TITLE PAGE

Protocol Title: A Phase 3 randomized, double-blind, active-controlled, parallel-group, multi-center study in hemodialysis participants with anemia of chronic kidney disease to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of daprodustat compared to recombinant human erythropoietin, following a switch from recombinant human erythropoietin or its analogs.

Protocol Number: 204837

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

Compound Number: GSK1278863

Sponsor Name and Legal Registered Address:

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1. SYNOPSIS

Protocol Title: A Phase 3 randomized, double-blind, active-controlled, parallel-group, multi-center study in hemodialysis participants with anemia of chronic kidney disease to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of daprodustat compared to recombinant human erythropoietin, following a switch from recombinant human erythropoietin or its analogs.

Short Title: Anemia **S**tudies in **C**KD: **E**rythropoiesis via a **N**ovel PHI **D**aprodustat-**T**hree-times weekly dosing in **D**ialysis (**ASCEND-TD**)

Rationale:

Based on its mechanism of action to stimulate erythropoiesis via inhibition of hypoxia-inducible factor (HIF) prolyl hydroxylase enzymes, daprodustat is postulated to be able to raise and maintain hemoglobin (Hgb) without inducing the supraphysiologic erythropoietin (EPO) concentrations associated with recombinant human EPO (rhEPO) therapy, CCI [redacted] CCI [redacted] CCI [redacted]. Currently, there are three ongoing Phase 3 studies evaluating the safety and efficacy of once daily daprodustat versus a rhEPO active control. This Phase 3 study in hemodialysis-dependent participants with anemia will evaluate the efficacy and safety of daprodustat administered three-times weekly compared to epoetin alfa, the current standard of care.

Key Objectives and Endpoints:

Objective	Endpoint
Primary	
• To compare the effect of daprodustat to epoetin alfa on Hgb efficacy when administered three-times weekly to hemodialysis-dependent participants (non-inferiority)	• Mean change in Hgb between baseline and over the evaluation period (EP, mean over Weeks 28 to 52)
Principal Secondary (tested for superiority, adjusted for multiplicity)	
• To compare daprodustat administered three-times weekly to epoetin alfa on the use of intravenous (IV) iron	• Average monthly IV iron dose (mg)/participant to Week 52
Safety	
• To compare the safety and tolerability of daprodustat administered three-times weekly to epoetin alfa	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest and MACE

Objective	Endpoint
	• Reasons for discontinuation of study treatment • Absolute values and changes from baseline in laboratory parameters, BP and heart rate (HR)

Overall Design:

- This is a randomized, double-blind, active-controlled, parallel-group, multi-center study in hemodialysis-dependent participants who have anemia of chronic kidney disease (CKD) and are currently treated with rhEPO or its analogs.
- This study includes a 4-week Screening Period, a 52-week Treatment Period and a Follow-up Period.
- The 52-week Treatment Period consists of:
  - The Stabilization Period (SP), defined as the period from Day 1 to Week 28 (up to but excluding the Week 28 visit), during which study treatment will be dose-titrated to achieve and maintain Hgb in the target range.
  - The Evaluation Period (EP), defined as the period from Week 28 to Week 52, to assess long-term efficacy and safety. The study treatment may be dose-titrated, if needed, during this period to achieve or maintain Hgb level in the target range.
- Randomization will be stratified by region. Following stratification, participants will be randomized 2:1 to daprodustat or epoetin alfa.
- An external independent Clinical Endpoint Committee (CEC) will conduct blinded adjudication of all clinical events reported during this study that meet defined clinical definitions.
- Safety oversight will be provided by an external Independent Data Monitoring Committee (IDMC).

Number of Participants:

A sufficient number of participants, which is expected to be approximately 800 participants, will be screened to achieve approximately 402 randomized participants (268 to daprodustat and 134 to epoetin alfa) and approximately 360 evaluable participants (i.e., participants with at least one evaluable Hgb assessment during the EP).

Treatment Groups and Duration:

- Each participant will remain in the study for up to 62 weeks, including a 4-week screening period, a 52-week treatment period, and a 4 to 6-week follow-up period.

- Participants will be randomized to either daprodustat administered three-times weekly or epoetin alfa (administered three-times weekly or once weekly, depending on dose level).
- Due to the difference in formulations between the investigational product and the active control (tablets versus IV injection), and in order to maintain the study blind, each participant will receive a tablet and an IV study treatment; one will be active and one will be inactive. Participants randomized to receive daprodustat will also receive saline IV injection. Participants randomized to receive epoetin alfa will also receive placebo tablets.
- Adjustment of both study treatments (tablets and IV injection formulation) will follow a protocol-specified study treatment dose adjustment algorithm to achieve and maintain Hgb within the target range of 10.0 to 11.0 g/dL, inclusive. Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both study treatment arms.
- To ensure participants remain iron replete and to minimize the potential for iron overload during the study, the investigator will follow the iron management criteria from randomization until the end of the study treatment period.
- 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.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of Activities

Procedure Visit window of ±3 days for Weeks 2 to 8, and ±1 week for all other visits. All visit timings are relative to Day 1. All assessments will be performed pre-dialysis unless otherwise specified.	**Screening (Week -4)**	**Treatment Period: Day 1 through Week 52**					**Follow-up Visit (4 to 6 weeks after last dose)**
		Day 1 [1]	**Full Study Visit Week 4, 16, 28, 40**	**Abbreviated Study Visit Week 2, 6, 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled** [2]	
Informed consent	X						
IRT system transaction [3]	X	X	X	X	X	X	X
Inclusion and exclusion criteria	X	X					
Randomization [4]		X					
Study Treatment Dispensing [5, 6]		X	X	X [7]		X [7]	
Study Treatment Compliance [6]			X	X [7]	X	X [7]	
Participant reminder to report changes in health [8]		X					
Medical history (including past and current medical conditions, hospitalization and transfusion) [9]	X						
Demography, height	X						
Weight (pre- and post-dialysis) and EDW [10]	X	X	X	X	X	X	X
SBP/DBP, HR (pre- and post-dialysis)	X	X (triplicate)	X	X	X (triplicate)	X	X
Kt/Vurea [11]		X	X		X		
12-lead ECG [12]	X				X		
Ultrasound of kidneys and adrenal glands [13]	X						
Estradiol and FSH (females only, if required) [14]	X						
Serum pregnancy test (WOCBP only) [15, 16]	X	X	X		X		X
HemoCue Hgb	X	X	X	X	X	X	
Hematology [17]	X	X	X	X (Hgb only)	X	X	X
Clinical chemistry [17]	X	X	X		X	X	X
Ferritin, total iron and UIBC [17]	X	X	X		X		X

Procedure Visit window of ±3 days for Weeks 2 to 8, and ±1 week for all other visits. All visit timings are relative to Day 1. All assessments will be performed pre-dialysis unless otherwise specified.	**Screening (Week -4)**	**Treatment Period: Day 1 through Week 52**					**Follow-up Visit (4 to 6 weeks after last dose)**
		Day 1 [1]	**Full Study Visit Week 4, 16, 28, 40**	**Abbreviated Study Visit Week 2, 6, 8, 12, 20, 24, 32, 36, 44, 48**	**Week 52**	**Unscheduled** [2]	
Lipids (non-fasting) [17]		X	X		X		
iPTH, hsCRP, HbA1c [17, 18]		X	Wk 28		X		
Hepcidin [17, 19]		X	Wk 4, 16, 28		X		
PD: EPO, VEGF [17]		X	X (once from Wk 28 to Wk 52) [20]				
PK		X	X (once from Wk 8 to Wk 52) [21]				
Stored samples for biomarkers [22]		X	Wk 28		X		
Genetic sample [23]		X					
Patient Global Impression of Severity (PGI-S) [24]		X	Wk 28	Wk 8, 12	X		
Patient Global Impression of Change (PGI-C) [24]			Wk 28	Wk 8, 12	X		
Non-serious AEs, SAEs, AEs of Special Interest, clinical events	X [25]	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X
Iron therapy, transfusions, rescue medications [26, 27]	X	X	X	X	X	X	X
Hospitalization or kidney transplant [26]			X	X	X	X	X

DBP, diastolic blood pressure; ECG, electrocardiogram; EDW, estimated dry weight; FSH, follicle stimulating hormone; HbA1c, glycated hemoglobin; HR, heart rate; hsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; UIBC, unsaturated iron binding capacity; VEGF, vascular endothelial growth factor; WOCBP, woman of childbearing potential.

Note: Pre-dialysis assessments should be performed in the following order, where applicable: patient reported outcomes, ECG, BP/HR, blood sample collection.

1. All assessments to be performed pre-dose.
2. If additional study treatment is required prior to the next scheduled study visit, it is not necessary to perform the unscheduled visit assessments other than dispensing study treatment.
3. Study treatment will be dispensed every 4±1 weeks, with the exception that it may be every 2 weeks ± 3 days up to the Week 6 visit. An IRT transaction will be required to dispense study treatment. Additional IRT transactions may occur if needed to dispense additional study treatment.
4. In circumstances where randomization of an eligible participant cannot be completed at the Day 1 visit, the visit may be rescheduled up to 1 week later. Clinical laboratory assessments performed at the original visit, no more than 1 week prior, do not need to be repeated, except for the HemoCue hemoglobin and the Q2 hemoglobin.
5. Study treatment will be dispensed, i.e., allocated to a specific participant, and stored at the dialysis center or research site. Participant may take study treatment tablets at home in preparation for PD visit. See Section 7 for further study treatment details.

6. In circumstances where a new supply of study treatment (including a new dose) cannot be dispensed on the day of the study visit, the new supply of study treatment can be dispensed at the next dialysis session. Prior study treatment should be continued unless on dose interruption, e.g., Hgb ≥12 g/dL. Compliance is deferred until study treatment is returned.
7. At the Week 2, Week 6 or unscheduled visits, if dose is not changed, new study treatment does not need to be dispensed and use of existing study treatment is continued. Compliance checking is required if new study treatment is dispensed.
8. Participant will be instructed to promptly notify site staff in the event of any changes to his or her health. Health changes include new symptoms, medical problems (e.g., pregnancy, hospitalization), and medication changes.
9. Medical history (including CV medical history/risk factors) will be assessed at screening (Week -4). Medical history will be re-assessed at Day 1 to confirm eligibility prior to randomization.
10. Estimated Dry Weight (EDW) to be recorded in the eCRF only at Day 1, full study visits, and Week 52.
11. A historical Kt/Vurea measurement within the last 12 weeks can be used. If a Kt/Vurea measurement is not available, then a urea reduction ratio (URR) measurement is acceptable.
12. The Week -4 (screening) ECG must be performed pre-dialysis, and may be performed on any dialysis day from the Week -4 visit to the Day 1 visit, except during the first dialysis session of the week. The result of the screening ECG, including physician interpretation, must be available to confirm eligibility prior to randomization. All other ECG assessments may be performed either pre- or post-dialysis. See Section 9.4.3.
13. Ultrasound of the kidneys and adrenal glands will be performed between the Week -4 and Day 1 visits. If the results of the kidney and adrenal ultrasound require follow-up testing, then the screening period may be extended by 1 additional week. A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria, provided the size and cyst category has been reported. If a more sensitive imaging study [e.g., magnetic resonance imaging (MRI), computed tomography (CT)] has been performed within this timeframe and a report is available, this may be used in place of the ultrasound. See Section 9.4.4.
14. Only required to confirm menopausal status if in question.
15. Repeat pregnancy test prior to study treatment re-administration if study treatment was interrupted for >7 days and there was also a lapse in contraceptive use, regardless of the reason for the interruption.
16. In Argentina only, pregnancy testing will be performed every 4 weeks for WOCBP as required by local law.
17. See details for laboratory assessments in Section 9.4.5.
18. HbA1c assessment is applicable only for participants with diabetes on Day 1 or diagnosed during the study.
19. At each visit specified in the table, a hepcidin sample will be collected prior to dosing with either study treatment and prior to administration of any iron supplementation.
20. Post-baseline PD samples (i.e., EPO and VEGF) may be taken during any week from Week 28 to Week 52, inclusive, preferably at the earliest opportunity. See Section 9.6 for additional details and requirements for the collection of PD samples.
21. Post-baseline PK samples will be taken at any one of the post-baseline visits indicated in the table, preferably at the earliest opportunity. See Section 9.5 for additional details and requirements for the collection of PK samples.
22. Biomarker samples will be collected and stored for potential future analysis for all participants, except if not permitted by local regulations or IRB/EC, or refused by participant.
23. Participation in genetics research is optional. A separate informed consent signature is required for participation. See Section 9.7 for additional details.
24. Participants who are unable to or require assistance to read must not complete the questionnaires. See Section 9.9 for additional details.
25. Only SAEs, which are assessed as related to study participation or a GlaxoSmithKline (GSK) product, are collected at this visit. See Section 9.2.1 for additional details.
26. Record in the eCRF, if applicable.
27. See details on Rescue in Section 7.9.

Table 2 Schedule of Activities for Participants Who Permanently Discontinue Study Treatment

Procedure	Early Treatment Discontinuation Visit (within 2 weeks of discontinuing study treatment)	Day 1 through Week 52 [1]	
		Week 4, 16, 28, 40, 52 ± 2 weeks	Un-scheduled
IRT system transaction	X	X	X
SBP/DBP, HR (pre- and post-dialysis)	X (triplicate)	X	X
12-lead ECG [2]	X		
Iron therapy, transfusions [3]	X	X	X
Serum pregnancy test (WOCBP only)	X [4]		
HemoCue Hgb	X	X	X
Hematology [5]	X	X	
Clinical chemistry [5]	X	X	
Ferritin, total iron, UIBC, lipids, iPTH [5]	X		
Hospitalization, kidney transplant [3]	X	X	X
Non-serious AEs, SAEs, AEs of Special Interest, clinical events	X	X	X
Review concomitant medications	X	X	X
PGI-S and PGI-C [6]	X		

1. Participants will attend those study visits up to Week 52 which have not been completed at the time of early treatment discontinuation. Phone visits are acceptable in exceptional circumstances.
2. ECG assessment may be recorded pre- or post-dialysis.
3. Record in the eCRF, if applicable.
4. Additional pregnancy test required at subsequent visit. Must be at least 4 weeks after the end of study treatment.
5. See details for laboratory assessments in Section 9.4.5.
6. Participants who are unable to or require assistance to read must not complete the questionnaires. See Section 9.9 for additional details.

3. INTRODUCTION

Daprodustat (GSK1278863) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). Daprodustat is currently being investigated as a treatment for anemia of chronic kidney disease (CKD) in both dialysis and non-dialysis participants. Previously conducted clinical trials have shown adequate safety and efficacy of daprodustat for up to 24 weeks with doses up to 12 mg administered once daily and for up to 29 days with doses up to 30 mg administered three-times weekly. Both pre-clinical and clinical data show that daprodustat stimulates erythropoietin (EPO) production, increases erythropoiesis resulting in elevation of hemoglobin (Hgb) concentrations. These increases in Hgb are achieved with peak EPO exposures substantially lower than those observed with recombinant human erythropoietin (rhEPO) using either once daily or three-times weekly dosing schedules. Data from completed clinical and pre-clinical studies are provided in the Daprodustat Investigator's Brochure (IB) [GSK Document Number RM2008/00267/08] and IB Supplements, if applicable.

Study 204837 is designed to match to the extent possible the once daily daprodustat cardiovascular (CV) outcomes study in dialysis-dependent participants [Study ID 200807, GSK Document Number 2015N226659_05], in order to evaluate the three-times weekly regimen under conditions that are comparable to those in the once daily study. A separate analysis is planned that will utilize the data obtained from the larger CV outcomes study in dialysis-dependent participants receiving once daily daprodustat and the same active comparator, epoetin alfa, to compare and assess the safety of three-times weekly daprodustat.

3.1. Study Rationale

Based on its mechanism of action to stimulate erythropoiesis via inhibition of HIF-prolyl hydroxylase enzymes, once daily daprodustat is postulated to be able to raise and maintain Hgb without inducing the supraphysiologic EPO concentrations associated with rhEPO therapy, CCI [redacted] CCI [redacted] CCI [redacted] Currently, there are three ongoing Phase 3 studies evaluating the safety and efficacy of once daily daprodustat versus a rhEPO active control, and the rationale for conducting study 204837 is to determine if the safety and efficacy of daprodustat is similar when administered three-times weekly.

A recently completed Phase 2A clinical trial in hemodialysis-dependent participants with anemia showed that three-times weekly, orally administered daprodustat increases Hgb levels with a corresponding transient increase in EPO concentration over 29 days in participants switched from rhEPO or its analogs [Study ID 204836, GSK Document Number 2016N309671_00]. Furthermore, a Phase 2B clinical trial in hemodialysis-dependent participants with anemia showed that once daily, orally administered daprodustat can maintain Hgb up to 24 weeks, also with plasma EPO concentration within the physiological range [Study ID PHI113633, GSK Document Number 2014N219785_00]. Both three-times weekly administered daprodustat for 29 days and once daily administered daprodustat for up to 24 weeks displayed an adverse event (AE)

profile consistent with that expected for this patient population. Data from completed clinical studies are provided in the Daprodustat IB and IB Supplements, if applicable.

This Phase 3 study in hemodialysis-dependent participants with anemia will evaluate the efficacy and safety of daprodustat administered three-times weekly compared to epoetin alfa, the current standard of care.

In most clinical studies to date, daprodustat has been administered employing a once daily regimen. However, several cost analysis studies have shown less frequent dosing of rhEPO and its analogs is economically beneficial with hemodialysis patients in both the US and Europe [Stephens, 2016; Burnier, 2009]. Since standard practice in many countries is to administer rhEPO and its analogs three-times weekly to match in-center dialysis sessions, this study will assess the safety and efficacy of daprodustat administered three-times weekly to accommodate this less frequent dosing schedule. This study aims to demonstrate that daprodustat dosed three-times weekly is effective for maintaining Hgb in hemodialysis (HD) participants switched from rhEPO or its analogs.

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 hemodialysis procedure.

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

- Iron: Poor compliance is seen with oral iron therapy due to gastrointestinal intolerance and IV iron may have an increased risk of infection, congestive heart failure, iron overload or anaphylaxis [Agarwal, 2015].
- rhEPO: In order to achieve target Hgb levels, which are lower than normal Hgb levels, treatment with IV rhEPO markedly increases EPO plasma concentrations to higher than normal levels. Treatment with rhEPOs has been associated with increased cancer-related morbidity and mortality and increased risk of major cardiovascular events (e.g., stroke, myocardial infarction and all-cause mortality) [FDA, 2011].
- Blood transfusions: These are avoided when possible because of potential alloimmunization which can preclude the possibility of receiving a kidney transplant and risk of infection.

Thus there is an unmet need for a safer alternative for treatment of anemia of CKD. Current clinical and nonclinical data suggest that daprodustat has the potential to provide similar or better efficacy to approved therapies with the potential for an improved safety profile, most notably compared to rhEPO and its analogs.

3.3. Benefit/Risk Assessment

A summary of the findings from clinical and non-clinical studies of daprodustat as well as more detailed information about the known and expected benefits and risks of daprodustat may be found in the Daprodustat IB and IB Supplements, if applicable.

3.3.1. Risk Assessment

The potential risks of clinical significance and the mitigation strategies for this protocol taking into account the results of completed clinical and nonclinical studies with daprodustat are outlined below. In addition to the mitigation strategies outlined, an IDMC will monitor accruing safety data for this trial (Section 12.2.5.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Daprodustat		
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion/inflammation, microthrombi, and tissue ischemia in a number of organs. Phase 2 dose-ranging studies, and associated statistical and exposure response modelling has informed Phase 3 dose rationale, starting doses, dose steps, and dose adjustment scheme to optimize Hgb management. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 6.1 and Section 6.2. • 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 (including rate of change) is provided in Section 7.2 and Section 8.1. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythemic conditions)	Marketed rhEPO and its analogs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD. In non-clinical studies, similar events were not observed at tolerated doses when hemoglobin/hematocrit within normal range for species. The clinical data received to date are insufficient to conclude or refute this risk.	• Specific eligibility criteria related to CV risk are outlined in Section 6.2. • Hgb will be closely monitored throughout the dosing period as outlined in the SoA in Section 2. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Esophageal and gastric erosions	In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ ulcers with hemorrhage were observed with daprodustat. In rats, stomach erosions were observed with intravenous and oral administration of daprodustat. Stomach erosions/ulcers also reported in rats with marketed rhEPOs and its analogs. In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported AE, however causal association has not been established. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	• Suspected GI bleeding or significant symptoms consistent with erosions or ulcers should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted. • Unblinded monitoring of safety data by an IDMC instream throughout the study.
Cancer-related mortality and tumor progression and recurrence	Marketed rhEPO and its analogs have been associated with increased risk of cancer related morbidity and mortality when used in patients with cancer. Administration of 60mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. There were no test article-related neoplastic findings in 2-year rat (oral daprodustat) or mouse (daprodustat + subcutaneous injection of the 3 major human metabolites; M2, M3 and M13) carcinogenicity studies. In clinical studies conducted to date, administration of daprodustat has been associated with:	• 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. • Unblinded monitoring of safety data by an IDMC instream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy

	Once daily administration:
	
	• In studies up to 4-weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg.
	• In studies up to 24-weeks duration at doses up to 25mg, changes in VEGF plasma concentration were variable but similar relative to control.
	• Systemic EPO concentrations within the physiologic range.
	
	Three times weekly administration:
	
	• In studies up to 4-weeks duration at doses of 10 to 30 mg:
	  ○ Dose dependent increases in plasma VEGF and EPO concentrations were observed.
	  ○ Pre-dose concentrations of EPO and VEGF were near or below baseline indicating no accumulation of EPO or VEGF after three times weekly dosing.
	
	Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	

Pulmonary artery hypertension (PAH)	A role for HIF-regulated pathways in the pathophysiology of PAH has been suggested based on well established effects of acute and chronic hypoxia in man on the pulmonary vasculature (vasoconstriction), and by findings in patients with naturally occurring mutations that result in decreased HIF degradation [Smith, 2006; Formenti, 2011]. There have been no histopathologic findings suggestive of PAH in pre-clinical safety studies with daprodustat (up to 13-weeks duration in dogs, up to 2 years in rats and mice,	• Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Cardiomyopathy	Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized. With lifetime exposure to daprodustat in a 2-year rat oral carcinogenicity study, an exacerbation of rat spontaneous, progressive cardiomyopathy (PCM) (focal myofiber degeneration/necrosis with inflammatory infiltrates) was observed at doses of 0.8 mg/kg/day and above, although total incidence and severity distribution within any daprodustat-group were within historical control ranges. This is consistent with an equivocal threshold for exacerbation of spontaneous, progressive cardiomyopathy at 0.8 mg/kg/day which is also the threshold dose for observing increased Hct values in individual rats. Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization. ECHO assessments performed in phase 2b studies (24-weeks treatment duration) did not identify any clinically meaningful changes in LVEF for daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
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	• Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	degeneration [Campochiaro, 2006]. Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. Aside from congestion of retinal vessels and optic disc hyperemia secondary to markedly increased red cell mass, there were no ocular abnormalities observed in non-clinical trials. In clinical studies up to 4-weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg administered once daily and from 10 to 30 mg administered three times weekly. In studies up to 24-weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. Ophthalmologic assessments performed in phase 2b studies (24-weeks treatment duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization with daprodustat. Following review of clinical data with daprodustat received to date, this has not been identified as a safety concern for daprodustat.	
Exacerbation of rheumatoid arthritis	In inflamed rheumatic joints, activation of HIF- related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra, 2010; Muz, 2009].	• Unblinded monitoring of safety data by an IDMC in-stream throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No abnormalities seen in non-clinical studies conducted to date for daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Drug-drug interactions	Daprodustat is a substrate of CYP2C8: Co-administration of daprodustat with a *strong* CYP2C8 inhibitor (gemfibrozil) increased the Cmax and AUC of daprodustat, 4- and 19-fold, respectively, while co-administration of a weak inhibitor (trimethoprim) increased the Cmax and AUC of daprodustat by 1.3- and 1.5-fold, respectively. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with a *moderate* CYP2C8 inhibitor (clopidogrel) leads to a ~2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Although CYP2C8 induction studies were not performed, co-administration of daprodustat with an inducer of CYP2C8 (e.g., rifampin/rifampicin) may decrease the exposure of daprodustat. Although co-administration of daprodustat with strong inhibitors and inducers of CYP2C8 is prohibited, inadvertent co-administration may occur. Due to the known time delay in enhancing erythropoiesis by daprodustat, co-administration with strong CYP2C8 inhibitors for up to 14 days is not anticipated to lead to immediate marked increases in hemoglobin levels. Therefore, there is adequate time to change to alternate therapy that does not inhibit CYP2C8. Additionally, as the time for maximum induction of CYP2C8 occurs approximately 10-14 days of dosing with rifampin [Brodie,	• Co-administration of daprodustat with strong CYP2C8 inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin/rifampicin) is not permitted as outlined in Section 7.7.2. • 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 7.7.1. • 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; however, periodic monitoring of hemoglobin will be performed as outlined in the SoA in Section 2 and specific guidance for dose adjustment or discontinuation is provided in Section 7.2 and Section 8.1. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 7.7. • Hgb will be closely monitored throughout the dosing

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	2013; Ohnhaus, 1989], daprodustat systemic exposure will decrease over time which will result in a lag period before an effect on Hgb is recognized and is of clinical concern. Daprodustat is an inhibitor of CYP2C8: A clinical drug interaction study between 25mg and 100mg daprodustat with a CYP2C8 substrate (pioglitazone) showed that there is no PK interaction at these doses of daprodustat. Daprodustat is a substrate of BCRP: Population PK analysis from Phase 2 studies suggested that while BCRP inhibitors were a covariate for daprodustat CL/F (8.6% lower clearance) the predicted change in exposure was not considered to be of clinical relevance. Daprodustat is an inhibitor of OATP1B1/1B3: A clinical drug interaction study between 25mg and 100mg daprodustat with an OATP1B1/1B3 substrate (rosuvastatin) showed that there is no PK interaction at these doses of daprodustat.	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. • Unblinded monitoring of safety data by an IDMC in-stream throughout the study.
Other		
rhEPO risks (Control)	See risks outlined in table for daprodustat for excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia, death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access, and for cancer-related mortality and tumor progression. Uncontrolled hypertension Pure red cell aplasia	• See mitigation strategies outlined in table for daprodustat for excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia; death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access; and for cancer-related mortality and tumor progression. • Specific eligibility criteria related to current uncontrolled hypertension are outlined in Section 6.2. • Specific eligibility criteria related to personal history of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		pure red cell aplasia are outlined in Section 6.2.

3.3.2. Benefit Assessment

Study participants may benefit from the clinical efficacy that is expected with daprodustat based on previous trials with once daily dosing of daprodustat for up to 24 weeks and three-times weekly dosing of daprodustat for up to 29 days. Daprodustat may present several important advantages over rhEPO and its analogs. It is an oral medication and does not require cold-chain storage, as does rhEPO, thus increasing ease of use for patients and health care providers. After administration of three-times weekly daprodustat, data suggest that equivalent increases in Hgb are achieved with EPO exposure lower than those observed with rhEPO. Treatment of anemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated increases in EPO exposure with rhEPO [Szczech, 2008]; CCI [redacted] CCI [redacted] CCI [redacted]. Other potential benefits include possibly improving iron availability for erythropoiesis, the potential to successfully treat rhEPO hyporesponders, and the potential to treat anemia without inducing rhEPO related hypertension.

3.3.3. Overall Benefit:Risk Conclusion

Daprodustat demonstrates a positive benefit versus risk based on the evidence as follows. In clinical trials up to 24 weeks in duration, daprodustat treats Hgb to target range with a safety profile consistent with the patient population.

This protocol employs precautions to mitigate known and potential risks to enrolled participants (See Section 3.3.1). Given these precautions, as well as the potential benefit that daprodustat holds for the treatment of anemia of 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 effect of daprodustat to epoetin alfa on Hgb efficacy when administered three-times weekly to hemodialysis-dependent participants (non-inferiority)	• Mean change in Hgb between baseline and over the evaluation period (EP, mean over Weeks 28 to 52)
Principal Secondary (tested for superiority, adjusted for multiplicity)	
• To compare daprodustat administered three-times weekly to epoetin alfa on the use of intravenous (IV) iron	• Average monthly IV iron dose (mg)/participant to Week 52
Safety	
• To compare the safety and tolerability of daprodustat administered three-times	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of

Objectives	Endpoints
weekly to epoetin alfa	special interest and MACE • Reasons for discontinuation of study treatment • Absolute values and changes from baseline in laboratory parameters, BP and heart rate (HR)
Secondary (endpoints tested for superiority[1], with no multiplicity adjustment)	
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on Hgb variability	• Hgb change from baseline to Week 52 [1] • % time Hgb in analysis range (10 to 11.5 g/dL) during the EP [1] • N (%) responders, defined as mean Hgb within the Hgb analysis range 10 to 11.5 g/dL during the EP
• To compare daprodustat administered three-times weekly to epoetin alfa on the time to rescue	• Time to stopping study treatment due to meeting rescue criteria
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on BP	• Change from baseline in SBP, DBP and mean arterial pressure (MAP) at Week 52 and at the end of study treatment • Number of BP exacerbation events per 100 patient years • N (%) with at least one BP exacerbation event during study
• To generate pharmacokinetic parameters of daprodustat and predominant metabolites following three-times weekly dosing	• Plasma daprodustat, M2, M3, M4, M5, M6 and M13 PK parameters pre-dose trough (Ctau) and Cmax
• To compare daprodustat administered three-times weekly to epoetin alfa on global symptom severity and change	• Change from Baseline at Weeks 8,12, 28, and 52 in PGI-S
Exploratory (no statistical testing planned)	
• To evaluate graphical relationships between exposure parameters and selected efficacy endpoints of daprodustat administered three-times weekly	• Extrapolated Cmax of daprodustat vs. the percent time within the Hgb target range during the EP • Extrapolated Cmax of daprodustat vs. mean Hgb over the 52-week treatment period

Objectives	Endpoints
	• Mean weekly daprodustat dose over 52 weeks vs. the percent time within the Hgb target range during the EP • Mean weekly daprodustat dose over 52 weeks vs. mean Hgb over the 52-week treatment period
• To evaluate graphical relationships between daprodustat administered three-times weekly against MACE and the combined safety endpoint of MACE + thromboembolic event + hospitalization for Congestive Heart Failure (CHF)	• Extrapolated Cmax of daprodustat in participants without MACE compared to those with MACE (as well as for the combined safety endpoint of MACE + thromboembolic event + hospitalization for CHF) • Mean weekly daprodustat dose in participants without MACE compared to those with MACE (as well as for the combined safety endpoint of MACE + thromboembolic event + hospitalization for CHF)
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on BP and BP medication changes	• Observed and change from baseline in SBP, DBP and MAP by visit • Number of BP medications per participant by visit • Change from baseline in the number or dose of BP medications per participant by visit • N (%) of participants who had no change in the number or dose of BP medications from baseline by visit • N (%) of participants who had an increase in the number or dose of BP medications from baseline by visit • N (%) of participants who had a decrease in the number or dose of BP medications from baseline by visit
• To further compare the effect of daprodustat administered three-times weekly to epoetin alfa on Hgb variability	• Hgb observed and change from baseline across all visits • % of time Hgb is above, within and below the analysis range of 10 to 11.5 g/dL during the EP • Number (%) of participants with mean Hgb

Objectives	Endpoints
	above, within and below the Hgb analysis range during the EP • Number (%) of participants with a Hgb <7.5 g/dL during the EP • Number of times Hgb <7.5 g/dL during the EP • Number (%) of participants with a >1 g/dL increase in Hgb within any 2-week period (assessed at Week 2 through Week 8), or with a >2 g/dL increase in Hgb within any 4-week period up to Week 52 • Number (%) of participants with a >1 g/dL decrease in Hgb within any 2-week period (assessed at Week 2 through Week 8), or with a >2 g/dL decrease in Hgb within any 4-week period up to Week 52 • N (%) of participants with a Hgb value ≥12 g/dL during the EP • Number of times Hgb ≥12 g/dL during the EP • % of time Hgb ≥12 g/dL during the EP
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on measures of iron parameters	• Observed and change from baseline in hepcidin, ferritin, transferrin saturation (TSAT), total iron, total iron binding capacity (TIBC) across all visits • Average quarterly ferritin • Average quarterly TSAT • Average quarterly IV iron dose/participant • N (%) of participants who met iron management criteria • N (%) of participants who reduced IV iron supplementation relative to baseline [defined as total iron (mg) over 4 weeks prior to randomization] during EP [defined as average monthly IV iron dose (mg) over Weeks 28 to 52]
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on the need for red blood cell (RBC)	• Number (%) of participants who receive at least one RBC or whole blood transfusion

Objectives	Endpoints
and whole blood transfusions	by Week 52 • Number of RBC and whole blood transfusions per 100 patient years • Number of RBC and whole blood units per 100 patient years
• Characterize the pharmacodynamic (PD) effect of daprodustat administered three-times weekly on EPO, vascular endothelial growth factor (VEGF) and RBC	• Maximum observed change from baseline in EPO • Maximum observed % change from baseline in VEGF • Change from baseline in hematocrit, RBC count, and reticulocyte count
• To compare the effect of daprodustat administered three-times weekly to epoetin alfa on lipid parameters.	• Observed and % change from baseline in lipid parameters by visit [total cholesterol, direct low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)]
• To evaluate the daprodustat dose adjustment scheme	• Assigned dose by visit and at Day 1, Week 28, and Week 52 • Most recent dose prior to Week 28, Week 52 and end of study treatment • Number (%) of participants with 0, 1, 2, or >2 dose adjustments during the following periods: o Day 1 to < Week 28 o Week 28 to < Week 52 o Day 1 to < Week 52 • Number of dose adjustments during the following periods: o Day 1 to < Week 28 o Week 28 to < Week 52 o Day 1 to < Week 52 • Number of dose adjustments per year during Day 1 to < Week 52 • Time dose held for Hgb ≥12 g/dL
• To further compare daprodustat administered three-times weekly to epoetin alfa on global symptom severity and change	• Shift tables (Baseline to Weeks 8, 12, 28, and 52) in PGI-S • N (%) of participants within each PGI-C symptom change level at Weeks 8, 12, 28, and 52

Conversion from g/dL to g/L is 1:10 and from g/dL to mmol/L is 0.6206. For example, Hgb of 10.0 to 11.0 g/dL is equivalent to 100 to 110 g/L or 6.2 to 6.8 mmol/L.

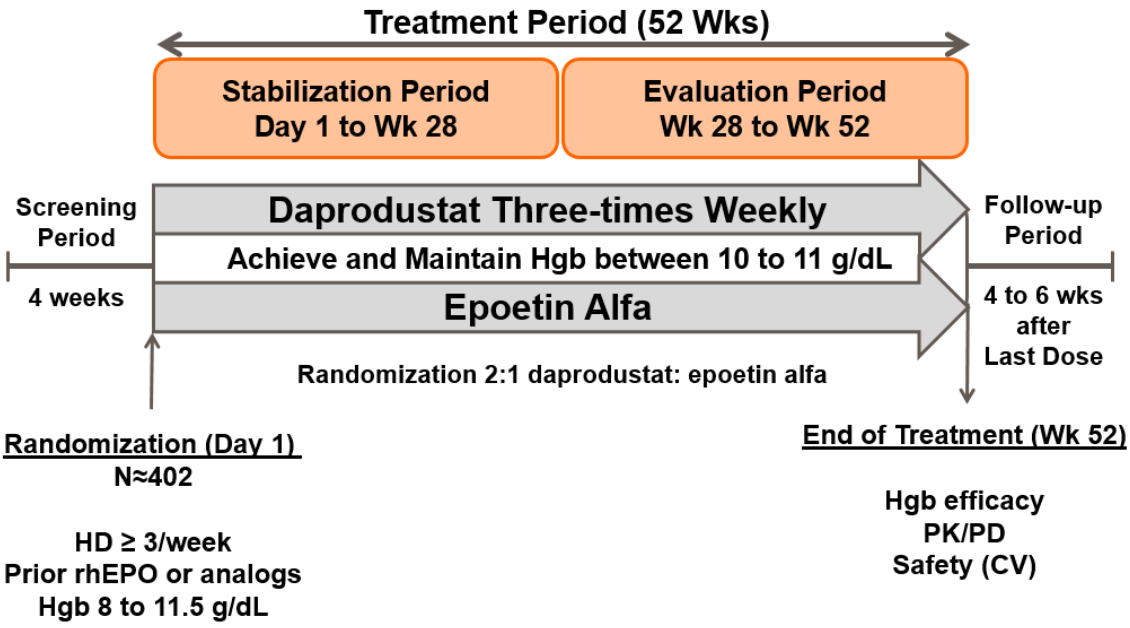
1. Hgb change from baseline to Wk 52 is tested for non-inferiority, using the -0.75 g/dL margin used in the primary analysis. % time in range is tested first for non-inferiority, then for superiority. The non-inferiority margin for % time in range will be defined in the RAP.

5. STUDY DESIGN

5.1. Overall Design

- This is a randomized, double-blind, active-controlled, parallel-group, multi-center study in hemodialysis-dependent participants, including combination methods such as hemodiafiltration or hemofiltration with HD, who have anemia of CKD and are currently treated with rhEPO or its analogs.
- This study includes a 4-week Screening Period, a 52-week Treatment Period and a Follow-up Period (Figure 1).
- The 52-week Treatment Period consists of:
  - The Stabilization Period (SP), defined as the period from Day 1 to Week 28 (up to but excluding the Week 28 visit), during which study treatment will be dose-titrated to achieve and maintain Hgb in the target range.
  - The Evaluation Period (EP), defined as the period from Week 28 to Week 52, to assess long-term efficacy and safety. The study treatment may be dose-titrated, if needed, during this period to achieve or maintain Hgb level in the target range.

Figure 1 Study Schematic



- Each participant will remain in the study for up to 62 weeks. Participants who permanently discontinue study treatment will remain in the study.

- Randomization will be stratified by region (see Appendix 7). Following stratification, participants will be randomized 2:1 to daprodustat or epoetin alfa. Daprodustat will be administered three-times weekly and epoetin alfa will be administered once weekly or three-times weekly, depending on dose level (Section 7).
- Due to the difference in formulations between the investigational product and active control (tablets versus IV injection), and in order to maintain the study blind, each participant will receive a tablet and an IV study treatment; one will be active and one will be inactive (Section 7). Participants randomized to receive daprodustat will also receive saline IV injection. Participants randomized to receive epoetin alfa will also receive placebo tablets.
- PK samples will be collected from all study participants to enable exposure-response and exposure-safety analyses (Section 9.5).
- Adjustment of both study treatments (tablet and IV injection formulations) will follow a protocol-specified study treatment dose adjustment algorithm to achieve and maintain Hgb within the target range of 10.0 to 11.0 g/dL, inclusive (Section 7.2). Dose changes will be made programmatically by the Interactive Response Technology (IRT) system for both study treatment arms.
- To ensure participants remain iron replete and to minimize the potential for iron overload during the study, the investigator will follow the iron management criteria from randomization until the end of the study treatment period (Section 7.8.1).
- 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 (Section 7.9).
- An external independent Clinical Endpoint Committee (CEC) will conduct blinded adjudication of all clinical events reported during this study that meet defined clinical definitions as outlined in Section 9.2.5.
- Safety oversight will be provided by an external Independent Data Monitoring Committee (IDMC) (Section 12.2.5.1).

5.2. Number of Participants

A sufficient number of participants, which is expected to be approximately 800 participants, will be screened to achieve approximately 402 randomized participants (268 to daprodustat and 134 to epoetin alfa) and approximately 360 evaluable participants (i.e., participants with at least one evaluable Hgb assessment during the EP).

5.3. Participant and Study Completion

A participant is considered to have completed the study if he or she has completed all study periods through the Week 52 visit. A participant who dies while on study is also considered to have completed the study.

Completion of the Treatment Period will also be captured, and will be distinct from study completion.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA or study contact for the last participant in the study globally, whichever is later.

5.4. Scientific Rationale for Study Design

- This study includes a Week -4 Screening Visit prior to randomization (Day 1). The screening period permits time to assess eligibility based on laboratory assessments and ultrasound evaluation.

- The total treatment period will be 52 weeks in order to allow sufficient time to demonstrate efficacy. The SP from Day 1 to Week 28 allows participants to have their study treatment dose titrated to achieve the Hgb target range. This period of time provides the best opportunity for participants to be titrated to their optimal dose of study treatment prior to the EP, from Week 28 to Week 52. A percentage of participants may still need dose titration during the EP.

- The selection of rhEPO as the active control (epoetin alfa) is based on clinical practice in the majority of participating countries.

- This study will be conducted in a double-blind fashion. Each participant will receive oral tablets (either daprodustat or matching placebo) and IV injections (either epoetin alfa or saline). Each participant will receive one active study treatment and one inactive study treatment, depending upon the treatment arm to which the participant is randomized. See Section 7.2 for further information about study treatment. Because it was not feasible to create a matching placebo/saline vial for the active control (epoetin alfa), the study treatment IV injections (either epoetin alfa or saline) will be prepared and administered by an unblinded nurse, or other properly qualified individual(s), in a manner that will maintain the blind. Further information about blinding considerations are presented in Section 7.4.

- Participants will be randomized in a 2:1 ratio to daprodustat or epoetin alfa. More participants will be randomized to daprodustat compared to epoetin alfa in order to obtain an adequately sized safety database of HD patients exposed to daprodustat administered three-times weekly for a longer duration (i.e., over a 52-week treatment period).

5.5. Dose Justification for Daprodustat

Clinical practice (standard of care) in the treatment of anemia in CKD patients on HD often utilizes a three-times weekly regimen consistent with their hemodialysis schedule. GSK proposes to assess this regimen as part of the planned Phase 3 clinical program in hemodialysis patients.

In addition to administration on a three-times weekly dosing schedule, extended interval dosing (i.e., weekly to monthly) is also routinely used with rhEPO and its analogs.

Evidence with epoetin alfa (Epogen), with Dosing and Administration guidance for three-times weekly dosing, has shown that increases in dosing interval (i.e., extended time between doses) can be achieved by a proportionate increase in the dose administered at each interval. As reported in a small study, epoetin alfa was administered subcutaneously at either 50 IU/kg three-times weekly, 10,000 IU/week, 20,000 IU every two weeks or 40,000 IU every 4 weeks with consistent management of Hgb levels for all 4 regimens in anemia patients with CKD not on dialysis [McGowan, 2008]. As the daprodustat dose response with Hgb is generally linear between 4 and 24 mg once daily, it is anticipated that a similar time-proportional efficacy relationship will exist for daprodustat and the management of Hgb levels as the dosing is extended from once every day to three-times weekly. These data suggest that the efficacy of PHIs is most likely related to total dose or AUC, rather than Cmax or Cmin. Additionally, the time to reach the steady-state response is determined by the RBC lifespan which on average is 2 to 3 months.

Daprodustat starting doses were selected to reach the target Hgb concentration after approximately one RBC lifespan of treatment (almost 3 months, pharmacodynamic steady-state), without the need for any individual dose adjustments. However, due to the between-subject variability in Hgb response to a given dose of daprodustat, and the relatively narrow Hgb target range, individual dose adjustments of daprodustat are expected during the first few months of treatment. If an individual dose adjustment is necessary, the participant's daprodustat dose will be increased or decreased through a series of dose steps, one dose step at a time.

The daprodustat starting doses and dose steps from the once daily Phase 3 study (200807) were selected based on exposure-response longitudinal modeling of Hgb data collected across the Phase 2 program and these doses serve as the foundation for the three-times weekly doses in this study. Similar to the Phase 3 study, the starting doses will be assigned based on the participant's prior dose of rhEPO or its analogs at study entry. Covariate analyses elucidated that baseline Hgb, body-weight, and prior dose of rhEPO and its analogs were the most relevant covariates of Hgb response to daprodustat. Simulations showed the effect of body-weight was not clinically important for dosing, so the relationship between prior dose of rhEPO and its analogs and response was used to determine starting doses of daprodustat relative to a participant's prior dose of rhEPO and its analogs. These findings apply to daprodustat administered three-times weekly as well, and therefore prior dose of rhEPO or its analogs will also be used in the determination of the starting dose in the current study.

The once daily doses used in the 200807 study were converted to corresponding three-times weekly doses using the estimated dose conversion ratio of approximately 2.0 that was determined in the Phase 2A three-times weekly daprodustat dose ranging study (204836). The dose conversion ratio was estimated by taking the ratio of three-times weekly daprodustat dose corresponding to the once daily dose that produced an equivalent Hgb response. Several approaches were explored to estimate the dose conversion ratio and the three-parameter Bayesian Emax dose-response models produced the most consistent estimates across the studied dose range. The ratio of approximately 2.0 estimated by this approach was used to calculate the three-times weekly doses.

The resultant three-times weekly starting doses of 8, 12, 16 and 24 mg were calculated by multiplying the once daily dosing algorithm by the conversion ratio estimated in study 204836. These doses are estimated to maintain equivalent Hgb concentrations to that achieved in the participants on prior rhEPO therapy and its analogs. The actual starting dose for each participant will be individualized based upon their prior therapy of rhEPO or its analogs. The highest available dose of daprodustat in the dose adjustment scheme is 48 mg administered three-times weekly.

Starting doses, dose steps, and elements of the dose adjustment scheme are provided in Section 7.2.

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 are eligible to be included in the study only if all of the following criteria apply at **screening (Week -4)** and **randomization (Day 1)**, unless otherwise specified:

1. **Age:** Participant must be 18 to 99 years of age inclusive, at the time of signing the informed consent.

   Note: Country-specific age requirements for Korea are provided in Appendix 8, Section 12.8.2.

2. **RhEPO or its analogs:** Use of any approved rhEPO or analog for at least 8 weeks prior to the screening visit and continuing during the screening period until randomization (Day 1).

3. **Hemoglobin** concentration (measured by HemoCue) within the following range:

	Hgb Range (inclusive)
Week -4	• Hgb 8 to 11.5 g/dL[1] (5 to 7.1 mmol/ L). • If Hgb is 11.6 to 11.9 g/dL[2] (7.2 to 7.4 mmol/L), up to two retests are allowed; the retest value must be between 8 to 11.5 g/dL1 (5 to 7.1 mmol/ L).
Day 1	• Hgb 8 to 11 g/dL[1] (5 to 6.8 mmol/L) **and** receiving at least the minimum rhEPO or analog dose [3]. • Hgb >11 to 11.5 g/dL[1] (6.8 to 7.1 mmol/L) **and** receiving greater than the minimum rhEPO or analog dose [3].

1. Conversion from g/dL to g/L is 1:10, e.g., Hgb of 8 to 10 g/dL is equivalent to 80 to 100 g/L.
2. The first retest will use the original Week -4 blood sample. If the retest value is >11.5 g/dL, one additional retest can be performed using a new blood sample on the study visit day. The **final** retest value is entered into the IRT system. Retests will be done prior to dialysis.
3. **Minimum rhEPO or analog dose**: Epoetins (including biosimilars): 1500 units (U)/week intravenous (IV) or 1000 U/week subcutaneous (SC); Darbepoetin alfa: 20 μg/4 weeks SC/IV; Methoxy PEG-Epoetin: 30 μg/month SC/IV.

4. **Dialysis**: On hemodialysis (including hemofiltration or hemodiafiltration) >90 days prior to screening and continuing during the screening period.
5. **Frequency of Dialysis**: On hemodialysis (in-center) ≥3 times per week.
6. **Sex:** Male and female participants are eligible. A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:
   - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4, or
   - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 from at least 28 days prior to first dose of study treatment and for at least 28 days after the last dose of study treatment.
7. **Informed Consent:** Capable of giving signed informed consent as described in Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

   Note: Country-specific requirements for France for the informed consent process are provided in Appendix 8 (see Section 12.8.1, Item 3 for details).

8. **Other Study Eligibility Criteria Consideration:** In France, a participant will be eligible for inclusion in this study if he or she is either affiliated to or beneficiary of a social security category.

   Note: Country-specific requirements for France for inclusion in this study are provided in Appendix 8 (see Section 12.8.1 Item 1 for details).

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply at **screening (Week -4)** and **at randomization (Day 1)**, unless otherwise specified:

CKD Related Criteria

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

Anemia Related Criteria

2. **Ferritin:** ≤100 ng/mL (≤100 µg/L), at screening.
3. **Transferrin saturation (TSAT):** ≤20%, at screening. If TSAT is 18 to 20%, then a retest using a new blood sample can be obtained within 7 days of the final laboratory report; the final retest value must be >20% to confirm eligibility.
4. **Aplasias:** History of bone marrow aplasia or pure red cell aplasia.
5. **Other causes of anemia**: Conditions, other than anemia of CKD, which can affect erythropoiesis. A partial list can be found in the Study Reference Manual (SRM).

Cardiovascular Disease

6. **MI or acute coronary syndrome** within 8 weeks prior to screening through to randomization (Day 1).
7. **Stroke or transient ischemic attack** within 8 weeks prior to screening through to randomization (Day 1).
8. **Heart failure (HF)**: Chronic Class IV HF, as defined by the New York Heart Association (NYHA) functional classification system.
9. **Current uncontrolled hypertension** as determined by the investigator that would contraindicate the use of rhEPO.
10. **Bazett's correction of QTc interval (QTcB)** at 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 ventricular paced rhythm.

Other Medical Conditions

11. **Liver Disease:** presence of any one of the following liver-related laboratory values or conditions, at screening, is exclusionary:

    - Alanine transaminase (ALT) >2x upper limit of normal (ULN);
    - Bilirubin >1.5x ULN; or

    NOTE: Isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.

    - Current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

    NOTE: Stable chronic liver disease (including asymptomatic gallstones, chronic hepatitis B or C, or Gilbert's syndrome) are acceptable if participant otherwise meets entry criteria.

12. **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).
13. **Malignancy:** History of malignancy within 2 years prior to screening through to randomization (Day 1), currently receiving treatment for cancer, or complex kidney cyst (e.g., Bosniak Category IIF, III or IV) >3 cm.

    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.

Prior/Concomitant Therapy

14. **Drugs and supplements:** Use of a strong inhibitor of CYP2C8 (e.g., gemfibrozil) or a strong inducer of CYP2C8 (e.g., rifampin/rifampicin).

Prior/Concurrent Clinical Study Experience

15. **Severe allergic reactions:** History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (refer to daprodustat IB), or epoetin alfa (refer to product labeling).
16. **Other interventional study participation:** Use of another investigational agent within 30 days or within five half-lives of the investigational agent (whichever is longer) or currently participating in a study of an investigational device prior to screening through to randomization (Day 1).
17. **Prior treatment with daprodustat:** Any prior treatment with daprodustat for treatment duration of >30 days.

Other Exclusions

18. **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 (e.g., intolerance to rhEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study.

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 7.7.2.

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 SAEs.

Participants who do not meet the criteria for participation in this study (i.e., screen failure) may be rescreened up to two additional times as soon as the investigator assesses they may meet eligibility criteria. Participants who are to be rescreened must sign a new informed consent form and will be assigned a new participant number. The association between the initial/prior screening participant number and the new participant number must be documented.

6.5. Participant Retention

- Participants will be educated on the importance of remaining in the study and attending scheduled study visits.
- Investigators should make every effort to keep participants in the study, including those participants who have permanently discontinued study treatment.

- Should a participant fail to attend the clinic for a required study visit, the site should attempt to contact the participant and re-schedule the missed visit as soon as possible. The site should also counsel the participant on the importance of maintaining the assigned visit schedule. In cases where the participant does not return for the rescheduled visit, or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the participant. The investigator (if allowed by local regulations) should obtain the name and phone number of a relative or friend to assist in contacting the participant.

7. TREATMENTS

Study treatment is defined as the investigational treatment or marketed product (i.e., daprodustat, matching placebo tablets, epoetin alfa or saline) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

GSK will provide the following study treatments: daprodustat and matching placebo tablets and epoetin alfa. Saline will be obtained locally. Study treatments are described in Table 3.

Table 3 Description of Study Treatments

Study Treatment Name:	Daprodustat	Matching Placebo Tablets	Epoetin alfa	Saline
Dosage formulation:	Round, biconvex, white, film-coated tablet	Round, biconvex, white, film-coated tablet	Single-dose, preservative-free vials	Saline for IV use vials or bags
Unit dose strengths/ Dosage levels:	Unit dose strengths: 7 mm tablets: 2 and 4 mg 9 mm tablets: 6, 8 and 10 mg Dosage levels: 2, 4, 8, 12, 16, 20, 24, 32 and 48 mg Dosages of 12 mg and greater will be provided using multiples of available tablet strengths. Details are provided in Table 5.	7mm tablets to match 2 and 4 mg daprodustat tablets 9 mm tablets to match the 6, 8 and 10 mg daprodustat tablets Dosage details are provided in Table 5.	Unit vial strengths: 2000, 3000, 4000 and 10,000 Units/mL Dosage level details are provided in Table 6.	0.9% sodium chloride Saline for IV use will be obtained locally; vial or bag size will vary. Dosage details are provided in Table 6.

Route of Administration	Oral	Oral	Intravenous	Intravenous
Dosing instructions:	Participants will be dispensed the prescribed number of tablets. The dose will be administered on a dialysis day, and may be given before, during or after the dialysis session. Participant may take dose at home prior to PD sampling visit. Participants will take tablets with water and can be taken without regard to food.	Participants will be dispensed the prescribed number of tablets. The dose will be administered on a dialysis day, and may be given before, during or after the dialysis session. Participant may take dose at home prior to PD sampling visit. Participants will take tablets with water and can be taken without regard to food.	Site staff will withdraw the prescribed dose from each single-use vial into a syringe. Multiple vials may be required to achieve the prescribed dose. The dose will be administered to the participant during the dialysis session.	Site staff will withdraw the prescribed dose into syringe(s). The dose will be administered to the participant during the dialysis session.
Packaging and Labeling	Tablets 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.	Tablets 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.	Epoetin alfa will be provided in single-use, preservative-free vials. Each vial will be labeled as required per country requirement.	Not applicable (Saline for IV use will be obtained locally.)
Manufacturer	GlaxoSmithKline	GlaxoSmithKline	Janssen	Not available (Saline for IV use will be obtained locally)

Participants will discontinue their therapy with rhEPO or its analogs prior to randomization so that the randomization date (Day 1) coincides, as closely as possible, with the date of next scheduled administration of rhEPO or analog. Examples of switching will be provided in the SRM.

All study treatments should be taken in the clinic, with the exception that the blinded study treatment tablets may be taken at home prior to the study visit at which PD samples will be collected (see Section 9.6). The site must ensure that the date and time the participant took each dose of study treatment is documented. Participants will be given diary cards to record the date and time of any study treatment tablets taken at home. Additional instructions can be found in the SRM.

7.2. Starting Dose and Dose Modification

Participants will be randomized to receive either daprodustat or epoetin alfa.

In order to maintain the treatment blind, each participant will be administered both tablets and IV injections, with one formulation containing active study treatment and the other formulation being an inactive treatment. Refer to Section 7.4 for additional information regarding blinding.

Participants who are randomized to the daprodustat arm will receive the required number of daprodustat tablets to achieve the prescribed dosage of daprodustat based upon the starting dose and dose adjustment algorithms (see Section 7.2.1), and the required number of syringes with saline for IV administration to achieve the prescribed inactive treatment (see Section 7.2.2.2).

Participants who are randomized to the epoetin alfa arm will receive the required number of vials of epoetin alfa to achieve the prescribed dosage of epoetin alfa based upon the starting dose and dose adjustment algorithms (see Section 7.2.2), and the required number of placebo tablets to achieve the prescribed inactive treatment (see Section 7.2.1.2).

The dose of both study treatments will be adjusted, based on the algorithm in Section 7.2.3, in order to maintain Hgb concentrations in the target range. Any required dose adjustments should be started on the day of the study visit at which the dose adjustment was prescribed. In circumstances where a new supply of study treatment (including a new dose) cannot be dispensed on the day of the study visit, the new supply of study treatment can be dispensed at the next dialysis session, and the prior study treatment should be continued unless on a dose interruption.

7.2.1. Participants Randomized to Daprodustat

Participants who are randomized to the daprodustat treatment arm will receive daprodustat tablets and saline IV. A starting dose will be assigned for daprodustat as described in Table 4. A starting dose will be assigned for saline, following the algorithm described for epoetin alfa in Section 7.2.2.1. Dose levels will be titrated for both the active and inactive study treatments, and new containers dispensed for each treatment with each change in dose.

7.2.1.1. Daprodustat Starting Dose

The starting dose of daprodustat will be assigned based on prior rhEPO or analog dose at randomization, Day 1 (Table 4).

Table 4 Daprodustat Starting Dose

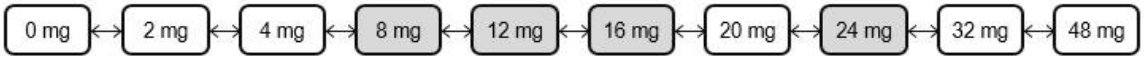
RhEPO or Analog Dose at Randomization (Day 1)			Daprodustat Dose
Epoetins (including biosimilars) (U/week IV) [1]	Darbepoetin (μg/4week SC/IV) [2]	Methoxy PEG-Epoetin beta (μg/month SC/IV) [3, 4]	(mg, three-times weekly)
1500 to 2000	20 to 30	30 to 40	8
> 2000 to < 10000	>30 to 150	>40 to 180	12
≥ 10,000 to < 20000	>150 to 300	>180 to 360	16
≥ 20,000	>300	>360	24

PEG=polyethylene glycol

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

7.2.1.2. Daprodustat (and Placebo) Titration Doses

The available dose steps of daprodustat are outlined below (gray toned boxes indicate possible starting doses). Dose adjustments will result in the daprodustat dose being increased or decreased by one dose step at a time, as described in the dosing algorithm (Table 7). Participants who are receiving the highest dose of daprodustat (48 mg) and require an additional dose increase, will maintain the same dose. Participants who are receiving the lowest dose of daprodustat (2 mg) and require an additional dose decrease will receive placebo (0 mg) in order to maintain the blind. When a dose interruption is required by the dosing algorithm (Table 7), both daprodustat tablets and saline injections will be interrupted in order to maintain the blind.



Participants who are randomized to daprodustat treatment will also receive inactive treatment for the IV formulation (saline IV). When a dose adjustment is required for these participants, their saline IV dose will be adjusted (in addition to the daprodustat dose) in order to maintain the blind, such that the number of syringes of saline to be administered match the number of vials/syringes required for the new corresponding epoetin alfa dose (Section 7.2.2.2, Table 6).

Table 5 Tablet Combinations to Achieve Prescribed Daprodustat or Placebo Treatment

Dosage Level [1] (mg)	Total Number of Tablets	Active Treatment for Daprodustat Randomized Participants						Inactive (Placebo) Treatment for Epoetin Alfa Randomized Participants	
		7 mm Placebo	2 mg Dapro	4 mg Dapro	6 mg Dapro	8 mg Dapro	10 mg Dapro	7mm Placebo	9 mm Placebo
0	1	1						1	
2	1		1					1	
4	1			1				1	
8	1					1			1
12	2				2				2
16	2					2			2
20	2						2		2
24	3					3			3
32	4					4			4
48	6					6			6

1. Dose to be administered three-times weekly

7.2.2. Participants Randomized to Epoetin Alfa

Participants who are randomized to the epoetin alfa treatment arm will receive placebo tablets and epoetin alfa IV. A starting dose will be assigned for epoetin alfa as described in Section 7.2.2.1. A starting dose will be assigned for placebo, following the algorithm described for daprodustat in Table 4, and as shown in Table 5. Dose levels will be titrated for both the active and inactive study treatments, and new containers dispensed for each treatment with each change in dose.

7.2.2.1. Epoetin Alfa Starting Dose

The starting dose(s) for participants receiving epoetin alfa are as follows:

- For participants with a Day 1 Hgb ≤11.0 g/dL:
  - For participants already on epoetin alfa the starting dose will be the same as their currently scheduled dose, rounded to the nearest available study treatment dose.
  - For participants receiving rhEPO analogs, the starting dose will be an IV epoetin alfa equivalent dose rounded to the nearest available study treatment dose. (Refer to Table 4 for conversion factors to determine equivalent epoetin alfa doses.)
- For participants with a Day 1 Hgb >11.0 g/dL and ≤11.5g/dL:
  - For participants already on epoetin alfa the starting dose of IV epoetin alfa will be reduced from their current scheduled dose, rounded to the nearest study treatment dose, to the next lower available dose with the aim of maintaining Hgb within the range of 10.0 to 11.0 g/dL.

- For participants receiving rhEPO analogs, the starting dose of IV epoetin alfa will be reduced from their current scheduled rhEPO analog equivalent dose, rounded to the nearest study treatment dose, to the next lower available dose of IV epoetin alfa with the aim of maintaining Hgb within the range of 10.0 to 11.0 g/dL. (Refer to Table 4 for conversion factors to determine equivalent epoetin alfa doses.)

7.2.2.2. Epoetin Alfa (and Saline) Titration Doses

Pre-defined dose steps of epoetin alfa are outlined in Table 6. Dose adjustments of epoetin alfa will be made by increasing or decreasing the dose one step at a time, as described in the dosing algorithm (Table 7). The epoetin alfa dose steps consist of a weekly dose change between 20 to 33% for most steps, except for an increase to a weekly dose of 3000 U, which is a 50% increase, or an increase to doses of 21,000 U per week or greater, which represent increases of approximately 10 to 15%.

Participants who are receiving the highest dose of epoetin alfa (i.e., 60,000 U/week) and require a dose increase will maintain the same dose. Participants who are receiving the lowest available dose of epoetin alfa (i.e., 1500 U/week IV) and require a dose decrease will receive saline in order to maintain the blind. When a dose interruption is required by the dosing algorithm (Table 7), both epoetin alfa and placebo tablets will be interrupted in order to maintain the blind.

Participants who are randomized to epoetin alfa treatment will also receive inactive treatment for the tablet formulation (placebo tablets). When a dose adjustment is required for these participants, their placebo tablet dose will be adjusted (in addition to the epoetin alfa dose) in order to maintain the blind, such that placebo tablets matching the new corresponding daprodustat dose will be administered (Table 5).

Additional information about the delivery of the respective epoetin alfa doses is provided in the SRM.

Table 6 Number of Vials and Vial Combinations to Achieve Prescribed Epoetin Alfa or Saline Treatment

Total Weekly Dose (Units)	Dose and Frequency	Epoetin Alfa Randomized Participants [1]					Inactive (Saline) Treatment for Daprodustat Randomized Participants
		Saline [3] (1 mL)	2000 U/ 1mL	3000 U/ 1mL	4000 U/ 1mL	10000 U/ 1mL	Saline [3] (1 mL)
0	0 U once a week	1					1
1500 [4]	1500 U once a week		0.75				0.75
2000	2000 U once a week		1				1
3000	3000 U once a week			1			1
4000	4000 U once a week		2				2
5000	5000 U once a week		1	1			2
6000	6000 U once a week		1		1		2
8000	8000 U once a week				2		2
10,000	10,000 U once a week		1		2		3
12,000	4000 U three times a week				1		1
15,000	5000 U three times a week		1	1			2
18,000	6000 U three times a week		1		1		2
21,000	7000 U three times a week			1	1		2
24,000	8000 U three times a week				2		2
27,000	9000 U three times a week		1	1	1		3
30,000	10,000 U three times a week					1	1
36,000	12,000 U three times a week		1			1	2
42,000	14,000 U three times a week				1	1	2
48,000	16,000 U three times a week		1		1	1	3
60,000	20,000 U three times a week					2	2

1. The vial combinations used to achieve a specific weekly dose of epoetin alfa (and number of saline syringes for the corresponding inactive dose) may be adjusted by the sponsor based on changes to the commercial availability of epoetin alfa or other supply considerations. Any change to the vial combinations will be made globally across the study in order to maintain the blind, and it will be managed centrally through the IRT system. Details of any changes will be detailed in the SRM.
2. Each epoetin alfa vial should be administered using a separate syringe.
3. For saline doses, the number of 'vials' indicated in the table refers to the number of syringes containing 1 mL of saline that will be administered in order to maintain the blind.
4. The 1500 U epoetin alfa dose will be achieved by administering 0.75 mL of a 2000 U/mL vial. The corresponding 1500 U saline dose, for daprodustat randomized participants, will be achieved by administering 0.75 mL of saline.

7.2.3. Daprodustat and Epoetin Alfa Dose Adjustment Algorithm

The dose adjustment algorithm for both daprodustat and epoetin alfa is provided in Table 7. Dose adjustments, i.e., increase, decrease, maintain, or interrupt if Hgb ≥12g/dL, will be determined programmatically for both the daprodustat and epoetin alfa arms by an Interactive Response Technology (IRT) system to maintain Hgb concentrations within the range of 10.0 to 11.0 g/dL based on the HemoCue Hgb value measured every 2 or 4 weeks, as specified in the SoA, and entered into the IRT by the Investigator or site staff.

When a dose adjustment is indicated, the dose of the active and inactive treatments will be titrated in order to maintain the blind, as described in Section 7.2.1 and Section 7.2.2.

Table 7 Study Treatment Dose Adjustment Schemes

HemoCue Hgb (g/dL) at current study visit [1]	HemoCue Hgb change since last study visit [1]	Randomized Treatment Dose Adjustment [5]
<7.5 [2]	Any change	Repeat Hgb and average values [6]; if confirmed, increase to the next higher dose step
7.5 to <9.5	Decreasing or No change [7]	Increase to the next higher dose step
7.5 to <9.5	Increasing [8]	Maintain dose
≥9.5 to <10 at two consecutive visits	Decreasing or No change	Increase to the next higher dose step
≥9.5 to ≤11.5	Any change	Maintain dose
>11 to ≤11.5 at two consecutive visits	Increasing or No change	Decrease to the next lower dose step
>11.5 to <12	Decreasing	Maintain dose
>11.5 to <12	Increasing or No change	Decrease to the next lower dose step
≥12 [3]	Any change	Repeat Hgb and average values [6]; if confirmed, temporarily interrupt the dose and re-check Hgb at next study visit [1]; restart at one dose step lower when Hgb <11.5 g/dL and provided it has been at least 2 weeks from the prior study visit.
Any	>2 g/dL increase over 4 weeks (>1 g/dL increase over 2 weeks [4])	Repeat Hgb and average values [6]; if confirmed, decrease to the next lower dose step
Any	>2 g/dL decrease over 4 weeks (>1 g/dL decrease over 2 weeks [4])	Repeat Hgb and average values [6], if confirmed, increase to the next higher dose step

1. Study visit refers to scheduled visits, i.e., every 2 weeks until Week 8, and then every 4 weeks through Week 52.
2. This rule applies to any scheduled visit 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. This rule applies to Week 2 through Week 8 visits only.
5. 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 receive inactive study treatment (placebo/saline).
6. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample) and take average.
7. No change may be redefined as an increase of <0.5 g/dL based on review of blinded instream Hgb data from the 200807 study/ASCEND program.
8. Increasing may be redefined as an increase of ≥0.5 g/dL based on review of blinded instream Hgb data from the 200807 study/ASCEND program.

Adjustments to the algorithm outlined in Table 7 may be implemented by the sponsor in order to maintain consistency with the 200807 study, if similar adjustments are made to the algorithm across the ASCEND program.

7.2.4. Temporary Study Treatment Interruption

Every effort must be made to attend study visits and to continue study treatment; however, the site should contact GSK if a participant cannot return to the site on a temporary basis for any reason, including hospitalization, or in case of any unforeseen issue that prevents a participant from receiving study treatment.

In exceptional circumstances, local standard of care for anemia management during this time may be considered based on consultation with the GSK medical monitor. If any non-study rhEPO or analogs are administered, doses should be recorded in the electronic case report form (eCRF).

Participants should return for study visits and restart administration of study treatment as soon as possible, unless the situation warrants permanent discontinuation of study treatment per Section 8.1.

7.3. Method of Treatment Assignment

Randomization will be stratified by region, as defined in Appendix 7, and participants will be assigned in a 2:1 ratio to either the daprodustat or epoetin alfa treatment arm, respectively, in accordance with the randomization schedule. The randomization schedule will be computer generated by Pharmaceutical Product Development, LLC (PPD) prior to the start of the study, using the validated randomization system Prism.

Participants will be randomized centrally using an Interactive Response Technology (IRT) system. Once a randomization number has been assigned by the IRT system, it must not be re-assigned.

Before the study is initiated, the telephone number and/or the log-in information and directions for the IRT system will be provided to each site.

Study treatment will be dispensed at the study visits summarized in SoA.

7.4. Blinding

This is a double-blind study, in which the participant, investigator, site staff and the sponsor will remain blinded to each participant's study treatment assignment throughout the course of the study, with the exception of a limited number of unblinded site staff who are necessary to maintain the blind, as well as a limited number of sponsor staff. The dose level of each study treatment (tablet and IV formulations) will not be blinded. A detailed Blinding Plan will describe the procedures that will be implemented in order to minimize the extent to which the treatment assignment blind may be compromised.

In order to maintain the blind to the treatment assignment given the formulation differences between the study treatments, each participant will receive both a tablet formulation and an IV formulation, of which one is an active treatment and the other is inactive. For each participant, both the tablet and IV formulations (active and inactive treatments) will be dose adjusted based upon hemoglobin values as described in Section 7.2.

In order to maintain the blind, unblinded site staff (e.g., study coordinator, nurse, or pharmacist) will be responsible for the handling, dispensation and preparation of unblinded study treatment (i.e., IV). Administration of study treatment will be done in a blinded fashion (e.g., IV formulation in blinded syringe) and may be performed by blinded site staff or unblinded site staff if required due to logistical considerations. To the extent possible, the unblinded site staff will take precautions during the dispensation and preparation of epoetin alfa and saline IV injections to minimize any risk of compromising the blind. Any discussion about study treatment that may occur between unblinded site staff and blinded individuals will occur in a blinded fashion. In situations where study treatment can be handled, dispensed or administered in a blinded fashion (e.g., tablets in blinded containers, IV formulation in blinded syringe), blinded site staff may perform that specific task. Further details and requirements for maintaining the blind are described in the Blinding Plan.

There will be a separate, unblinded sponsor team (e.g., study manager and medical monitor) with whom the unblinded site staff (e.g., study coordinator or nurse) will interact and communicate any study issues. Unblinded site staff will not communicate directly with any blinded sponsor personnel.

Unblinded monitors and the auditor(s), in the event of a Quality Assurance audit, will be allowed access to unblinded study treatment records at the site(s) to verify that randomization and dispensing has been done accurately.

The IRT will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. 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 (e.g., antidote is available). In this case, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

If a participant's treatment assignment is unblinded, that participant may remain in the study, and may continue study treatment if appropriate.

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.

7.5. Preparation/Handling/Storage/Accountability

The unblinded site staff (e.g., nurse, study coordinator) 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. Only authorized site staff may handle, prepare or administer study treatment, as described in Section 7.4. In order to maintain the blind (with respect to the participant, investigator and blinded site staff), careful consideration will be given to which site staff will be authorized to perform study treatment related tasks, in particular tasks involving unblinded study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized unblinded site staff. **Maintenance of a temperature log (manual or automated) is required.**

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records). In this study, in order to maintain the blind, unblinded site staff will perform study treatment accountability, reconciliation, and record maintenance during the conduct of the study. Further information related to blinding is provided in Section 7.4.

Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

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) or 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

Participants will be dosed with daprodustat and placebo tablets at the site, and will receive study treatment directly from the site staff, with the exception that a participant may dose with blinded study treatment tablets at home in preparation for the collection of PD samples (see Section 9.6). Epoetin alfa and saline will be intravenously administered to participants at the site. The details, including the date and time, of each dose administered in the clinic will be recorded in the source documents. Study treatment dosing details, including date and time, and dates for study treatment interruptions will be recorded in the eCRF.

When participants self-administer study treatment at home, i.e., blinded study treatment tablets taken prior to the collection of PD samples, compliance with daprodustat/placebo tablets will be assessed through querying the participant during the site visits and documented in the source documents and eCRF. In addition, the participant will be given a diary card to record the dose taken at home. A record of the number of blinded study treatment tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records.

7.7. 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 in the eCRF, including the start and end dates of administration, the reason for use, and the route of administration.

Additional details (e.g., dose and frequency, changes in dose, reason for change, reason for addition or termination) will be recorded for certain medications at each visit (e.g., iron and anti-hypertensive medications).

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

7.7.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 7.7.2, all concomitant medications should be considered permitted provided they are not contraindicated for the individual participant concerned.

Co-administration of daprodustat with moderate CYP2C8 inhibitors (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should subsequently be monitored every 4 weeks for the following 12 weeks.

7.7.2. 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 study treatment is prohibited and will constitute a protocol violation.

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

No other investigational treatments or investigational devices are permitted from screening (Week -4) until completion of the last study visit (or withdrawal from study), with the exception of the study treatments administered for this study.

7.8. 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) guidelines or local equivalent (e.g., phosphate and albumin).

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

7.8.1. Iron Management Criteria

Participants must remain iron replete throughout the study. The investigator will follow the iron management criteria from randomization (Day 1) through Week 52 for participants who are receiving study treatment.

From Day 1 onwards, iron therapy will be administered if ferritin is ≤100 ng/mL and/or TSAT is ≤20%. The investigator should choose the route of administration and dose of iron based on the participant's iron status and local clinical practice.

All iron (excluding multivitamins) must be stopped and cannot be administered if:

- Ferritin >800 ng/mL and TSAT >20%, or
- TSAT >40%

Investigators should be guided by local/regional guidelines and may stop administration of iron at a lower ferritin or TSAT level as long as participants are maintained at a ferritin >100 ng/mL and TSAT >20%.

7.9. Rescue Therapy

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 8.

This rescue algorithm **does not** apply to participants with a low Hgb as a result of an acute or subacute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery or from their vascular access). In these cases, treatment should be directed to the specific cause and study treatment will be continued. If a participant is transfused as part of the treatment, then study treatment will be maintained at the current dose (unless Hgb is ≥12 g/dL which requires a dose hold).

Table 8 Rescue Algorithm for Anemia Management

Evaluate Participant for Rescue if: • HemoCue Hgb remains <9 g/dL (at a scheduled study visit, Week 4 onwards) despite three [1] consecutive dose increases above the starting or post-rescue [2] dose (where HemoCue Hgb is <9 g/dL prior to each dose increase), or • HemoCue Hgb is <7.5 g/dL [3] despite a dose increase at the prior study visit [4].	
Step 1: **Initial Intervention**	The following actions will be taken for the initial intervention: • Continue with study treatment (increase dose if HemoCue Hgb <7.5 g/dL; otherwise maintain current dose) • A single course of IV iron up to 1000 mg, in addition to following the iron management criteria (Section 7.8.1), if clinically indicated. • Transfusion of up to two units of packed red blood cells (PRBC), if clinically indicated. At the next study visit, in 4 ± 1 weeks after the initial intervention, recheck HemoCue Hgb as described below in Step 2 (Rescue). Earlier checks of HemoCue Hgb may be obtained to advise further intervention as clinically indicated.

Step 2:
Rescue
	• Check HemoCue Hgb 4 ± 1 weeks after the initial intervention
	• **Study treatment should be permanently discontinued and the participant should be rescued according to local clinical practice:**
	  • If HemoCue Hgb remains <9 g/dL, despite initial intervention, based on the average of two HemoCue Hgb values [3], or
	  • If more than two units of PRBC were needed for transfusion (and was not related to acute bleeding).
	The participant will remain in the study, and follow the visit schedule in SoA, Table 2.

1. Two consecutive dose increases if starting/post-rescue dose is daprodustat/placebo 24 mg or epoetin alfa/saline 42000 U per week; one dose increase if starting/post-rescue dose is daprodustat/placebo 32 mg or epoetin alfa/saline 48000 U per week; and no prior dose increase if starting/post-rescue dose is daprodustat/placebo 48 mg or epoetin alfa/saline 60000 U per week (top dose). This criterion applies to both study treatments for each participant, and is met when either study treatment reaches one of the specified doses; if both, then follow criteria based on highest dose level.
2. For participants who were previously evaluated for rescue and who are able to continue in the trial, "post-rescue" dose is the dose of study treatment that a participant is receiving at the study visit after the initial intervention.
3. Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample); take average of 2 values.
4. A dose increase at the prior study visit is not required, if the dose was already at the top dose (daprodustat/placebo 48 mg or epoetin alfa/saline 60000 U per week).

The study site will supply the rescue medication, which will be obtained locally.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7.10. Participants Changing Dialysis Modality

Participants changing dialysis modality from hemodialysis (includes hemodiafiltration and hemofiltration) to peritoneal dialysis or home hemodialysis will discontinue study treatment, and should be treated according to local clinical practice and standard of care (see Section 8.1). The participant will remain in the study, unless consent is withdrawn, and will follow the SoA, Table 2, for participants permanently discontinuing study treatment.

7.11. 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

A participant may permanently discontinue study treatment at any time at his or her own request, or at the discretion of the investigator for safety or compliance reasons. A participant must permanently discontinue study treatment for any of the pre-specified reasons below:

- Participant receives a kidney transplant
- Participant meets the criteria (Step 2 of algorithm) to receive rescue therapy (Section 7.9)
- Participant becomes pregnant or intends to become pregnant during the study.
- Liver chemistry abnormalities exceed the threshold criteria (Section 8.1.2)
- Diagnosis of cancer (new or recurrent), with the exception of localized squamous cell or basal cell carcinoma of the skin.
- Participant switches dialysis modality to peritoneal dialysis or home hemodialysis, or is switched to a standing dialysis schedule that is less often than three-times weekly.
- Need for more than 14 days use of a prohibited medication (Section 7.7.2)

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. Procedures Following Discontinuation of Study Treatment

Participants who permanently discontinue study treatment will remain in the study. Participants will be asked to attend an Early Treatment Discontinuation visit and will be expected to attend study visits according to the SoA, Table 2, unless consent is actively withdrawn.

- Early Treatment Discontinuation visit: This visit should occur within 2 weeks of stopping study treatment.
- Remaining in-clinic visits: Study visits at Weeks 4, 16, 28, 40 and 52. Phone visit is acceptable in exceptional circumstances.

If a participant does not agree to continue attending in-clinic or phone visits, other follow-up options to collect study outcomes and vital status for up to 52 weeks after the participant's randomization visit should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the participant, then the participant will be considered to have remained in the study and not to have withdrawn consent.

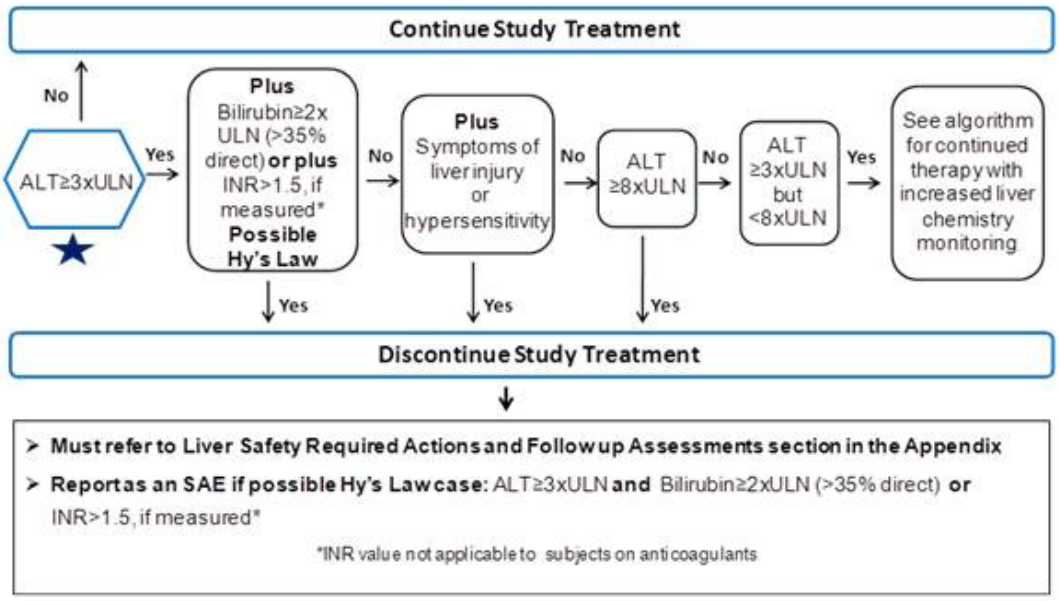
8.1.2. Liver Chemistry Stopping Criteria

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

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

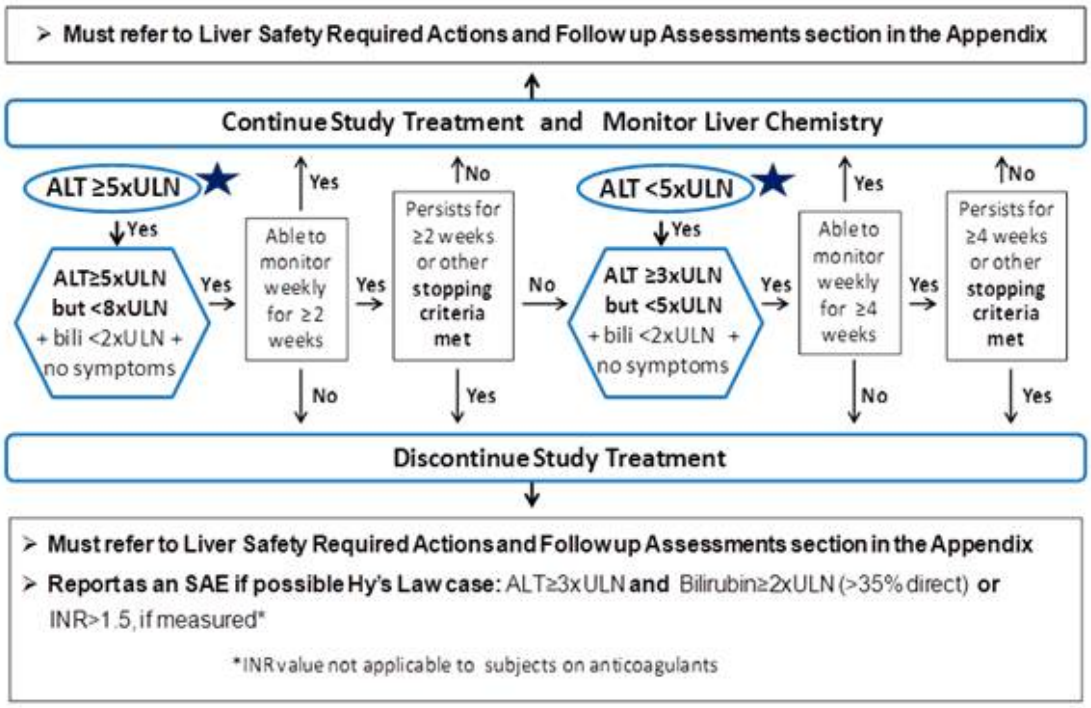
- A participant meets one of the conditions outlined in the algorithm.
- In the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes that study treatment discontinuation is in the best interest of the participant.

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 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 Appendix 6.

8.1.3. Study Treatment Restart

If participant meets liver chemistry stopping criteria, do not restart study treatment unless there is a clear underlying cause for the elevated liver enzymes other than drug-induced liver injury, and the following requirements are met:

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

Refer to Appendix 6 for full guidance.

8.2. Withdrawal from the Study

Every effort should be made to keep participants in the study. For participants that choose to withdraw consent or are lost to follow up, the reason for not completing the study will be recorded in the participant's eCRF.

- A participant may withdraw from the study at any time at his or 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 or 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 discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1. Withdrawal of Consent for Contact

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 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.

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 investigator should make every effort to contact any participant who has failed to attend a required study visit, and who has not withdrawn consent to follow-up contact.

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

- 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, 3 telephone calls and, if necessary, a 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.
- As permitted by local regulations, a third party may be used to obtain alternative participant contact information that will be provided to the investigator. All attempts to contact the participant will be documented in the participant's source notes and a final status contact will be recorded in the eCRF.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2). Pre-dialysis assessments should be performed in the following order, where applicable: patient reported outcomes, ECG, BP/HR, blood sample collection.
- Protocol waivers or exemptions are not allowed.
- 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.
- All visits should be referenced back to the Randomization visit (Day 1). The allowable visit window is ±3 days for Week 2 to Week 8 visits, and ±1 week for all other visits; however, 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.
- Because Hgb levels become more variable with increased time between dialysis sessions, the designated study visit should occur during the dialysis session with the shortest interval from the previous session. For participants on a three- to five-times weekly dialysis schedule, the designated study visit must not occur on the first dialysis session of the week, i.e., the dialysis session immediately following the longest interval between dialysis sessions. For example, if on a Monday-Wednesday-Friday schedule, the study visit should be on Wednesday or Friday.

- Procedures conducted as part of the participant's routine clinical management (e.g., renal and adrenal gland ultrasound) and obtained before signing of the 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 not exceed 375 mL. This blood volume does not include any repeat or unscheduled samples that may be taken.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- 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. Efficacy Assessments

- Planned time points for all Hgb efficacy assessments are listed in the SoA (Section 2).
- GSK will supply a point-of-care Hgb analyzer (i.e., HemoCue) to each site for rapid Hgb measurements. Further details about the HemoCue device are provided in the SRM.
- Blood samples for measurement of Hgb concentrations via HemoCue and also by the central laboratory will be collected as specified in the SoA (Section 2).
- Central laboratory Hgb values will be used for the primary efficacy analyses. HemoCue Hgb values may be used if central laboratory Hgb values are missing. Further details about handling of missing data are provided in the RAP.

9.2. Adverse Events

The definitions of an AE or SAE can be found in 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 study treatment (see Section 8).

Events should be reported as an AE or SAE according to the definitions in Appendix 3.

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of study 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 participant consents to participate in the study.

- All AEs will be collected from the start of 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 case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor 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 the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. 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 9.2.7), 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 Appendix 3.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE 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.
- The sponsor 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. The sponsor 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 sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Events Referred to the Clinical Events Committee

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

- All-cause mortality (CV and non-CV mortality)
- Hospitalization for heart failure
- Non-fatal MI
- Non-fatal stroke
- 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 of the event differ, the CEC's decision will be considered final. The detailed descriptions of the endpoint definitions used for adjudication are contained within the CEC Charter (available on request).

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

9.2.6. Other CV Events

GSK has identified other CV events of interest for all clinical studies. Investigators will be required to fill out the specific CV event page of the eCRF for the following CV AEs and SAEs or any event that may potentially be one of the categories listed:

- Arrhythmias
- Pulmonary hypertension (also an AE of special interest, see Section 9.2.7).
- Valvulopathy
- Revascularization

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 eCRF within one week of receipt of a CV Event data query prompting its completion.

9.2.7. 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, myocardial infarction (MI), stroke, heart failure, thromboembolic events, thrombosis of vascular access (see also Section 9.2.5)
- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis
- Cardiomyopathy
- Pulmonary artery hypertension (see also Section 9.2.6)
- Cancer-related mortality or tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

The results of any investigation should be recorded on the AE or SAE page, as appropriate, and the relevant AE of special interest page of the participant's eCRF.

9.2.8. 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 and SAE pages, as appropriate).

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

9.2.9. 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 GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

There is no specific antidote for overdose with daprodustat. The expected manifestations of a daprodustat overdose include signs and symptoms associated with an excessive or rapid increase in Hgb concentration. Daprodustat is highly protein bound; thus, clearance of daprodustat by dialysis is very low and these are not effective methods to enhance the elimination of daprodustat. Daprodustat metabolites are, in part, cleared via dialysis. 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 HR, and hematologic abnormalities.

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

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

Safety endpoints will include monitoring of safety events including deaths (Section 9.2.5), other CV events (Section 9.2.6), AEs of special interest (Section 9.2.7), AEs, SAEs and AEs leading to discontinuation of randomized treatment, laboratory parameters, BP and HR.

Pre-specified events leading to permanent discontinuation of randomized treatment are described in Section 8.1. Liver chemistry stopping and follow-up criteria are described in Section 8.1.2 and Appendix 6.

9.4.1. Height and Weight

- Height and weight will be measured as specified in the SoA (Section 2). Weight will be measured with the participant wearing indoor daytime clothing with no shoes. Weight will be measured pre- and post-dialysis.
- Estimated dry weight (EDW) will be reported at each study visit as specified in the SoA (Section 2).

9.4.2. Blood Pressure and Heart Rate

Measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR will be taken at the time points specified in the SoA (Section 2).

- On Day 1, Week 52, and at the Early Treatment Discontinuation visit (if applicable), BP and HR will be measured in triplicate. At all other visits, single measurements will be taken.
- Measurements will be taken both pre-dialysis and post-dialysis.
- Measurements will be taken with the participant in a semi-supine or seated position in the dialysis chair after at least a 5-minute rest period, pre- and post-dialysis.

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

9.4.3. 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).
- For the screening (Week -4) ECG, which may be conducted anytime between the Week -4 visit and the Day 1 visit, two additional ECGs are required if the screening 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 over-read locally by a physician with experience in reading and interpreting ECGs. The over-read of the screening ECG is required to confirm eligibility. Additional details are provided in the SRM.
- ECGs that are performed prior to dialysis will be performed **before** measurement of SBP, DBP, and HR and **before** collection of blood samples for laboratory testing, where applicable (e.g., would not apply if ECG is performed post-HD).

9.4.4. Ultrasound

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

A documented ultrasound of the kidneys within 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.

9.4.5. Clinical Laboratory Assessments

- Refer to Table 9 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. Details for the preparation and shipment of samples are detailed in the SRM.
- The tests detailed in Table 9 will be performed by a central laboratory with the exception of HemoCue Hgb which will be performed at the clinical site. The results of each HemoCue Hgb assessment must be entered into the participant's eCRF.
- Blood samples for clinical laboratory tests will be collected prior to dialysis.
- 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 considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal or 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 9, must be conducted in accordance with the laboratory manual and the SoA (Section 2).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Analyte results that could unblind the study (e.g., EPO) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Table 9 Protocol Required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count	*RBC indices:*	*WBC count with Differential:*
	RBC count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	MCHC	Monocytes
	Reticulocyte count	RDW	Eosinophils
			Basophils
Clinical Chemistry [1]	Potassium (serum)	AST	Albumin (serum)
	Calcium (total and albumin-adjusted)	ALT	Urea (serum)
	Inorganic phosphate	Bilirubin (total, direct and indirect)	
Iron parameters	Iron (serum)	Ferritin	UIBC
	Hepcidin [2]	TIBC	TSAT
Lipid parameters	Total cholesterol	LDL-C (direct)	HDL-C
Other laboratory tests	Serum pregnancy test [3]	hsCRP	HemoCue Hgb
	Estradiol [4]	iPTH	Stored sample (blood) [6]
	FSH [4]	Erythropoietin (EPO)	
	HbA1c [5]	Vascular Endothelial Growth Factor (VEGF)	

WBC, white blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; AST, aspartate transaminase; ALT, alanine transaminase; UIBC, unbound iron binding capacity; TIBC, total iron binding capacity; TSAT, transferring saturation; LDL-C, low density lipoprotein-C; HDL-C, high density lipoprotein-C;

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.2 and Appendix 6.
2. At each visit specified in SoA, Section 2, a sample for hepcidin will be collected prior to dosing with either study treatment and prior to administration of any iron supplementation.
3. For women of child-bearing potential (WOCBP) only.
4. Screening only. As needed in postmenopausal women where their menopausal status is in doubt (see Inclusion Criteria Section 6.1).
5. Only participants with diabetes.
6. Refer to Section 9.8.

9.5. Pharmacokinetics

Pharmacokinetic (PK) samples will be collected for measurement of plasma concentrations of daprodustat and its predominant metabolites. In order to maintain the blind, samples relative to the tablet formulation will be taken for all participants, regardless of treatment assignment. Only samples from participants who are randomized to daprodustat will be analyzed.

Blood samples (6 in total) will be collected at the Day 1 visit pre-dose and at any one post-baseline visit between Week 8 and Week 52, inclusive, as specified in the SoA (Section 2), preferably at the earliest opportunity. The post-baseline samples will be collected at pre-dose and 0.5, 1, 2 and 3 hours post-dose. The actual date and time (24-

hour clock time) of each sample will be recorded. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up).

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded sponsor personnel until the study has been unblinded.

The post-baseline PK visit can be repeated if necessary to obtain evaluable PK samples, e.g., samples from initial PK visit are damaged and not evaluable.

9.5.1. PK Visit

On the day of the scheduled (post-baseline) PK visit:

- The participant will take the required dose of study treatment tablets in the clinic after the pre-dose sample is collected.
- The participant must not be on a dose interruption or be receiving a dose of 0 mg (tablets). If the participant's study treatment is interrupted or decreased to a 0 mg on the day of the planned PK visit, then the PK samples should be collected at the next possible study visit up to Week 52, inclusive.
- Record the date and actual time that the study treatment tablets were taken in the clinic, and the date and actual time of all PK samples collected. Samples may be collected within ± 20 minutes of the planned collection time.
- Based on the time of dosing, samples may be obtained before, during, or after any dialysis procedure. The start and stop time of the dialysis procedure will also be recorded at this visit.

Plasma PK analysis will be performed under the control of GSK PTS-IVIVT-BIB, the details of which will be included in the SRM. Concentrations of parent daprodustat and metabolites (GSK2391220 [M2], GSK2506104 [M3], GSK2487818 [M4], GSK2506102 [M5], GSK2531398 [M6], and GSK2531401 [M13]) will be determined in plasma samples using the currently approved bioanalytical methods. Raw data will be archived at the bioanalytical site.

9.6. Pharmacodynamics

Samples will be collected for measurement of EPO and VEGF at the Day 1 visit pre-dose and during any post-baseline week from Week 28 to Week 52, inclusive, as specified in the SoA (Section 2), preferably at the earliest opportunity. Refer to the SRM for more information regarding pharmacodynamics.

PD samples will be evaluated for both the daprodustat and epoetin alfa treatment arms. In order to maintain the blind, samples relative to both the tablet and IV formulation will be taken for all participants. Therefore, 2 sets of post-baseline PD samples will be taken; one set relative to each formulation. It is preferred that both sets of PD samples be taken in the same study week.

9.6.1. PD Visit (EPO and VEGF)

- On the day of the (post-baseline) PD visit, the participant must not be on a dose interruption or be receiving a dose of 0 mg (tablets) or 0 U (IV). If the participant's study treatment is interrupted or decreased to a 0 mg or 0 U dose on the day of the planned PD visit, then the PD samples should be collected at the next possible study visit up to Week 52, inclusive.
- Samples relative to the IV formulation will be taken at pre-dose and within 15 minutes after dosing with the study treatment IV injection. The dosing of the study treatment may occur at any time relative to the dialysis treatment, and follow local practices.
- Samples relative to the tablets will be taken at pre-dose and 2, 4, 6 and 8 hours after dosing with the study treatment tablets. Samples will be collected within ± 30 minutes of the planned collection time. These 5 samples may be taken either on one dialysis day or taken over 2 consecutive dialysis days, as outlined below:
    - All samples collected in one dialysis day: The pre-dose and the four post-dose samples may be collected in a single visit. The dosing of the study treatment may occur at any time relative to the dialysis treatment.
    - Samples collected over 2 consecutive dialysis days:
        - The participant must receive the same dose of the tablet formulation on both consecutive dialysis days at which PD samples are taken.
        - First dialysis session: This visit must not occur on the first dialysis day of the week (see Section 9). The pre-dose, and 2- and 4-hour post-dose samples are collected at this visit. The dosing of the study treatment may occur at any time relative to the dialysis treatment, but it is recommended that the participant be dosed prior to or at the start of the dialysis treatment.
        - Second dialysis session: This visit will occur on the next dialysis day following the first visit, and must not occur on the first dialysis day of the week (see Section 9). The 6- and 8-hour post-dose samples are collected at this visit. The participant may take the required dose of study treatment tablets at home, approximately 4 to 5 hours prior to their scheduled dialysis treatment, to allow collection of the PD samples during the dialysis treatment. The participant will also be instructed to record the date and time of dosing in the diary card. Alternatively, if there are any concerns with the participant dosing at home, the participant may be dosed in the clinic.

The date and time of dosing of study treatments and the collection date and time of the PD samples will be recorded in the eCRF.

9.7. 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 Appendix 5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

9.8. Biomarkers

Blood (serum and plasma) samples will be collected and stored as outlined in the SoA (Section 2) and in Table 9, for potential future analysis of biomarkers of CV risk and iron metabolism. Biomarker samples for storage will be collected from all participants, except if not permitted by local regulations or IRB/EC, or refused by participant.

9.9. Patient Reported Outcomes

The patient-reported effect of daprodustat and rhEPO on global symptom severity and change will be assessed. Symptom severity will be assessed using the Patient Global Impression of Severity (PGI-S) and overall symptom change using the Patient Global Impression of Change (PGI-C).

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.

All questionnaires used in this study have been translated, and culturally adapted for use in local country languages. Specific instructions on how the participant is to complete the scales and the process for data entry is provided in the SRM.

The questionnaires should be completed by the participant at a clinic visit, in the order specified (PGI-S then PGI-C), and before performing any of the following assessments: ECG, vitals or blood samples. Participants who are unable to or require assistance to read must not complete the questionnaires.

9.10. Participant Feedback Survey

An optional smartphone mobile application (or "App") or website may be made available for use by participants during the study. If available for use, participants may be asked for feedback on their experience during the study, in the form of an anonymized mobile application or website based survey. The purpose of this survey is for GSK to learn about participants' experience in the study.

10. STATISTICAL CONSIDERATIONS

The primary Hgb efficacy objective will assess the estimand defined as the comparative treatment effect in mean Hgb change between baseline and EP (i.e., Weeks 28 to 52 inclusive) in all randomized participants who remain in follow-up throughout the period of stabilization and have at least one Hgb assessment during the EP (i.e., Weeks 28 to 52) regardless of adherence to study treatment.

The analysis will test whether daprodustat is non-inferior to rhEPO according to the following statistical hypotheses:

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

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

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

10.1. Sample Size Determination

10.1.1. Sample Size Assumptions

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

Approximately 402 participants are planned to be randomized in a 2:1 ratio to daprodustat or rhEPO (268 to the daprodustat arm and 134 to the rhEPO arm), in order to provide at least 100 participants exposed to daprodustat for one year. Participants will be treated to achieve and maintain Hgb between 10 and 11 g/dL. The expected difference in mean Hgb change from baseline and the EP, between arms, is 0 g/dL and the anticipated between participant standard deviation (SD) is 1.5 g/dL, based on historical rhEPO trials and daprodustat clinical trial experience to date. With a prespecified non-inferiority margin of -0.75 g/dL, a two-sample T-test and assuming that up to approximately 10% of

participants will have no Hgb values measured during the EP, 402 randomized participants will provide >90% power to test the primary hypothesis.

With 402 randomized participants, it is anticipated that the difference in mean Hgb change from baseline between arms will be estimated with a precision of 0.33 g/dL (half width of the two-sided 95% CI) and the largest (most negative) difference between arms that would meet the statistical criterion for non-inferiority would be -0.42 g/dL.

Note: Country-specific requirements for France for the sample size consideration are provided in Appendix 8 (see Section 12.8.1, Item 2 for details).

10.1.2. Sample Size Sensitivity

The following table illustrates the impact on power for the primary efficacy analysis based on alternative assumptions for the between participant SD and the expected difference between the treatment groups.

Between participant Hgb SD (g/dL)	True difference between treatments in Hgb (g/dL) (daprodustat – rhEPO)				
	0.1	0	-0.1	-0.2	-0.3
1	>99%	>99%	>99%	>99%	98%
1.25	>99%	>99%	>99%	98%	89%
1.5	>99%	>99%	97%	91%	76%
1.75	>99%	97%	91%	80%	63%
2	97%	92%	83%	69%	52%

10.1.3. Sample Size Re-Estimation or Adjustment

No sample size re-estimation is planned for this study.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF
All Randomized (ITT)	All randomized participants. This is the primary population for Hgb efficacy analyses. Participants will be analyzed according to the treatment to which they were randomized. Note: While the primary analysis of the primary parameter will exclude those randomized participants who do not have at least one Hgb assessment during the EP, the sensitivity analysis to define the "tipping point" as described in Section 10.3.1 will include all randomized participants.

Population	Description
Per-Protocol (PP)	All ITT participants who are not major protocol violators. This population will be the basis for a sensitivity analysis of the primary efficacy parameter. Participants will be analyzed according to the treatment to which they were randomized. Details will be defined in the RAP.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	All randomized participants for whom a PK sample was obtained and analyzed. This will be the population used for all the PK displays.

Additional populations may be defined in the RAP.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	**Mean change in Hgb between baseline and EP (Weeks 28-52):** The primary efficacy estimand is to compare the effect of treatment for the evaluation of mean change from baseline in Hgb during a 24-week evaluation period (Weeks 28 to 52 inclusive) in all ITT participants with at least one Hgb during the EP. The analysis will use an analysis of covariance (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 Weeks 28 to 52 inclusive regardless of adherence to randomized treatment. The ANCOVA model will include randomization stratification factor, baseline hemoglobin, and treatment. It will provide a point estimate and two-sided 95% CI for the treatment effect, together with the one-sided non-inferiority test p-value. Non-inferiority will be established if the lower limit of the two-sided 95% CI is greater than the margin of -0.75 g/dL. There will be no imputation for missing data but imputation will be explored via sensitivity analyses **Sensitivity and Supplementary Analyses:** Sensitivity analyses for the primary estimand will include a multiple imputation-based “tipping point” analysis where assumptions are adjusted until non-inferiority is lost by imputing data for participants who did not fully complete the EP. A further supplementary analysis will evaluate efficacy in those participants who adhere to randomized treatment, defined as ITT participants with at least one

<table>
<tr><th>Endpoint</th><th>Statistical Analysis Methods</th></tr>
<tr><td></td><td>on-treatment Hgb during the EP (this approach corresponds to evaluating an efficacy estimand). A similar “tipping point” analysis as that described above for the primary analysis will be performed for this “on-treatment” analysis. In addition, a supplementary per-protocol analysis will estimate the treatment effect in participants who strongly adhere to the protocol, and sensitivity analyses to explore a shorter EP (Weeks 28 to 36) will be performed for the primary effectiveness estimand and “on-drug” efficacy estimand. Full details of all sensitivity and supplementary analyses will be provided in the RAP.

Covariates and Subgroups of Interest: The primary endpoint will be evaluated for a set of pre-specified subgroups to support the proposed indication. Subgroup analyses are aimed to assess for consistency with the overall result, they may have low power if the subgroup is small. Statistical models will be adjusted for the covariates used in the original analysis (randomization stratification factor and baseline hemoglobin), 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.

<table>
<tr><th>Category</th><th>Subgroups</th></tr>
<tr><td>Age</td><td><65 years, ≥65 to <75 years, ≥75 years</td></tr>
<tr><td>Gender</td><td>Female, Male</td></tr>
<tr><td>Race group</td><td>American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race</td></tr>
<tr><td>Ethnicity</td><td>Hispanic, non-Hispanic</td></tr>
<tr><td>Region</td><td>Regions listed in Appendix 7</td></tr>
<tr><td>Country</td><td>Countries listed in Appendix 7</td></tr>
<tr><td>Dialysis vintage</td><td>0 to <2 years, 2 to <5 years, ≥5 years</td></tr>
<tr><td>Prior rhEPO dose</td><td><7,000 U/week, ≥7,000 U/week</td></tr>
<tr><td>rhEPO Hypo-responsiveness</td><td>No, Yes (see RAP for definition)</td></tr>
<tr><td>Baseline Hgb</td><td><9 g/dL, 9 to <10 g/dL, 10 to 11 g/dL, >11 g/dL</td></tr>
<tr><td>BMI</td><td><30 kg/m^2, ≥30 kg/m^2</td></tr>
<tr><td>Weight</td><td>< 75kg, ≥75kg</td></tr>
<tr><td>Baseline hsCRP</td><td>≤3 mg/L, >3 mg/L</td></tr>
<tr><td>United States</td><td>US, Non-US</td></tr>
</table>

Additional exploratory subgroups may be defined in the RAP. Additional subgroup analysis for other study endpoints may be performed, and will be defined in the RAP.</td></tr>
<tr><td>Principal Secondary</td><td>Conditional on the primary endpoint achieving non-inferiority at the one-sided 2.5% level, statistical testing will progress to the principal secondary endpoint with a focus on superiority using a one-sided 2.5% significance level.</td></tr>
</table>

Endpoint	Statistical Analysis Methods
	For the principal secondary endpoint of average monthly IV iron dose up to Week 52 endpoint, IV iron use for all participants will be recorded in the eCRF and the average monthly IV iron dose up to week 52 while on treatment will be calculated. An ANCOVA model will be used to compare the difference in this average monthly IV iron dose per participant between arms, including factors for baseline dose, treatment and the randomization stratification factor.
Secondary	All analyses of secondary endpoints are of exploratory nature. Summary statistics along with nominal one-sided p-values and two-sided 95% confidence intervals will be used to describe the results.
Exploratory	Will be described in the reporting and analysis plan
Patient Reported Outcomes	Analysis to compare the participant reported effects of daprodustat and rhEPO on symptoms, as discussed in Section 9.9, will be described in the RAP.

10.3.1.1. Multiplicity Strategy

The primary endpoint will be tested first for non-inferiority, using the lower limit of the 2-sided 95% confidence interval. Conditional on achieving statistical significance (i.e., passing the primary gate by establishing non-inferiority) the single principal secondary endpoint will be tested for superiority using a one-sided 2.5% significance level. This two-step hierarchical strategy will preserve the study-wise Type I error rate at a one-sided 2.5% level.

The additional secondary/exploratory endpoints, if tested, will not be adjusted for multiplicity. A nominal one-sided 2.5% significance level will be applied per test.

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Adverse Events	All AEs (i.e. Non-serious, serious, and AEs of special interest) will be descriptively summarized by treatment group.
Vital signs	Summary statistics at each visit will be generated by treatment group
Laboratory data	Summary statistics at each visit will be generated by treatment group. Number of participants who meet protocol defined stopping criteria (e.g. liver chemistry) will be summarized by treatment group.
Randomized	The number of participants who discontinued randomized treatment will be

Endpoint	Statistical Analysis Methods
treatment discontinuations	summarized by reason for discontinuation and treatment group. The time to discontinuing randomized treatment will be presented graphically and assessed.
Cardiovascular Safety Endpoints	This study is not designed or sufficiently powered for formal statistical analyses to assess cardiovascular safety. With fewer than 80 first-occurrence MACE (defined as all-cause mortality, non-fatal MI, or non-fatal stroke) expected to occur during the trial, incidence rates and two-sided 95% CIs will be computed for the following mortality and CV composite or component endpoints: 1) MACE; 2) MACE or a thromboembolic event (vascular access thrombosis, a symptomatic deep vein thrombosis or a symptomatic pulmonary embolism); 3) MACE or hospitalization for heart failure; 4) all cause mortality; 5) CV mortality; 6) MI (fatal and non-fatal); 7) stroke (fatal and non-fatal); 8) CV mortality or non-fatal MI; 9) all cause hospitalization.

Full details of all safety data reporting will be described in the RAP.

10.3.3. Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the RAP.

10.3.3.1. Patient Reported Outcome Analyses

Analysis to compare the participant reported effects of daprodustat and rhEPO on symptoms as discussed in Section 9.9, will be described in the RAP.

10.3.3.2. Pharmacokinetic/Pharmacodynamic Analyses

The following plasma PK parameters will be determined for daprodustat and its predominant metabolites: Ctau (pre-dose) and Cmax.

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

The exploratory graphics described below will be created. Based on these, and the efficacy and safety results obtained, post-hoc exploratory exposure-response/safety modeling may be conducted.

- Scatter plots of Cmax of three-times weekly dosed daprodustat extrapolated to daprodustat dose at the PK sample multiplied by the mean weekly daprodustat dose during the EP vs. the percent time within the Hgb target range during the EP
- Scatter plots of Cmax of three-times weekly dosed daprodustat extrapolated to daprodustat dose at the PK sample multiplied by the mean weekly daprodustat dose over 52 weeks vs. mean Hgb over the 52-week treatment period

10.3.3.3. Other Exploratory Analyses

The exploratory graphics described below will be created.

- Scatter plots of mean weekly daprodustat dose over the EP vs. the percent time within the Hgb target range during the EP
- Scatter plots of mean weekly three-times weekly daprodustat dose over 52 weeks vs. mean Hgb over the 52-week treatment period
- Boxplots of mean weekly three-times weekly daprodustat dose, while on study treatment for participants without MACE, and before the event for participants with MACE or combined safety endpoint
- Boxplots of Cmax of three-times weekly dosed daprodustat extrapolated to daprodustat dose at PK sample multiplied by the daprodustat dose at the time of MACE or combined safety endpoint (or end of study if no endpoint) by participants with or without MACE or combined safety endpoint

10.3.4. Interim Analyses

The IDMC will periodically receive unblinded safety reports containing clinical endpoints (whether adjudicated or pending adjudication) and SAEs, from an independent Statistical Data Analysis Center (SDAC) while Phase 3 studies with daprodustat are ongoing. The IDMC may recommend stopping this study for safety at any time.

There are no plans to evaluate interim data for the purposes of stopping based on Hgb efficacy data.

Further details will be specified in the IDMC charter and RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
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 Committee
CHF	Congestive Heart Failure
CI	Confidence interval
CKD	Chronic kidney disease
CNIL	Commission Nationale de I'Informatique et des Libertés
CPK	Creatine phosphokinase
CRA	Clinical Research Assistant
CT	Computed tomography
CTR	Clinical Trials Register
CV	Cardiovascular
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDW	Estimated dry weight
EP	Evaluation period
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HbA1c	Glycated hemoglobin
HD	Hemodialysis
HDL-c	High density lipoprotein-C
HDPE	High density polyethylene
Hgb	Hemoglobin
HIF	Hypoxia-inducible factor
HIF-PHI	Hypoxia inducible factor prolyl hydroxylase inhibitor
HR	Heart rate
HRT	Hormone replacement therapy

hsCRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein-C
M2	GSK2391220, M2 metabolite of GSK1278863 (daprodustat)
M3	GSK2531403 and GSK2506104, stereoisomers of the M3 chiral metabolite of GSK1278863 (daprodustat)
M4	GSK2487818, M4 metabolite of GSK1278863 (daprodustat)
M5	GSK2531399 and GSK2506102, stereoisomers of the M5 chiral metabolite of GSK1278863 (daprodustat)
M6	GSK2531398 and GSK2531407, stereoisomers of the M6 chiral metabolite of GSK1278863 (daprodustat)
M13	GSK2531400 and GSK2531401, stereoisomers of the M13 chiral metabolite of GSK1278863 (daprodustat)
MACE	Major adverse cardiovascular event
MAP	Mean arterial pressure
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
PASP	Pulmonary artery systolic pressure
PD	Pharmacodynamic
PEG	Polyethylene glycol
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHI	Prolyl hydroxylase inhibitor
PK	Pharmacokinetic
PP	Per protocol
PPD	Pharmaceutical Product Development, LLC
PRBC	Packed red blood cells

PSRAE	Possible Suicidality Related Adverse Events
QC	Quality control
QT	Q-T interval
QTc	Q-T interval corrected for heart rate
QTcB	Bazett's correction of QT interval
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RDW	Red blood cell distribution width
rhEPO	Recombinant human erythropoietin
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDAC	Statistical Data Analysis Center
SRM	Study Reference Manual
TIBC	Total iron binding capacity
TSAT	Transferrin saturation
U	Units
UIBC	Unsaturated iron binding capacity
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WBC	White blood cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Epogen
HemoCue
MedDRA

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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is 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. Committees Structure

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

12.2.5.1. Independent Data Monitoring Committee

An IDMC will be utilized in this study to ensure external objective review of safety and efficacy data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter.

12.2.5.2. Clinical Events Committee

An external independent Clinical Events Committee (CEC) blinded to study treatment allocation will adjudicate all events reported during this study that constitute events of MACE, thromboembolic events and hospitalization for heart failure, as outlined in

Section 9.2.5. Further details are contained within the CEC Charter (available on request).

12.2.6. 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.

12.2.7. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- 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.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

12.2.8. 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.
- 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 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.

12.2.9. 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.
- Definition of what constitutes source data can be found in the study specific monitoring plan.

12.2.10. 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.

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

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

12.3.1. 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., 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 (e.g., 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.

12.3.2. Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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 inpatient hospitalization or prolongation of existing hospitalization

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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

- 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 with 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 SAE 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 events should usually be considered serious. Examples of such events include 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.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Arrhythmias • Valvulopathy • Pulmonary hypertension • Revascularization

12.3.4. Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 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 causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory

reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

12.3.5. 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 or SAE coordinator by telephone.
- Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF

- The site will use the paper SAE data collection tool in order to report the event

within 24 hours, **only** if the electronic system is unavailable.

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

12.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants 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 10, from at least 28 days prior to the first dose of study treatment and until at least 28 days after the last dose of study treatment and completion of the Follow-up visit (4 to 6 weeks after the end of study treatment); those who permanently discontinue study treatment prior to the end of 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 study treatment) as described in the SoA in Section 2.

Table 10 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[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • 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.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 4 weeks after the last dose of study treatment, and until the follow-up visit is performed or until the final pregnancy test assessment at a subsequent study visit for participants who permanently discontinued study treatment.

Pregnancy Testing

- WOCBP should only be included after a confirmed negative highly sensitive serum pregnancy test during screening (Week -4).

- Additional pregnancy testing should be performed as specified in the SoA (Section 2), and as required locally.
- Pregnancy testing will be assayed in the central laboratory.

Collection of Pregnancy Information

Female Participants who become pregnant

- 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 24 hours 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 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 will discontinue study treatment.

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 of chronic kidney disease and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to daprodustat or PHIs, and anemia of chronic kidney disease. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome, as appropriate.
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- 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.
- The sponsor 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 of chronic kidney disease continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

12.6. Appendix 6: Liver Safety Required Actions and Follow-up Assessments and Study Treatment Restart Guidelines

12.6.1. Liver Safety Required Actions and Follow-up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase III-IV 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	
Actions	**Follow Up Assessments**
• Immediately discontinue study 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) • **Do not restart** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Section 12.6.2)	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • 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]. • Obtain blood sample for pharmacokinetic (PK) analysis, within 24 hours after last dose[6] • Serum creatine phosphokinase (CPK) and

• If restart is **not allowed or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor 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 to 72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications case 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 high performance liquid chromatography (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 computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
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 study treatment prior to blood sample draw on the CRF. 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 III-IV liver chemistry increased monitoring criteria with continued therapy

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

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12.6.2. Liver Safety Study Treatment Restart Guidelines

Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcoholic hepatitis.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has a confirmed genetic marker associated with liver injury, the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on study treatment restart in Section 8.1.3 will apply.
- There is no evidence of alcoholic hepatitis.
- IRB/IEC approval of study treatment restart has been obtained.

If restart of study treatment is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the restart of study treatment. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK
- Participants approved by GSK for restart of study treatment must return to the clinic twice a week for liver function tests until stable liver function tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If the participant meets protocol-defined liver function stopping criteria after study treatment restart, study treatment should be permanently discontinued.

- GSK Medical Monitor, and the IRB/IEC, must be informed of the outcome for the participant following study treatment restart.
- GSK must be notified of any adverse events, as per Appendix 3.

12.7. Appendix 7: Stratification by Region - Region Groupings

Region	Countries[1]
1	• Republic of Korea
2	• Poland • Russian Federation
3	• Australia • France • Germany • Spain
4	• Argentina • Brazil
5	• US

1. Countries that do not participate or do not randomize any participants will be removed from the regional grouping. If any additional countries are added during the course of the study, they will be added to the regional grouping consistent with study 200807, and such changes will be detailed in the RAP.

12.8. Appendix 8: Country-specific requirements

12.8.1. French Administrative Considerations and Specifics Requirements

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

1. Concerning the « STUDY POPULATION»

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

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

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

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

3. Concerning the "STUDY CONDUCT CONSIDERATIONS"

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

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

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

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

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

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

  In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The

Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

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

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

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

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

4. Monitoring visits

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

5. Data entry into the eCRF

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

The Health Institution and the Investigator undertake:

1) That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the

eCRF of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.

2) That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.

3) That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.

4) To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.

5) That the Investigator and the staff of the investigator center enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.

6) That the Investigator resolves and returns to GLAXOSMITHKLINE the data queries issued by GLAXOSMITHKLINE or a service provider designated by GLAXOSMITHKLINE within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GLAXOSMITHKLINE and/or a company designated by GLAXOSMITHKLINE.

7) To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.

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

6. CTR publication

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

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

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GLAXOSMITHKLINE to monitor and follow the implementation and the progress of the Study are declared with the Commission Nationale de l'Informatique et des Libertés (CNIL) by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to him a right of access, of rectification and of

opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GLAXOSMITHKLINE Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

12.8.2. Country-Specific Requirements for Korea

The following information pertains to all sites in Korea.

Inclusion Criteria – Age Range

In Korea, an adult is considered to be any individual who is ≥19 years old.

In regards to Inclusion Criterion #1, in Korea per local laws, only adult participants, who are between 19 and 99 years of age, inclusive, at the time of signing the informed consent will be eligible for inclusion in this study.

Clinical Laboratory Assessments – Point-of-Care Hemoglobin Analyzer

The following point-of-care HemoCue hemoglobin analyzer, or similar device, will be supplied to each study site. Any changes to the details of the device listed below will be provided in the SRM, and will not constitute a protocol amendment.

- Name of device: HemoCue Hb201+ hemoglobin analyzer
- Model number: 121704
- Manufacturer: HemoCue AB: SE-262 23 Angelholm, Sweden