approximately 200 participants have completed 28 weeks of study in order to preserve power for the primary endpoint should the study be discontinued.

If the observed difference for the QoL vitality endpoint between daprodustat and placebo is less than 2 points at the time of the interim analysis, study enrolment will be stopped. This decision guideline was determined to have favorable operating characteristics, such as an unconditional power of <30%, and an acceptably low probability of a false stop (<10%). Since the study will not be stopped for positive results, type I error will not be inflated. Inference on the aforementioned Hgb parameters will still be made as per Section 10.4, even if the study is stopped for futility based on QoL SF-36 vitality sub-score.

The interim analysis will be performed and the results reviewed by a small team who are not involved in the conduct of this study. Access to the interim results will be restricted to this small team until the study has been completed and the database is finalized and unblinded. Details regarding the justification for the interim analysis, including the blinding plan and associated measures to protect the integrity of the trial will be included in the RAP.

10.4.6. Analysis of Patient-Reported Outcomes Measures and Actigraphy

Analyses to compare the patient reported effects of daprodustat and placebo on symptoms, severity, HR-QoL, and health status, as discussed in Section 9.6, will be described in the RAP. Analyses regarding the effects of daprodustat and placebo on physical activity and sleep measured by the actigraphy assessment as discussed in Section 9.7 will also be described in the RAP.

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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

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

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

12.2. Appendix 2: Study Governance Considerations

12.2.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure [IB GlaxoSmithKline Document number RM2008/00267/07], and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- 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
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.2.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.2.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

12.2.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.2.5. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK 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.

GSK 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

12.2.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final

Clinical Study Report(CSR)/equivalent summary unless local unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor

12.2.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

12.2.8. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. If GSK determine such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.2.9. 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.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

12.2.10. Dissemination of Clinical Study Data

- Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- All study investigators will be provided with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

12.2.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will

generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements

12.2.12. Clinical Events Committee

An external independent CEC blinded to treatment allocation will adjudicate all clinical events reported during this study that are referred for adjudication, including major adverse cardiovascular events (MACE; composite of all-cause mortality [CV and non-CV mortality], non-fatal MI and non-fatal stroke) and additional components for a broader definition of MACE including thromboembolic events (vascular access thrombosis, symptomatic deep vein thrombosis, symptomatic pulmonary embolism), and hospitalization for heart failure (Section 9.3.5).

12.2.13. Safety Review Team (SRT)

An internal Safety Review Team, which includes GSK personal involved in the conduct of the study, will review periodically blinded safety data from this trial.

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. • 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). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • 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. • "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. • 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. • 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. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

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. • 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. • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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. • 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. • 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. • Contacts for SAE reporting can be found at the beginning of this protocol on the Medical Monitor Contact Information page.

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 • 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 • 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. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
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
Is a congenital anomaly/birth defect
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 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. • 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
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 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. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE eCRF page. • 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. • 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. • Participant-completed Patient Reported Outcomes questionnaires and the collection of AE data are independent components of the study.

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.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.4. Appendix 4: Female Eligibility Criteria, Contraceptive Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential (WOCBP)

- A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

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

    - Reproductive potential and agrees to follow one of the options listed in the List of Highly Effective Contraceptive Methods (Table 9) in WOCBP from 30 days prior to the first dose of randomized treatment and until completion of the Follow-up visit (4-6 weeks after the end of randomized treatment); those who permanently discontinue randomized treatment prior to the end of the study should continue contraceptive methods following the Early Treatment Discontinuation Visit until the final pregnancy test assessment at a subsequent study visit (at least 4 weeks after the end of randomized treatment) as described in the SoA (Section 2)

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - Documented tubal ligation

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - Postmenopausal defined as 12 months of spontaneous amenorrhea. In questionable cases, a blood sample with simultaneous FSH and estradiol consistent with menopause is confirmatory ≥23 MIU/mL (≥23 IU/L) and estradiol ≤10 pg/mL (or ≤37 pmol/L) is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

Contraception Guidance

Women of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9.

Table 9 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative urine FRP test.

- Additional pregnancy testing should be performed per SoA (Section 2) during the treatment period and 30 days after the last dose of study treatment and as required locally
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.3 (Appendix 3). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

12.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to daprodustat or anemia associated with CKD and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to daprodustat (or study treatments of this drug class), and anemia associated with CKD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analyzed initially using genome-wide genotyping and performing genome-wide and candidate gene analysis of efficacy measures. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data, such as investigating PK and/or safety endpoints as well as sequencing of the DNA.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to daprodustat or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- GSK will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on daprodustat (or study treatments of this class) or anemia associated with CKD continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

Study Population

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

Study Assessments and Procedures

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

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

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

Subject Withdrawal from Study

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

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

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

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.
- Screen and Baseline Failures
- If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.
- Provision of Study Results and Confidentiality of Subject's Genetic Data

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

12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 3-4 liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue randomized treatment • Report the event to GSK **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for PK analysis, obtained within 24 hour after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN

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 hours** • Monitor participants 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 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<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 participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue randomized treatment for that 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

best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify GSK **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue randomized treatment • Participant 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 participant 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 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.

12.7. Appendix 7: Country Specific Requirements

12.7.1. French Administrative Considerations and Specifics Requirements

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

- A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study if authorised by the Ethics Committee).

  It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:
  - is either affiliated to or beneficiary of a social security category;
  - has got an authorisation by the Ethics Committee.

2. Concerning the "STATISTICAL CONSIDERATIONS AND DATA ANALYSES" and specially in the "SAMPLE SIZE ASSUMPTIONS"

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

3. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

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

⇒ Concerning **the process for informing the subject and/**or his/her legally authorized representative, the following text is added:
French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.

⇒ **Concerning the management of the Patient Informed Consent Forms,** the following text is added:

French Patient Informed Consent Form is in triplicate (quadruplicate for minor subject)

The first page of the Patient Informed Consent Form is given to the investigator. The second copy is kept by the Medical Direction of GlaxoSmithKline France and the last copy is kept by the patient or legally authorized representative.

Maintenance of confidentiality of the returned consent form by GlaxoSmithKline France is specified on the form.

The second copy of all the consent forms will be collected by the Clinical Research Assistant (CRA) under the Investigator's control, and placed in a sealed envelope bearing only:

- the study number,
- the identification of the Centre: name of the principal investigator and centre number,
- the number of informed consents,
- the date,
- and the principal investigator's signature.

Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

  In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- **INFORMATION TO THE HOSPITAL PHARMACIST** the following text is added:

  In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

4. Concerning the " DATA MANAGEMENT " the following text is added:

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

- **DEMOGRAPHIC DATA**

  In accordance with the Data Protection French Law n° 78-17 of 6th January 1978 – article 8, the ethnic origin can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

  In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

5. SAE

In case of paper notification, the SAE Reports have to be transmitted to the GlaxoSmithKline France Drug Safety Department, which name, address and phone number are:

Département de Pharmacovigilance
Laboratoire GlaxoSmithKline
23, rue François Jacob
92 500 Rueil-Malmaison
Tel : PPD
Fax :
PPD

6. Monitoring visits

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

7. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's electronic Case Report Form (eCRF) use here below:

The Health Institution and the Investigator undertake:

1. That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the electronic Case Report Form (eCRF) of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
2. That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they

are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.

3. That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
4. To keep the IT Equipment and/or access codes in a safe and secure place and to authorize only the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
5. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
6. To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

8. CTR publication

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

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

In accordance with the Data Protection French Law of 6 January 1978 updated the 20th of June 2018, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference (MR-001) or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. Personal information can be transferred or be accessed to/by other entities of GLAXOSMITHKLINE Group, what the Investigator agrees by the signature of the present Protocol.

12.8. Appendix 8: Stratification by Region-Region Groupings

Region	Countries[2]
1	• Republic of Korea[1]
2	• Poland • Romania • Russian Federation • South Africa • Czech Rebuplic • Hungary
3	• Australia[1] • Canada[1] • Italy • Germany • France • United Kingdom[1] • Spain[1] • Netherlands[1] • Sweden[1]
4	• Argentina • Brazil[1] • Mexico
5	• US[1]

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

12.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Prot-ITA-1: 02-Apr-2018

Overall Rationale for the Amendment: A country specific amendment has been published per the Italian regulatory request.

Protocol Amendment Summary of Changes

Section# and Name	Description of Change	Brief Rationale
Section 2: Schedule of Activites	Edited footnote #11 to include evaluation of all iron parameters at week 4	A check of all iron parameters at week 4 was requested by AIFA
Section 6.1 Exclusion Criteria Exclusion #18	Exclude participants with a lower ECG criteria based on QTcF and not QTcB. . Exclude participants with second or third degree atrioventricular (AV) block	AIFA recommended a lower threshold for inclusion of participants with prolonged QTc measured by Fridericia equation. AIFA recommended to exclude participants with second or third degree AV block.
Section 9.5.3 Electrocardiograms	Replaced QTcB with QTcF	Based on change to exclusion criteria #18.

Type of Protocol Amendment	Numbering	Type of changes
Country-specific	**Amendment ITA-1**	**Changes requested by Italian regulatory agency added to original protocol to create Italy Specific Protocol.**

DOCUMENT HISTORY	
Document	**Date**
Country Specific Protocol ITA-1	*02-Apr-2018*
Original Protocol	*22-Aug-2017*