TITLE PAGE

Protocol Title: A repeat dose, open label, two period, randomized, cross over study to compare the effect of daprodustat to recombinant, human erythropoietin (rhEPO) on oral iron absorption in adult participants with anemia associated with chronic kidney disease who are not on dialysis

Protocol Number: 201771 /Amendment 3

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

Compound Number:	GSK1278863

Study Phase 2b

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM)

Regulatory Agency Identifying Number(s): IND Number: 101,291

Approval Date: 14-JUL-2021

SPONSOR SIGNATORY:

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Alexander R. Cobitz, MD, PhD Senior Director Daprodustat Clinical Development Lead Specialty (Clinical Sciences) GlaxoSmithKline	**Date**

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 3	14-Jul-2021	TMF-13854840
Amendment 2	13-Aug-2019	2016N298210_02
Amendment 1	30-Nov-2017	2016N298210_01
Original Protocol	12-May-2017	2016N298210_00

Amendment 3: 14-JUL-2021

Overall Rationale for the Amendment:

Amendment 3 was implemented to facilitate enrolment and the maintenance of participants once randomized in the study and to correct noted typographical errors.

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	Table 1: number to be enrolled in each possible sequence corrected from 6 to 3 Day of crossover changed from Day 28 to Day 29	To correct discrepancy
5.4 Scientific Rationale for Study Design	Bullet 9: deleted hepcidin level assessment as eligibility criterion	Exclusion criterion related to hepcidin was removed after observing variability in the range of hepcidin results and the lack of standardization of hepcidin assays making it difficult to establish a cut-off value for this study population.
6.1 Exclusion Criteria	Deletion of Exclusion Criteria #12 Hepcidin >150 ng/ml	
9.4.1 Entry Criteria (Table 4)	Hepcidin was removed as an entry criteria assessment	
8.2.1.2 Iron Stopping Criteria	Amended to allow the Investigator to use his clinical judgement and removed TSAT and ferritin values as discontinuation criteria.	The intent of the iron stopping criteria is to ensure participants remain on the same dose of oral iron supplement throughout the study. Therefore, the stopping criteria was amended to allow the Investigator to use his clinical judgement to determine if a

Section # and Name	Description of Change	Brief Rationale
		participant's iron supplement required adjustment.
5.4 Scientific Rationale for Study Design	Removed mention of absolute change in Hemoglobin to define the evaluable population	Hemoglobin variability is managed through the hgb stopping criteria
10.3.1.3 Evaluable Population	Deleted the criterion of absolute changes from baseline (Day 1 pre dose) in haemoglobin ≤0.75 g/dL from the evaluable population definition	
12.3 Appendix 3 Risk Assessment	Drug Interaction information updated	Modified to maintain consistency with current Risk Assessment
12.7 Appendix 7 Contraceptive Guidance and Collection of Pregnancy Information	Urine pregnancy testing kit sensitivity corrected from 2 mIU/mL to 25 mIU/mL	To correct typographical error.

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1. SYNOPSIS

Protocol Title: A repeat dose, open label, two period, randomized, cross over study to compare the effect of daprodustat to recombinant, human erythropoietin (rhEPO) on oral iron absorption in adult participants with anemia associated with chronic kidney disease who are not on dialysis

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

Rationale: Several proteins involved in iron absorption/metabolism are known to be HIF target genes. In this regard, daprodustat is equipotent against 3 human PHD enzymes (PHD1, PHD2 & PHD3) thereby stabilizing both HIF1α and HIF2α. Increased iron absorption correlates with increased expression in enterocytes and proerythroblasts of divalent metal-iron transporter 1 (DMT1), duodenal cytochrome b561 (DcytB) and ferroportin (FPN) mRNA. HIF-2α is reported to up-regulate the expression of these genes by direct binding to consensus hypoxia response elements (HRE). Thus, there is the potential that daprodustat administration, by virtue of increasing HIF levels, can increase oral iron absorption and incorporation into Hgb. Therefore, the purpose of this study is to compare the effect of daprodustat to rhEPO (i.e., epoetin alfa or darbepoetin alfa) on non-heme oral iron absorption using stable isotopic iron (^{57}Fe & ^{58}Fe) by measuring incorporation of iron in erythrocytes.

Objectives and Endpoints:

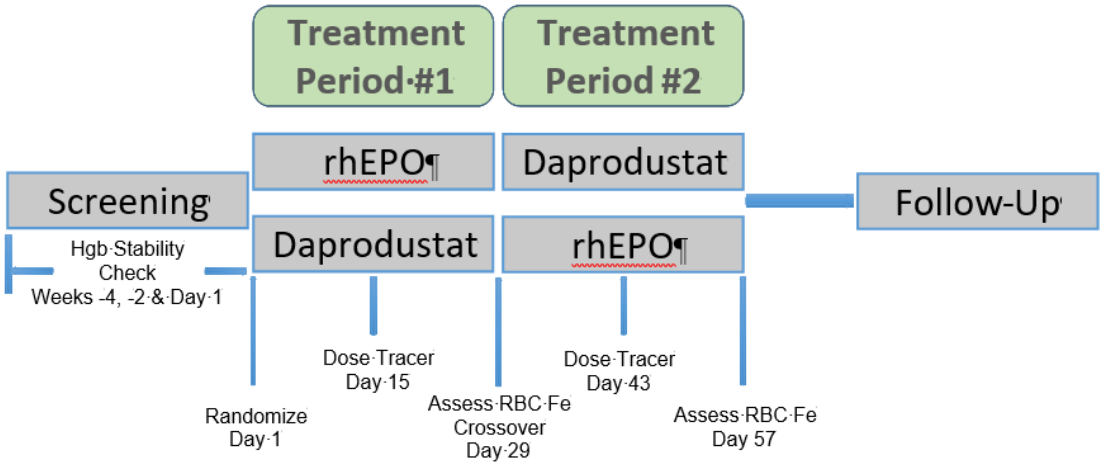
Objectives	Endpoints
Primary	
• Compare the efficacy of daprodustat to rhEPO (i.e., epoetin alfa or darbepoetin alfa) on iron absorption	• Difference in fractional oral iron absorption (%) between daprodustat and rhEPO
Secondary	
• Characterize the effect of daprodustat or rhEPO on markers of iron status	• Change from baseline (Day 1) at 14 and 28 days following treatment with daprodustat or rhEPO in serum iron, transferrin, transferrin saturation, soluble transferrin receptor, ferritin, hepcidin and erythroferrone
• Characterize the effect of daprodustat or rhEPO on indices of erythropoiesis	• Change from baseline (Day 1) at 14 and 28 days following treatment with daprodustat or rhEPO in Hgb, hematocrit, red blood cell number, mean corpuscular volume, reticulocyte Hgb and reticulocyte number

Objectives	Endpoints
Safety	
• Assess safety and tolerability	• Incidence and severity of adverse events and serious adverse events • Reasons for discontinuation of study medication • Vital signs assessments

Overall Design: This study will be a randomized, repeat dose, open label, two period cross-over study in adult, male and female participants with anemia associated with chronic kidney disease who are not on dialysis currently treated with stable doses (≤ 50% change in 4-weekly dose) for at least 8 weeks prior to and including the screening period, of rhEPO (i.e., epoetin alfa or darbepoetin alfa).

Number of Participants: Sufficient participants will be enrolled such that at least 12 participants comprise the Evaluable Population.

Treatment Groups and Duration:



- There will be a 4-week screening period in order to confirm that participants have stable Hgb levels and to assess entry criteria
- A 28-day Treatment Period 1 for incorporation of iron into erythrocytes while on randomized study treatment
- A 28-day Treatment Period 2 for a second incorporation of iron into erythrocytes while on randomized study treatment
- A follow-up visit 14 ± 3 days after completing treatment.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening[1]		Treatment Period[2]					Follow-up[1]
	Week -4	Week -2	Day 1	Day 15	Day 29[3]	Day 43	Day 57	Day 70
Informed Consent	X							
Entry Criteria	X[4]	X[4]	X[4]					
Physical, Medical History, Demography, Height	X[5,9]	X[5,9]	X[5,9]					
Weight	X		X	X		X		
HemoCue Hgb	X	X	X	X	X	X	X	
eGFR	X							
Females: Urine Pregnancy Test[6]	X		X		X		X	X
Females: Estradiol & FSH[7]		X						
HIV screening and Hepcidin	X							
Randomization			X					
Administration of isotopic iron				X		X		
Blood sampling for isotopic iron					X	X	X	
Crossover[8]					X			
ECG		X						X
Vital signs	X		X		X		X	X
Clinical chemistry & hematology[10]	X							X
Urinalysis[10]	X							X
Liver chemistry monitoring[11]				X		X		
Folate & Vitamin B_{12}		X						
hsCRP		X						
Ferritin and TSAT		X						
Iron status markers[12]			X	X	X	X	X	
Indices of erythropoiesis[13]			X	X	X	X	X	
Blood draw for PGx			X					
AE and SAE Assessment[14]	X[15]	X[15]	X	X	X	X	X	X
Review Concomitant Medications	X	X	X	X	X	X	X	X

[1] Allowable time window ± 3 days.
[2] Allowable time window ± 2 days.
[3] All assessments to be performed **PRIOR** to crossing over.
[4] Criteria to be assessed can be found in Section 9.4.1.
[5] Complete physical examination, medical history & demography to be performed at Week -4, while a brief physical examination to be performed at Week -2 and Day 1.
[6] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
[7] As detailed in Inclusion Criteria.
[8] Participants that had been administered daprodustat during treatment Period 1 will be switched to rhEPO, while those on rhEPO will be switched to daprodustat. Examples on switching are provided in the Study Reference Manual (SRM).
[9] Height is only collected at Week -4.
[10] Clinical laboratory assessments guidance can be found in Section 9.4.5
[11] Liver chemistry monitoring guidance can be found in Section 9.4.6.
[12] Iron status markers include serum iron, ferritin, transferrin, transferrin saturation (TSAT), soluble transferrin receptor, hepcidin and erythroferrone and are described in Section 9.8.2. All samples for iron status markers to be taken pre dose.
[13] Indices of erythropoiesis include Hgb, hematocrit, red blood cell number, mean corpuscular volume, reticulocyte Hgb and reticulocyte number and are described in Section 9.8.3.
[14] Guidance on the timing and need for collection of AEs & SAEs are described in Section 9.2.
[15] SAEs assessed as related to study participation or a GSK product are collected at this visit. See Section 9.2.1 for additional details.

- The timing and number of planned study assessments, including safety or biomarker assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

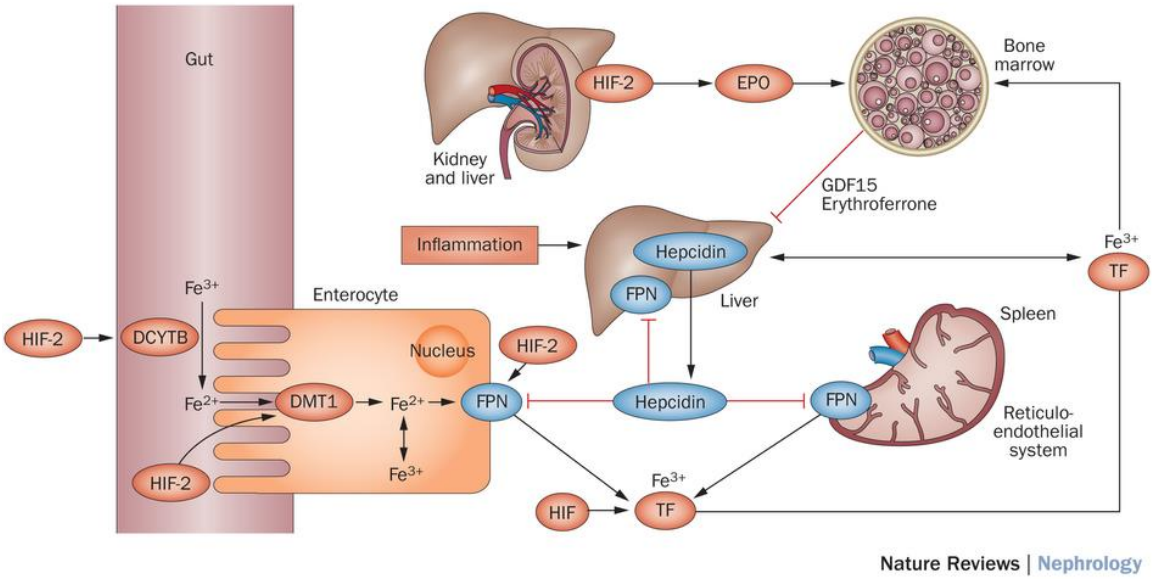
Daprodustat (GSK1278863) is a small molecule, oral inhibiter of the hypoxia-inducible factor (HIF) prolyl-4-hydroxylase (PHD) enzymes which may present several important advantages over recombinant, human erythropietin (rhEPO). It is an oral medication and does not require cold-chain storage as do some rhEPOs, thus increasing ease of use for patients. Moreover, data indicate that, similar to other HIF-PHD inhibitors, daprodustat can effectively raise hemoglobin (Hgb) concentrations with lower erythropoietin (EPO) levels than those observed after administration of rhEPOs (Besarab, 2015; Holdstock, 2016). Because of the increased cardiovascular (CV) risk associated with raising Hgb concentrations through large increases in EPO levels (Pfeffer, 2009), daprodustat has the potential to treat patients with less CV risk than rhEPOs. Additional benefits include the potential to treat anemia without causing rhEPO-induced hypertension, to improve iron availability for erythropoiesis, and the potential to successfully treat rhEPO hypo-responders (Holdstock, 2016).

3.1. Study Rationale

Sufficient iron availability is critical for normal erythropoiesis and all rhEPO labels carry guidance with regard to iron availability. It is anticipated that the majority of patients with chronic kidney disease (CKD) will require supplemental iron during the course of rhEPO therapy. However, poor compliance is seen with oral iron therapy due to gastrointestinal intolerance, while intravenous (IV) iron has an increased risk of infection and/or iron overload as well as an increased risk of anaphalaxis and congestive heart failure. Excess accumulation of iron in tissues with IV iron is clearly associated with increased morbidity and mortality with organ dysfunction primarily seen in the liver, heart, pancreas, joints and endocrine organs. Further, most of the morbidity and mortality due to iron overload disorders is the result of iron accumulation in the heart (Macdougall, 2016). Finally, administration of IV iron is associated with additional costs related to in-hospital administration and the need for patient monitoring.

Several proteins involved in iron absorption/metabolism are known to be HIF target genes. In this regard, daprodustat is equipotent against 3 human PHD enzymes (PHD1, PHD2 & PHD3) thereby stabilizing both HIF1α and HIF2α. Increased iron absorption correlates with increased expression in enterocytes and proerythroblasts of divalent metal-iron transporter 1 (DMT1), duodenal cytochrome b561 (DcytB) and ferroportin (FPN) mRNA. HIF-2α is reported to up-regulate the expression of these genes by direct binding to consensus hypoxia response elements (HRE) (Koury, 2015). Thus, there is the potential that daprodustat administration, by virtue of increasing HIF levels, can increase oral iron absorption and incorporation into Hgb. Therefore, the purpose of this study is to compare the effect of daprodustat to rhEPO (i.e., epoetin alfa or darbepoetin alfa) on non-heme oral iron absorption using stable isotopic iron (^{57}Fe & ^{58}Fe) by measuring incorporation of iron in erythrocytes. The coordination of erythropoietin synthesis with iron metabolism by HIF is shown in Figure 1.

Figure 1 HIF in erythropoietin synthesis and iron metabolism



DcytB: Duodenal cytochrome *b* reductase 1; DMT1: Divalent metal transporter-1; FPN: Ferroportin; TF: Transferrin; EPO: Erythropoietin; GDF15: Growth Differentiation Factor 15 (Koury, 2015)

3.2. Background

HIF prolyl hydroxylase inhibitors (PHIs) are an emerging class of agents under investigation for the treatment of anemia associated with CKD. These molecules stimulate erythropoiesis through inhibition of HIF-prolyl hydroxylase domain enzymes (PHD1, PHD2, PHD3). This activity results in the accumulation of HIFα transcription factors which leads to increased transcription of HIF-responsive genes, stimulating components of the natural response to hypoxia. During hypoxia, the PHD enzymes are inhibited, resulting in the accumulation of unhydroxylated HIFα subunits, which dimerize with HIFβ subunits to affect the transcription of HIF-responsive genes, including EPO and others involved in increasing oxygen availability and utilization. Other functions regulated by HIFs include iron metabolism and utilization, angiogenesis, extracellular matrix metabolism, apoptosis, energy and glucose metabolism, vascular tone, cell adhesion, and motility (Haase, 2013).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks of daprodustat may be found in the Investigator's Brochure (IB) and supplements.

3.3.1. Risk Assessment

The potential risks of clinical significance including adverse events (AEs) of special interest (AESI; Section 9.2.4), and the mitigation strategies for this protocol taking into account the results of completed clinical and nonclinical studies with daprodustat, are outlined in Appendix 3.

3.3.2. Benefit Assessment

In clinical trials of up to 24 weeks in duration, in participants with anemia associated with CKD, daprodustat has been shown to increase Hgb to target range. Data from prior studies with daprodustat suggest that the increases in Hgb are achieved with EPO levels lower than those observed with rhEPO (Holdstock, 2016).

3.3.3. Overall Benefit:Risk Conclusion

Daprodustat demonstrates a positive benefit vs. risk balance based on the evidence as follows. In clinical trials up to 24 weeks in duration, daprodustat maintained Hgb to target range in participants with anemia associated with CKD (both nondialysis dependent (ND) and hemodialysis dependent (HD)) with a safety profile consistent with the patient population.

This protocol employs precautions to mitigate known and potential risks to enrolled participants (See Appendix 3). Given these precautions, as well as the potential benefit that daprodustat holds for the treatment of anemia associated with CKD compared to the current standard, the overall benefit:risk balance is considered to be positive.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Compare the efficacy of daprodustat to rhEPO (i.e., epoetin alfa or darbepoetin alfa) on iron absorption	• Difference in fractional oral iron absorption (%) between daprodustat and rhEPO
Secondary	
• Characterize the effect of daprodustat or rhEPO on markers of iron status	• Change from baseline (Day 1) at 14 and 28 days following treatment with daprodustat or rhEPO in serum iron, transferrin, transferrin saturation, soluble transferrin receptor, ferritin, hepcidin and erythroferrone
• Characterize the effect of daprodustat or rhEPO on indices of erythropoiesis	• Change from baseline (Day 1) at 14 and 28 days following treatment with daprodustat or rhEPO in Hgb, hematocrit, red blood cell number, mean corpuscular volume, reticulocyte Hgb and reticulocyte number
Safety	
• Assess safety and tolerability	• Incidence and severity of adverse events and serious adverse events • Reasons for discontinuation of study medication • Vital signs assessments

5. STUDY DESIGN

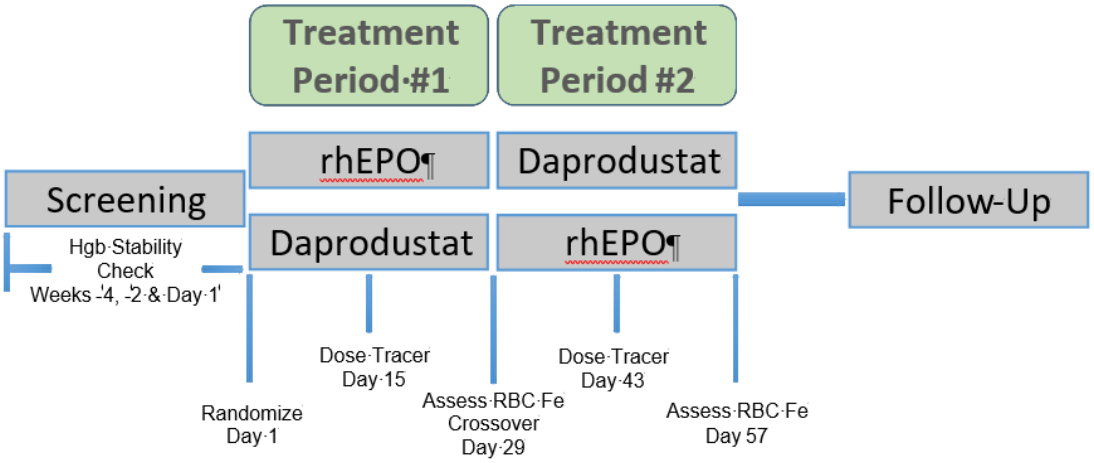
5.1. Overall Design

This study will be a randomized, repeat dose, open label, two period cross-over study in adult, male and female participants with anemia associated with chronic kidney disease who are not on dialysis currently treated with stable doses (≤ 50% change in 4-weekly dose) for at least 8 weeks prior to and including the screening period, of rhEPO (i.e., epoetin alfa or darbepoetin alfa).

Sufficient participants will be enrolled such that at least 12 participants comprise the Evaluable Population (See Section 10.3.1.3).

The study design is outlined in Figure 2.

Figure 2 Study Design



- There will be a 4-week screening period in order to confirm that participants have stable Hgb levels and to assess entry criteria
- A 28-day Treatment Period 1 for incorporation of iron into erythrocytes while on randomized study treatment
- A 28-day Treatment Period 2 for a second incorporation of iron into erythrocytes while on randomized study treatment
- A follow-up visit 14 ± 3 days after completing treatment.

Participants will be randomly assigned either to remain on their current therapy (either epoetin alfa or darbepoetin alfa) or be switched to daprodustat for Treatment Period 1. For assessment of incorporation of iron into erythrocytes, enrolled participants will be administered ferrous sulfate containing a stable isotope of iron (^{57}Fe or ^{58}Fe) orally in a randomized fashion following 2 weeks of administration of randomized study treatment. Thus, there are 4 possible treatment sequences as shown in Table 1. Two weeks following oral iron administration a blood sample will be taken in order to assess the incorporation of the iron isotope into red blood cells by thermal ionization mass

spectrometry (TIMS) using published methods (IAEA Human Health Series No. 21, 2012).

At Day 29 participants will be crossed over to the study treatment they did not receive in Treatment Period 1, i.e., for participants that remained on their current therapy they would be switched to daprodustat, while subjects that had been administered daprodustat would be switched back to their previous therapy at the dose prior to randomization. At 2 weeks following initiation of dosing, participants will again be administered ferrous sulfate containing the stable iron isotope not administered following the assessment in Treatment Period 1 orally. Two weeks following oral iron administration a blood sample will again be taken in order to assess the incorporation of the iron isotope into red blood cells by TIMS.

Participants will attend a follow-up visit 14 ± 3 days following the final blood sample for assessment of red blood cell iron.

Table 1 Possible Treatment Sequences

	Sequence A N=3	**Sequence B N=3**	**Sequence C N=3**	**Sequence D N=3**
Treatment Period 1	rhEPO ^{57}Fe	rhEPO ^{58}Fe	Daprodustat ^{57}Fe	Daprodustat ^{58}Fe
Treatment Period 2	Daprodustat ^{58}Fe	Daprodustat ^{57}Fe	rhEPO ^{58}Fe	rhEPO ^{57}Fe

5.2. Number of Participants

Sufficient participants will be enrolled such that at least 12 participants comprise the Evaluable Population (See Section 10.3.1.3).

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

This study will use a randomized, repeat dose, open label, two period cross over design in adult, ND, male and female participants with anemia associated with chronic kidney disease currently treated with stable rhEPO doses (≤ 50% change in 4-weekly dose) for at least 8 weeks prior to and including the screening period.

- This will be an open label study as oral iron absorption is an objective measure and unlikely to be influenced by the participant's knowledge of the treatment administered. Additionally, blinding of treatment would be difficult as rhEPO is

administered by subcutaneous injection, while daprodustat is administered orally once daily as a tablet.

- Iron absorption will be assessed over a 2 week period commencing after 2 weeks of study treatment, a period of time when it is anticipated that any changes in oral absorption mediated by changes in expression of HIF-dependent DcytB and DMT1 will be apparent (Shah, 2009).
- This study will use a cross over design, with oral iron absorption assessed in each participant following both rhEPO and daprodustat administration, in order for each participant to serve as their own control.
- Participants will need to be currently treated with stable doses (≤ 50% change in 4-weekly dose) of rhEPO for at least 8 weeks prior to and including the screening period. Additionally, participants need to have stable Hgb levels for the 4 weeks of screening. Finally, participants will be switched from their current rhEPO to daprodustat using a switching algorithm that was designed to result in no change in Hgb levels. All of these aspects are intended to minimize any potential for a change in erythropoiesis during the course of the study in order to minimize any potential change in oral iron absorption due to a change in erythropoiesis (Skikne, 2000).
- The planned population is participants currently on rhEPO for anemia associated with chronic kidney disease that are non-dialysis dependent. This population was chosen as those most likely to be administered oral iron therapy for the treatment of anemia. Additionally, as oral iron is inferior to IV iron likely due to elevated levels of hepcidin and pro-inflammatory cytokines that restrict intestinal iron absorption, this is the population most likely to benefit from an increase in oral iron absorption (Macdougall, 2016).
- This study uses iron incorporation into erythrocytes in order to assess oral iron absorption. While it is appreciated that changes in erythrocyte iron content can be due to many factors, erythrocyte iron content is a well-recognized surrogate for iron absorption (IAEA Human Health Series No. 21, 2012). Additionally, fractional iron absorption as an endpoint allows for comparison to studies in non-anemic participants.
- At present, three methodologies are primarily recognized for assessing fractional iron absorption: fecal recovery of the ingested isotope, plasma appearance of the ingested isotope and iron incorporation into erythrocytes following oral ingestion. Of the three, the most frequently used approach is iron incorporation into erythrocytes using single or multiple oral labels as it is more sensitive than either the fecal recovery or plasma appearance methods (IAEA Human Health Series No. 21, 2012). The majority (80%) of the iron that is absorbed is incorporated into red blood cells in Hgb, a process which occurs over 10 to 12 days. Once incorporated, the iron is stable for the lifespan of the red blood cell, a period of up to 120 days in non-anemic participants and approximately 70 days in individuals with chronic kidney disease.
- Iron absorbed from the diet is obtained from animal-based sources, and is known as heme iron, while plant-based iron is non-heme iron. This study will assess the

absorption of non-heme iron as most of the understanding of iron absorption is related to non-heme iron which typically comprises the majority of dietary and supplemental iron.

- ND-CKD patients which have elevated levels of C-reactive protein (CRP) and hepcidin typically experience poor intestinal iron absorption (Macdougall, 2014). Therefore, hsCRP will be assessed at screening for eligibility in order to minimize the recruitment of participants with poor intestinal iron absorption due to inflammation.
- Finally, stable isotopic iron will be administered in the fasted state as the fraction of iron absorbed in the fasted state is typically much higher than that which occurs when a component of a mixed meal. A recent publication using this methodology in 18 healthy, adult female participants reported an average absorption ± SD of 14.71 ± 10.7% in the fasted state compared to 3.63 ± 6.5% in the fed state (Young, 2009). In this regard, it is considered that a 30% change in oral iron absorption is clinically relevant.

5.5. Dose Justification

- The dose of rhEPO in this study will be the stable doses (≤ 50% change in 4-weekly dose) administered for at least 8 weeks prior to and including the screening period.
- The goal of the starting doses of daprodustat in this study is to maintain Hgb levels achieved on the prior rhEPO dose so that, on average, there is no change from baseline Hgb. Starting doses of 1, 2 or 4 mg of daprodustat are estimated to maintain Hgb levels observed with participant's prior rhEPO therapy based on population dose-response longitudinal modelling of Hgb data collected across the Phase 2 program (GlaxoSmithKline Document Number 2015N248947_00, 2016).

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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 the following criteria apply:

Age

1. Participant must be at least 18 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are Stage 3, 4 or 5 CKD (confirmed at Week -4 only) defined by eGFR using the CKD Epidemiology Collaboration (CKD-EPI) formula (Levey, 2009). See the Study Reference Manual (SRM) for details on calculation.

3. Participants who are currently treated with stable doses (≤ 50% change in 4-weekly dose) for at least 8 weeks prior to and including the screening period, of rhEPO (i.e., epoetin alfa or darbepoetin alfa).
4. Participants with Hgb levels between 9.0 and 11.5 g/dL, inclusive, who meet the Hgb stability criteria as outlined in Section 6.2.1.
5. Participants may be on stable maintenance oral iron supplementation (<50% change in overall dose and compliance of 80% of prescribed doses in the 4 weeks prior to and including the screening period). If participants have been on IV iron, then participants will not have received IV iron for 8 weeks prior to the Day 1 visit.

Sex

6. Male or female

   a. Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 7), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 7

   OR

   (ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 7 during the treatment period to the follow-up visit.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 5 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. On dialysis or clinical evidence of impending need to initiate dialysis within 90 days after study start (i.e., Day 1).
2. Planned kidney transplant within 3 months after study start.
3. A positive test for HIV antibody.

Prior/Concomitant Therapy

4. History of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational products (see Daprodustat IB for list of excipients).
5. Use of any prescription or non-prescription drugs or dietary supplements that are prohibited from screening until the end of Treatment Period 2 (see Section 7.7.2).
6. Planned or current administration of Mircera (methoxy PEG-epoetin beta).

Prior/Concurrent Clinical Study Experience

7. The participant has participated in a clinical trial and has received an experimental investigational product within the prior 30 days or 5 half lives, whichever is longer, from screening through Day 1.

Diagnostic assessments

8. At or below the lower limit of the reference range at screening for Vitamin B_{12} (may rescreen in a minimum of 8 weeks).
9. Ferritin outside the range between 100 and 500 ng/mL, inclusive, at screening.
10. Transferrin saturation (TSAT) outside the range between 15% and 40%, inclusive, at Screening.
11. Folate < 2.0 ng/mL (4.5 nmol/L; may rescreen in a minimum of 8 weeks) at screening.
12. High sensitivity C-reactive protein (hsCRP) ≥ 20 µg/mL at screening.

Other Exclusions

13. Myocardial infarction or acute coronary syndrome: ≤ 8 weeks prior to screening through Day 1.
14. Hospitalization for greater than 24 hours: ≤ 8 weeks prior to screening through Day 1
15. Stroke or transient ischemic attack ≤ 8 weeks prior to screening through Day 1.
16. Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system.
17. Current uncontrolled hypertension as determined by the investigator.
18. QT interval corrected for heart rate using Bazett's formula (**QTcB**): QTcB > 500 msec, or QTcB > 530 msec in participants with Bundle Branch Block. There is no QTc exclusion for participants with a predominantly paced rhythm.
19. Active chronic inflammatory disease that could impact erythropoiesis. A partial list can be found in the Study Reference Manual (SRM).
20. History of bone marrow aplasia or pure red cell aplasia.
21. Conditions, other than anemia associated with chronic kidney disease, which can affect erythropoiesis. A partial list can be found in the SRM.
22. Evidence of actively bleeding gastric, duodenal, or esophageal ulcer disease OR clinically significant GI bleeding from ≤ 4 weeks prior to screening through Day 1.
23. Liver disease (any of the following):

- Alanine transaminase (ALT) > 2x upper limit of normal (ULN; screening only)
- Bilirubin > 1.5x ULN (screening only)
  NOTE: Isolated bilirubin > 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%

- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

24. Major surgery (excluding vascular access surgery) within the 8 weeks prior to screening through Day 1 or planned during the study.
25. Blood transfusion within 8 weeks prior to screening through Day 1, or an anticipated need for blood transfusion during the study.
26. Clinical evidence of an acute infection, or history of infection requiring IV antibiotic therapy from 4 weeks prior to screening through Day 1.
    NOTE: Prophylactic antibiotics are allowed.
27. History of malignancy within the two years prior to screening through Day 1 or currently receiving treatment for cancer, with the exception of localized squamous cell or basal cell carcinoma of the skin definitively treated 12 weeks prior to Day 1.
28. Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study.

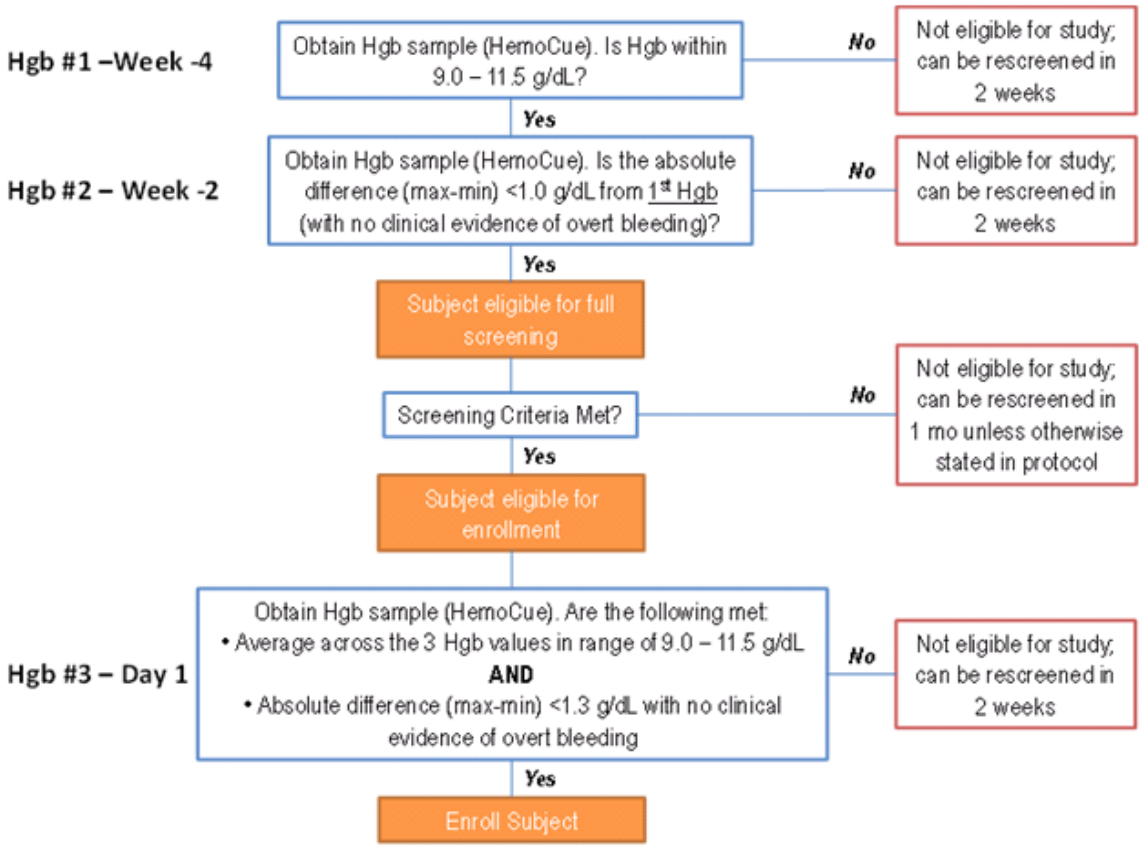
6.2.1. Hgb Stability Criteria

Entry into the study requires a stable Hgb between **9.0 - 11.5 g/dL**.

- This criterion is assessed from an average of **three** Hgb values obtained via a validated point-of-care device to measure Hgb (HemoCue) on site during the screening period at Week -4, Week -2 and on Day 1.
- The Hgb stability assessment is the difference between the maximum and minimum values of the three Hgb measurements obtained between Week -4 and Day 1.

A decision algorithm for Hgb stability is shown in Figure 3.

Figure 3 Hgb Stability Criteria



6.3. Lifestyle Restrictions

No lifestyle restrictions are required.

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Participants at study entry will discontinue their rhEPO therapy (i.e., epoetin alfa or darbepoetin alfa) prior to randomization so that the randomization date (Day 1) should coincide, as closely as possible, with the date of the next scheduled rhEPO administration. Examples of switching are provided in the SRM.

7.1. Treatments Administered

Study Treatment Name:	**Daprodustat**	**rhEPO (epoetin alfa OR darbepoetin alfa)**	**^{57}Fe**	**^{58}Fe**
Dosage formulation:	Tablet	Solution for injection	$^{57}FeSO_4$ Oral solution	$^{58}FeSO_4$/ $^{56}FeSO_4$ Oral solution
Unit dose strength(s)/ Dosage level(s):	1 mg, 2 mg, 4 mg tablet strengths/1 mg, 2 mg, 4 mg dosage levels	rhEPO is commercially available in various single-dose vials and single-dose prefilled syringes	$^{57}FeSO_4$ (containing 10 mg of ^{57}Fe) 10 mg total dose of Fe	$^{58}FeSO_4$ (containing 3 mg of ^{58}Fe) $^{56}FeSO_4$ (containing 7 mg of ^{56}Fe) 10 mg total dose of Fe
Route of Administration	Oral	Subcutaneous injection	Oral	Oral
Dosing instructions:	1 tablet to be taken daily without regard for food	As per product labelling	Full dosing instructions can be found in the SRM	Full dosing instructions can be found in the SRM
Packaging and Labeling	Study Treatment will be provided in a bottle. Each bottle will be labeled as required per country requirement.	As per product labelling	N/A	N/A
Manufacturer	GSK	Amgen	Formulated by extemporaneous compounding	Formulated by extemporaneous compounding

7.1.1. Daprodustat Dosing Information

Doses of daprodustat to be administered are based on the rhEPO dose at randomization (Day 1) as described in Table 2.

Table 2 Daprodustat Doses

Darbepoetin alfa (µg/4 wk SC/IV)	Epoetin alfa (convert SC to IV U/week)[1]	Daprodustat dose (mg, once daily)
20 to 30	1500 to 2000	1
>30 to 300	>2000 to <20000	2
>300	≥20000	4

[1] Standardized rhEPO IV dose (U/week) = 161/113 x (epoetin SC dose (units)/frequency)

7.1.2. rhEPO Dosing Information

Participants are required to be currently treated with stable doses (≤ 50% change in 4-weekly dose) of rhEPO for at least 8 weeks prior to and including the screening period. The dose of rhEPO to be administered during the study as randomized study treatment will be the rhEPO dose at randomization (Day 1). This dose is to be administered whether a participant is randomized to rhEPO on Treatment Period 1, or is switching back to rhEPO following 4 weeks of administration of daprodustat on Treatment Period 2.

7.1.3. ^{57}Fe Dosing Information

An oral solution will be administered containing 10 mg of ^{57}Fe as ferrous sulfate. Exact doses will be measured, calculated, and captured for each individual participant. The solution is to be taken following an overnight fast. Further details will be outlined in the compounding document and SRM.

7.1.4. ^{58}Fe Dosing Information

An oral solution will be administered containing 3 mg of ^{58}Fe as ferrous sulfate with 7 mg of ^{56}Fe as ferrous sulfate (natural abundance Fe). Exact doses will be measured, calculated, and captured for each individual participant. The solutions are to be taken following an overnight fast. Further details will be outlined in the compounding document and SRM.

7.2. Dose Modification

No dosage modification is anticipated in this study. However, if it becomes medically necessary to adjust the dose of either rhEPO or daprodustat, the participant is to be withdrawn from the study.

7.3. Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site.

7.4. Blinding

This is an open-label study; potential bias will be reduced by using central randomization. Further, fractional iron absorption is an objective endpoint, such that participant knowledge of the treatment received is unlikely to affect the results.

7.5. Preparation/Handling/Storage/Accountability

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

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.
- When participants self-administer study treatment(s) at home, compliance will be assessed through querying the participant during the site visits and documented in the source documents and eCRF. A record of the study treatment dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

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 enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

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.

Participants are to be advised to maintain use of the following medications at a consistent dosage and frequency:

- Oral iron supplementation (except ferric citrate, which is prohibited; see Section 7.7.2)
- Acid-reducing agents (e.g., H_2 receptor antagonists, proton pump inhibitors, antacids)

7.7.2. Prohibited Medications and Non-Drug Therapies

Use of any of the following prescription drugs from screening (Week -4) until the end of Treatment Period 2 is prohibited and will constitute a protocol deviation:

- Strong inhibitors of CYP2C8 (e.g., gemfibrozil, high dose clopidogrel [300 mg])
- Strong inducers of CYP2C8 (e.g., rifampin/rifampicin)
- The oral iron supplement ferric citrate
- Intravenous administration of iron
- Any rhEPO other than epoetin alfa or darbepoetin alfa

7.7.3. Standard of Care

During the study, investigators are expected to monitor the participant's overall clinical status to ensure standards of care are met to enable consistency of practice with KDIGO guidelines or local equivalent.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that discontinue study treatment should be withdrawn from the study. See Section 8.2 for a description of withdrawal procedures.

8.1.1. Liver Chemistry Stopping Criteria

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

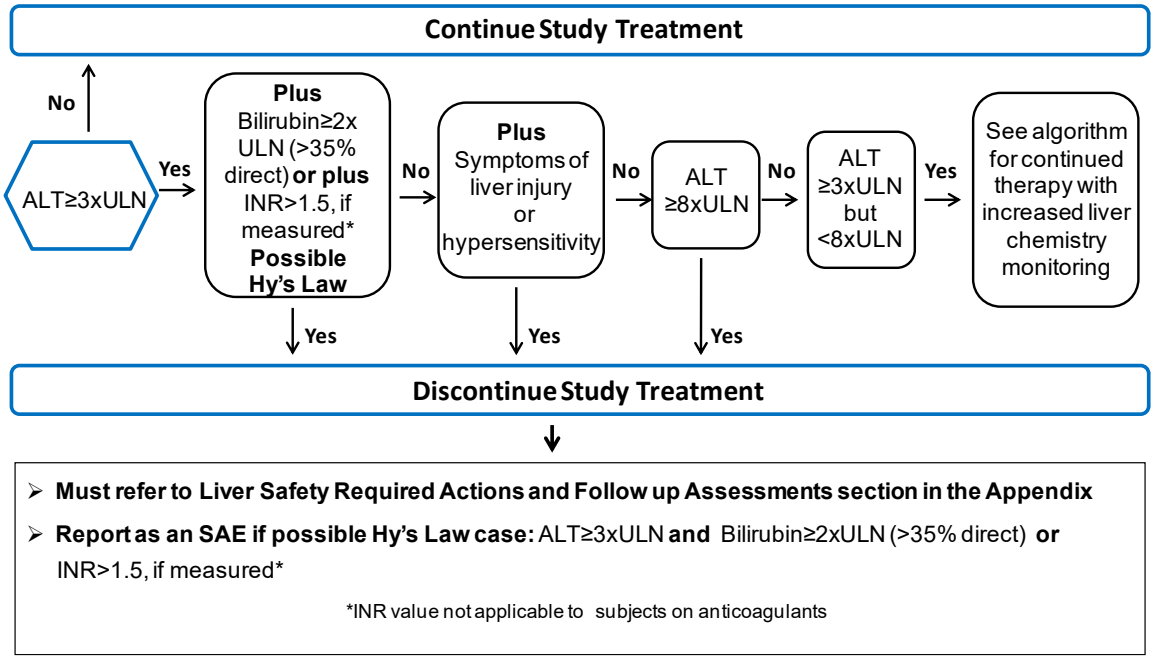
Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Figure 4

  OR

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

Figure 4 Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Participants that withdraw/are withdrawn from the study treatment are encouraged to attend the follow-up visit 14 ± 3 days following discontinuation of study treatment. Assessments to be conducted are listed in the SoA (Section 2).

8.2.1. Criteria for Permanent Discontinuation from Study Treatment and Early Withdrawal

Participants must **permanently discontinue study treatment** and be withdrawn from the study for the following reasons:

- Meets Hgb stopping criteria (See Section 8.2.1.1)
- Meets iron stopping criteria (See Section 8.2.1.2)
- If it becomes medically necessary to adjust the dose of either rhEPO or daprodustat
- Receives a blood transfusion
- Receives a kidney transplant
- Becomes pregnant or intends to become pregnant during the study
- Active GI bleeding
- Diagnosis of cancer, with the exception of squamous cell or basal cell carcinoma
- Liver chemistry abnormalities exceeding the threshold criteria (See Section 8.1.1)
- Use of prohibited medication (See Section 7.7.2)
- Active chronic inflammatory disease that could impact erythropoiesis
- Any new diagnosis of hematological disease including those affecting platelets, white or red blood cells, coagulation disorders, or any other cause of anemia of chronic disease other than renal disease

8.2.1.1. Hgb Stopping Criteria

GSK will supply a point-of-care Hgb analyzer (HemoCue) to each site for rapid and convenient monitoring of Hgb levels and to ensure consistency of Hgb measurements across sites participating in the study.

Blood samples for measurement of Hgb concentrations via HemoCue will be collected and recorded in the eCRF. Table 3 summarizes the Hgb values and corresponding action to be taken at each visit.

Table 3 Hgb Stopping Criteria

Hgb (g/dL) at visit		Action
<7.5		Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study treatment and withdraw participant from the study.
≥7.5 - <13.0 With:	≥2.0 g/dL **decrease** in Hgb over the **previous 2 weeks**	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study treatment and withdraw participant from the study.
≥7.5 - <13.0 With:	<1.0 absolute change in Hgb over the **previous 2 weeks**	Continue study treatment.
≥7.5 - <13.0 With:	≥1.0 increase in Hgb over the **previous 2 weeks**	Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study treatment and withdraw participant from the study.
≥13.0		Repeat HemoCue assessment on the same sample at same study visit to confirm; take average of 2 values. If confirmed, permanently discontinue study treatment and withdraw participant from the study.

8.2.1.2. Iron Stopping Criteria

Participants must remain iron replete throughout the study, and should remain on their regular oral iron supplement as described in Section 7.7.1.

Based on the PI's clinical judgement in consultation with Medical Monitor, if the subject cannot be maintained on the same oral iron dose during the study treatment periods, the subject must be withdrawn.

8.3. Lost to Follow Up

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

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

- 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.

- Should the participant continue to be unreachable, he/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).
- 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, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., Hgb levels) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

Efficacy is not evaluated in this study.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

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

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. 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 6.

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 9.2.4), 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 6.

9.2.4. Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) have been identified based on non-clinical studies with daprodustat, clinical experience with rhEPOs, and current information regarding HIF-regulated pathways in mediating hypoxia-associated pathophysiology. The currently identified AESI for daprodustat are as follows:

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

9.2.5. 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.

9.2.6. Cardiovascular and Death Events

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

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- 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.

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

9.2.7. 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.

9.2.8. Pregnancy

- Details of all pregnancies in female participants and the outcome for the neonate, if applicable, will be collected from the start of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

For this study, any dose of daprodustat greater than 4 mg within a 24-hour time period will be considered an overdose.

There is no specific antidote for overdose with daprodustat. The expected manifestations of daprodustat overdosage include signs and symptoms associated with an excessive and/or rapid increase in Hgb concentration. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted, as dictated by the participant's clinical status. Additionally, participants should be monitored closely for CV events, increased heart rate and hematologic abnormalities.

9.4. Safety Assessments

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

9.4.1. Entry Criteria

Entry criteria are to be assessed during the screening period, at Week -4, Week -2 and Day 1. The timing for assessment of specific criteria are detailed in the SoA (Section 2), and are described in Table 4

Table 4 Timing of Entry Criteria Assessments

Timing	Procedures
Week -4	Informed consent, complete physical examination, medical history, demography, height, weight, vital signs, clinical safety laboratory assessments, pregnancy test, eGFR, Hgb, HIV, concomitant medications, rhEPO dose
Week -2	Brief physical examination, Hgb, estradiol & FSH (as needed), ECG, folate, Vitamin B_{12}, hsCRP, ferritin, TSAT, concomitant medications, rhEPO dose
Day 1	Brief physical examination, weight, vital signs, Hgb, pregnancy test, concomitant medications, rhEPO dose

9.4.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.3. Vital Signs

- Oral temperature, pulse, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure

readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

9.4.4. Electrocardiograms

- ECG measurements will be obtained as outlined in the SoA (Section 2). Full 12-lead ECGs will be recorded with the participant in a supine position. Heart rate, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcB will be calculated (machine read or manually).
- At each time point at which ECGs are required, two additional ECGs are required if the initial ECG measurement indicates prolonged QTc (see Section 6.1) using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility.

9.4.5. Clinical Laboratory Assessments

Refer to Appendix 4 for the list of protocol-required clinical chemistry and hematology (Table 8) and additional clinical laboratory assessments (Table 9) to be performed and to the SoA (Section 2) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. 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 48 hours 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/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 Appendix 4, must be conducted in accordance with the laboratory manual and the SoA.

9.4.6. Liver Chemistry Monitoring

Clinical laboratory assessments for liver chemistry monitoring include ALT, AST, bilirubin and alkaline phosphatase. Refer to the SoA (Section 2) for the frequency of monitoring. Additionally, all of these tests are also part of the Clinical Chemistry Assessments and will be performed at the timepoints where those assessments are done. These assessments must be conducted in accordance with the laboratory manual.

9.5. Pharmacokinetics

Pharmacokinetic (PK) parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamics (PD) are not evaluated in this study.

9.7. Genetics

A 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 8 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

9.8.1. Fractional oral iron absorption

Venous blood samples will be collected for measurement of erythrocyte iron content at the times specified in the SoA (Section 2). Further details for blood collection procedures can be found in the SRM. Calculations for fractional iron absorption will be included in the Reporting and Analysis Plan (RAP).

9.8.2. Iron status markers

Markers of iron status (i.e., serum iron, transferrin, TSAT, soluble transferrin receptor, ferritin, hepcidin and erythroferrone) will be assessed at the times listed in the SoA. Measurement of erythroferrone is dependent upon available of a suitable assay methodology, so may not be assessed. All blood samples for iron status markers to be taken pre dose. Further details for blood collection procedures can be found in the SRM.

9.8.3. Indices of erythropoiesis

Indices of erythropoiesis (i.e., Hgb, hematocrit, red blood cell number, mean corpuscular volume, reticulocyte Hgb and reticulocyte number) are planned to be assessed at the times listed in the SoA (Section 2). Further details for blood collection procedures can be found in the SRM.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary analysis will test whether daprodustat is superior to rhEPO (i.e., epoetin alfa or darbepoetin alfa) according to the following statistical hypotheses:

Null: The difference in fractional iron absorption between treatment arms (daprodustat-rhEPO (i.e., epoetin alfa or darbepoetin alfa)) is equal to zero.

Alternative: The difference in fractional iron absorption between treatment arms (daprodustat-rhEPO (i.e., epoetin alfa or darbepoetin alfa)) is not equal to zero.

10.2. Sample Size Determination

Sufficient participants will be enrolled such that at least 12 participants comprise the Evaluable Population (See Section 10.3.1.3).

A sample size of 12 participants provides 90% power to detect a paired mean difference of 11% between the two treatment groups under an assumed between-participant standard deviation (SD) of 10.7%. Note this is a conservative estimate of the SD of the paired differences as it is based on a parallel design study (Young, 2009).

10.2.1. Sample Size Sensitivity

Table 5 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.

Table 5 Impact on power based on alternative assumptions for the between participant SD and the expected difference between the treatment groups

Between participant SD (%)	Expected difference between treatments in Fractional Iron Absorption (%) (daprodustat – rhEPO (i.e., epoetin alfa or darbepoetin alfa))				
	7	9	11	13	15
7	88%	98%	>99%	>99%	>99%
9	69%	88%	97%	>99%	>99%
10.7	54%	76%	**90%**	97%	>99%
12	43%	66%	82%	93%	98%
14	35%	53%	70%	83%	92%

10.2.2. Sample Size Re-estimation

No sample size re-estimation will be performed.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

10.3.1.1. Screened Population:

This population consists of all participants who signed an ICF to participate in the clinical trial. This population will be used for summarizing screening failure rates and reasons for screening failure.

10.3.1.2. Safety Population:

This population consists of all randomized participants who received at least one dose of study treatment. This will be the primary population for the safety analyses.

10.3.1.3. Evaluable Population:

This population consists of all randomized participants who received study medication and completed the iron absorption assessment for both treatment periods. This population will be used for the primary endpoint analysis.

10.3.1.4. Modified Intent to Treat (mITT) Population:

This population consists of all randomized participants who received study medication and completed the iron absorption assessment at the end of the first treatment period. This population will be used for the sensitivity analysis of the primary endpoint.

10.3.2. Interim Analyses

No interim analysis will be performed for this study.

10.4. Key Elements of Analysis Plan

10.4.1. Primary Analysis

To compare daprodustat to rhEPO (i.e., epoetin alfa or darbepoetin alfa) on fractional iron absorption, a mixed effect model will be fitted with fixed effect terms for treatment, sequence, period and iron isotope and a random effect for participant-within-sequence. The term sequence will consist of the four combinations of treatment and iron isotope assignments. Point estimates and corresponding 95% confidence intervals will be constructed for the comparison of efficacy of daprodustat to rhEPO.

A sensitivity analysis for this primary analysis will be performed using the same mixed modeling approach, except with the mITT population.

Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum) will be calculated for fractional iron absorption (%) at the Day 29 and Day 57 visits.

10.4.2. Secondary Analysis

Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum) will be calculated for iron markers and indices of erythropoiesis at each scheduled visit.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Further details will be given in the Reporting Analysis Plan (RAP).

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Table 6 List of Abbreviations

Ab	Antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
BUN	Blood urea nitrogen
CI	Confidence Interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease Epidemiology Collaboration
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum observed concentration
CPK	Creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
hsCRP	High sensitivity C-reactive protein
CV	Cardiovascular
CYP	Cytochrome P450 enzyme
DcytB	Duodenal cytochrome b561
dL	deciliter
DMT1	Divalent metal-iron transporter 1
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
Fe	Iron
FPN	Ferroportin
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GDF15	Growth differentiation factor 15
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HD	Hemodialysis dependent
Hgb	Hgb
HIF	Hypoxia-inducible factor
HIV	Human Immunodeficiency Virus
HIPAA	Health Insurance Portability and Accountability Act

HPLC	High performance liquid chromatography
HRE	Hypoxia response element
IAEA	International Atomic Energy Agency
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational new drug
INR	International normalization ratio
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
KDOQI	Kidney Disease Outcomes Quality Initiative
Kg	Kilogram
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular Hgb
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Myocardial infarction
mL	Milliliter
mmHg	Millimeters of mercury
MSDS	Material Safety Data Sheet
msec	Milliseconds
µM	Micromolar
ng	Nanogram
ND	Nondialysis dependent
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
PCI	Potential clinical importance
PD	Pharmacodynamic
PHD	prolyl-4-hydroxylases
PHIs	Prolyl hydroxylase inhibitors
PK	Pharmacokinetic
PRVP	Peak right ventricular pressure
PSRAE	Possible Suicidality Related Adverse Events
QTc	Corrected QT interval
QTcB	QT duration corrected for heart rate by Bazett's formula
RAP	Report and Analysis Plan
RBC	Red blood cells
rhEPO	Recombinant human erythropoietin
RNA	Ribonucleic acid

SAE	Serious Adverse Event
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SO_4	Sulfate
SoA	Schedule of Assessments
sPAP	systolic Pulmonary Artery Pressure
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
TIMS	Thermal ionization mass spectrometry
TF	Transferrin
TSAT	Transferrin saturation
VEGF	Vascular endothelial growth factor
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WBC	White blood cells
WOCBP	Woman of Child Bearing Potential

Trademark Information

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Aranesp (darbepoetin alfa)
Chiron RIBA
Epogen (epoetin alfa)
HemoCue
Procrit (epoetin alfa)
SAS
WinNonlin

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase III-IV liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Table 7 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 following ANY Liver Stopping Event	
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 (Day 1 predose) (see **MONITORING** below)	• 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].

Liver Chemistry Stopping Criteria - Liver Stopping Event	
• **Do not restart/rechallenge** participant **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 (Day 1 predose) • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline (Day 1 predose)	• Blood sample for pharmacokinetic (PK) analysis, obtained within 48 hrs after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

[1] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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 subjects receiving anticoagulants

[3] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
[4] Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
[5] If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
[6] PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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12.3. Appendix 3: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Excessive erythropoiesis leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis (Hgb/Hct > upper limit normal) attributed to daprodustat was associated with vascular congestion, microthrombi, and tissue ischemia in a number of organs. In the phase 2 proof of concept study, a high incidence of discontinuation due to hemoglobin stopping criteria (Hgb > 13.5 g/dL or Hgb increased > 1 g/dL over any 2-week period) was observed. In non-dialysis subjects administered 10 mg, 25 mg, 50 mg or 100 mg of daprodustat daily, a total of 21 of 61 subjects (34%) met these criteria. In hemodialysis-dependent subjects administered either 10 mg or 25 mg of daprodustat daily, a total of 8 of 31 subjects (26%) met these criteria. Phase 2 dose-ranging studies, and associated statistical and dose response modelling has informed Phase 3 dose rationale, starting doses, dose steps, and dose adjustment scheme to optimize Hgb management. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: Few subjects experienced a possible thrombosis related adverse event in the setting of excessive erythropoiesis [3/688 (0.5%) subjects on daprodustat vs. 0/404 on rhEPO]. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat when dose is managed appropriately according to target Hgb. However, experience with daprodustat is currently insufficient to fully characterize this risk.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 6.2.1. • Hgb will be closely monitored throughout the dosing period as outlined in the SoA Table Section 2. • Specific guidance for discontinuation of daprodustat based on achieved Hgb is provided in Section 8.2.1.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team.
Worsening hypertension	In a dog cardiovascular study, single oral doses of daprodustat (up to 90 mg/kg) did not produce effects on blood pressure. Marketed rhEPO and its analogues have been associated with risks related to uncontrolled hypertension, including the need for initiation of or increases in antihypertensive therapy when used in patients with	• Specific eligibility criteria related to blood pressure, including exclusion of subjects with uncontrolled hypertension, are detailed in Section 6.2 .

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	anemia of CKD (i.e. 25% Epogen, 27% Mircera, and 40% Aranesp treated patients with renal anemia required initiation or increase in their anti-hypertensive medications; hypertensive encephalopathy and seizures have been reported. The contribution of rhEPO-associated hypertension to the unfavourable effects on cardiovascular outcomes remains uncertain). Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: ○ The majority (>90%) of subjects had baseline history of hypertension. ○ No meaningful difference was seen between treatment groups in AEs (preferred term) of "hypertension" [29/688 (4%) daprodustat vs. 19/404 (4%) rhEPO; 0.91 relative risk (RR) (95% confidence interval: 0.5, 1.67)] or "blood pressure increased" [16 (2%) daprodustat vs. 7 (2%) rhEPO; RR 1.22 (0.48,3.11)]. Results were not substantively different between non-dialysis and haemodialysis subjects. ○ Although no clinically meaningful changes in blood pressure were observed, subjects in both treatment groups required increases in anti-HTN medications: ○ In the 24-week global phase 2b studies, 25/170 (15%) of ND subjects receiving daprodustat vs. 18/80 (14%) control and 22/177 (12%) of HD subjects receiving daprodustat vs. 2/39 (5%) control. ○ In the 52-week Japan phase 3 studies, 57/149 (38%) of ND subjects receiving daprodustat vs. 68/150 (45%) rhEPO and 51/136 (38%) of HD subjects receiving daprodustat vs. 66/135 (49%) for rhEPO. The data received to date from completed clinical trials with daprodustat are insufficient to refute this risk.	• Blood pressure will be closely monitored throughout the dosing period as outlined in the SoA Table Section 2. • Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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/ESAs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD. Clinical studies with marketed rhEPO/analogs have suggested "higher" target hemoglobin, rate of hemoglobin rise of greater than 1 g/dL in any 2-week period, and/or higher doses may contribute to these risks. Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in the overall incidence of this AESI: [39/688 (5.5%) daprodustat vs. 25/404 (6%) rhEPO; 0.92 relative risk (95% confidence interval: 0.55, 1.53)]. Within this composite AESI, the most frequent event types were heart failure (at least 12 events daprodustat vs. at least 13 events rhEPO) and thrombosis (at least 14 events daprodustat vs. at least 8 event rhEPO); and a numerical imbalance was noted in events of myocardial ischemia (at least 7 events daprodustat vs. at least 1 event rhEPO). The small number of events makes it difficult to draw any firm conclusions. The data received to date from completed clinical trials with daprodustat are insufficient to substantiate or refute this risk.	• Specific eligibility criteria related to CV risk are outlined in Section 6.2. • Hgb will be closely monitored throughout the dosing period as outlined in the SoA (Section 2). • Monitoring of emerging safety data by an internal GSK Safety Review Team.
Esophageal and gastric erosions	In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ulcers with hemorrhage were observed with daprodustat. In rodents stomach erosions observed with intravenous and oral administration of daprodustat. Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat).	• Suspected GI bleeding or significant symptoms consistent with erosion should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted. • Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported adverse event, however causal association has not been established. Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in reports of this AESI [17 (2.7%) daprodustat vs. 10 (2.3%) rhEPO; 1.16 relative risk (95% confidence interval: 0.52, 2.58)]. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	
Cancer-related mortality and tumor progression and recurrence	Marketed rhEPOs have been associated with increased risk of cancer related morbidity and mortality when used in patients with cancer. Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. In clinical studies with daprodustat up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations, an angiogenic factor that has been implicated in tumor growth, was observed at doses ranging from 10 to 150 mg. In clinical studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in the occurrence of this AESI: [8/688 (1.1%) daprodustat vs. 4/404 (0.9%) rhEPO; 1.14 relative risk (95% confidence interval: 0.31, 4.28)]. Clinical experience to date is not yet sufficient to substantiate or refute this as a safety concern for daprodustat.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 6.2. • Stopping criteria for participants with treatment emergent malignancy are outlined in Section 8.2.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pulmonary artery hypertension (PAH)	A role for HIF-regulated pathways in the pathophysiology of PAH has been suggested based on well-established effects of acute and chronic hypoxia in man on the pulmonary vasculature (vasoconstriction), and by findings in patients with naturally occurring mutations that result in decreased HIF degradation [Smith, 2006; Formenti, 2011]. There have been no histopathologic findings suggestive of PAH in pre-clinical safety studies with daprodustat (up to 13 weeks duration in mice and dog, up to 26 weeks in rat, and up to 39 weeks in monkeys. Acute hypoxic challenge (rats): Daprodustat produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. These hypoxia-induced PRVP changes fall within the range of PRVP differences noted among non-treated rats. Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with daprodustat 5 mg or 100 mg has no clinically significant effect on echocardiographically-estimated systolic pulmonary artery pressure (sPAP) under either normoxic or hypoxic conditions. ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically-meaningful changes in sPAP in participants not on dialysis for daprodustat. In hemodialysis participants, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (Daprodustat: 8 [7%]; Control 0) in participants reaching the sPAP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 participants with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study treatment; and there was no dose relationship for participants meeting the sPAP PCI	• Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat. A post-hoc analysis was performed using a definition of PAH commonly cited in the literature [Navaneethan, 2016]. Subjects with sPAP >35 mmHg and/or tricuspid regurgitation maximum jet velocity (TRV) >2.5 m/s were considered as having PAH. Regardless of baseline status of PAH, there was no clinically meaningful difference in the proportion of subjects with on-treatment PAH between the two treatment groups: ○ Subjects with PAH at baseline: 35/113 (31%) vs. 21/54 (39%) (ND) and 37/115 (32%) vs. 7/21 (33%) (HD), daprodustat vs. control, respectively. ○ Subjects without PAH at baseline: 25/113 (22%) vs. 12/54 (22%) (ND) and 22/115 (19%) vs. 6/21 (29%) (HD), daprodustat vs. control, respectively. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: Four (0.5%) non-serious AEs in the daprodustat group vs 0 in rhEPO. • Review of subject level information did not suggest adverse treatment effect: 2 subjects from phase2b that met protocol specified stopping criteria on scheduled ECHO had non-serious AEs of 'pulmonary arterial pressure increased' and 2 subjects from Japan Phase 3 had non-serious AE 'pulmonary hypertension' in setting of concurrent serious AEs of acute pulmonary embolus and mitral regurgitation identified during hospitalization for coronary angiography. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Cardiomyopathy	Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized.	• Monitoring of emerging safety data by an internal GSK Safety Review Team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Small increases in cardiac troponin in 6 month rat study with daprodustat were consistent with the background finding of spontaneous rodent cardiomyopathy. There were no elevations observed in cardiac troponin in 9 month monkey study with daprodustat. Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization. ECHO assessments performed in phase 2b studies (24 weeks treatment duration) did not identify any clinically meaningful changes in LVEF for daprodustat. Integrated AE data from clinical trials with daprodustat [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in reports of this AESI [1 (0.1%) daprodustat vs. 1 (0.2%) rhEPO; 0.64 relative risk (95% confidence interval: 0.02, 18.07)]. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	
Proliferative retinopathy, macular edema, choroidal neovascularization	Increases in local (ocular) VEGF production with retinal neovascularization and macular edema observed in diabetic retinopathy and to choroidal leakage, edema and neovascularization seen in age-related macular degeneration [Campochiaro, 2006]. Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating VEGF while significant EPO increases were observed. No ocular abnormalities with daprodustat were seen in non-clinical studies of up to 13 weeks duration in mice and dogs, 26 weeks in rats, and 39 weeks in monkeys. In clinical studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10	• Suspected proliferative retinopathy, macular edema, choroidal neovascularization or symptoms consistent with these events should be investigated by ophthalmologic consultation as clinically warranted. • Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	to 150 mg. 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. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in reports of this AESI [9 (2.9%) daprodustat vs. 6 (2.5%) rhEPO; 1.19 relative risk; (95% confidence interval: 0.42, 3.43)]. Following review of clinical data with daprodustat received to date, this has not been identified as a safety concern for daprodustat.	
Exacerbation of rheumatoid arthritis	In inflamed rheumatic joints, activation of HIF-related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Campochiaro, 2006; Westra, 2010; Muz, 2009]. No abnormalities seen in non-clinical studies conducted to date for daprodustat. Integrated AE data [including 2 global phase 2b studies (24-week treatment duration) and 2 Japanese phase 3 studies (52-week treatment duration)]: No meaningful difference was seen between treatment groups in reports of this AESI [2 (0.3%) daprodustat vs. 1 (0.2%) rhEPO; 1.20 relative risk; (95% confidence interval: 0.07, 20.87) and the incidence of musculoskeletal AEs was generally lower in the daprodustat treatment group]. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug-drug interactions	Daprodustat is a substrate of CYP2C8. Co-administration of daprodustat with the strong CYP2C8 inhibitor, gemfibrozil increased the Cmax and AUC of daprodustat, 4- and 19-fold, respectively, while co-administration of the 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, coadministration of daprodustat with an inducer of CYP2C8 (e.g.,rifampin/rifampicin) may decrease the exposure of daprodustat.	• 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. • 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 period as outlined in the SoA in Section 2. • Specific guidance for discontinuation of daprodustat based on achieved Hgb is provided in Section 8.2.1.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team.
Cyst progression in patients with autosomal dominant polycystic kidney disease (ADPKD)	Published data provide in vivo evidence for a potential role of HIF-1a in the growth of polycystic kidneys; Hif-1a deletion was sufficient to significantly mitigate a progressive polycystic phenotype in an ADPKD mouse model, while conversely pharmacologic HIF-1a stabilization was sufficient to convert a mild polycystic disease into a severely aggravated phenotype with marked loss of renal function. However, the dose of FG-2216 (a PHI) used resulted in a significant erythropoietic response as reflected by ≥10% relative increases in hematocrit over the course of the study. (Kraus, 2018; Hofherr, 2018). A review of the non-clinical data from toxicity studies conducted with daprodustat does not indicate an exacerbation in incidence or severity of kidney cysts in daprodustat-treated animals in comparison to controls. However, the wild type animals used in these toxicity	• Kidney function will be monitored throughout the dosing period as outlined in the SoA (Section 2). • Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	studies have a very low background incidence of renal cysts and are not comparable to the mice used in the Kraus article (Kraus, 2018) which are an inducible kidney epithelium-specific Pkd1-deletion model. There is limited experience with daprodustat in subjects with ADPKD in completed clinical trials. In the Japan phase 3 study in non-dialysis subjects, there were 5 subjects with ADPKD (all CKD stage 5) in each treatment group. Mean baseline eGFR was 10 mL/min/1.73m2 in the daprodustat subjects vs. 16 mL/min/1.73m2 in the rhEPO subjects. The mean (SD) percent change from baseline at Week 52 in eGFR was: -18% (8) vs. -21% (14) in daprodustat vs. rhEPO, respectively. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	

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12.4. Appendix 4: Clinical Laboratory Assessments

The tests detailed in Table 8 will be performed by a central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- 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.

Table 8 Clinical Laboratory Assessments

Assessments	Parameters			
Hematology	Platelet Count RBC Count Hgb Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

Assessments	Parameters
Other Laboratory Analyses	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • HIV antibody • Folate, high sensitivity C-reactive protein, Vitamin B_{12} • Serum iron, ferritin, transferrin, transferrin saturation, soluble transferrin receptor, hepcidin, erythroferrone • Hemoglobin, hematocrit, red blood cell number, mean corpuscular volume, reticulocyte hemoglobin, reticulocyte number

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 2. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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).
[2] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.5. Appendix 5: Study Governance Considerations

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

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.

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.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

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.

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.

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 subjects, as appropriate.

- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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 eCRF.
- 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 eCRF 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 15 years after study completion 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.

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 SRM.

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

12.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • 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 intervention.

Events <u>Meeting</u> 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 (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention 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 intervention 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.

Events <u>NOT</u> 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.

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.

c. 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 fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in 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.

e. Is a congenital anomaly/birth defect

f. 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.

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: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK/AE/SAE eCRF 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 sufficient 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 intervention 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 eCRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

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 by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor. • 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.

12.7. Appendix 7: 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 enrolment.

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 9.

Table 9 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[1] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[2] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[2] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[2] • 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.)*

[1] 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.
[2] 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 at least to the follow-up visit.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the test kit provided by the central laboratory and in accordance with instructions provided in its package insert.

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 6. 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 and be withdrawn from the study.

12.8. Appendix 8: 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 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 or other period as per local requirements.

12.9. Appendix 9: Protocol Amendment History

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

Previous Amendment:

Amendment 2 13-Aug-2019

Overall Rationale for the Amendment:

After the publication of the first protocol amendment, the iron for ingestion needed to be compounded differently.

In order to ensure tighter control of iron supplementation given the purpose of this study, specific parameters for iron supplementation were provided. Similarly, a revision was made to include additional weight measurements of participants in case of significant unexpected weight loss or gain during the study. This could have bearing on blood volume and ultimately iron content within an individual.

Exclusion criterion #18 was revised to exclude all individuals with hypertension deemed "uncontrolled" per the discretion of the primary investigator instead of specific blood pressure parameters in order to align with the daprodustat program.

Discrepancies were noted between Section 9.2.8 and the pregnancy guidance in Appendix 7; these respective sections were updated accordingly.

Revisions were made throughout the protocol to align with GSK standard language and for clarity where necessary. More specific rationales are provided for each item in this category in the table below.

Section # and Name	Description of Change	Brief Rationale
Short title and 1 Synopsis	The short title was changed.	All studies for this asset have a similar nomenclature; this change is to align globally.
1 and 4 Objectives and Endpoints	Safety endpoints were moved into their own section. No additions or deletions in the endpoint text.	To permit easier identification of safety endpoints.
2 Schedule of Activities	A weight assessment was added to several visits throughout the study period.	To allow more accurate calculations of the fractional iron absorption should a participant experience a significant weight change during the study.
6.1 Inclusion Criteria	Criterion 5 was updated to provide parameters for consistent provision of iron supplementation.	For clarity.
6.2 Exclusion Criteria	Updated the language in the exclusion criterion #18 surrounding blood pressure.	To align with the daprodustat program.

Section # and Name	Description of Change	Brief Rationale
7.1 Treatments Administered	The revised formulation of the iron isotope solution was provided.	To reflect the contents of the revised iron isotope solution.
7.1.3 ^{57}Fe Dosing Information	The description and formulation of the iron isotope (^{57}Fe) was updated.	To reflect the revised procedure for provision of the ^{57}Fe isotope used in the study.
7.1.4 ^{58}Fe Dosing Information	The description, dosing, and formulation of the iron isotope (^{58}Fe) was updated.	To reflect the revised procedure for provision of the ^{58}Fe isotope used in the study.
7.7.2 Prohibited Medications	High dose clopidogrel (300 mg) was added.	An additional example of a strong CYP2C8 inhibitor was added.
8.2.1.1 Hgb Stopping Criteria	The structure of Table 2 was modified.	For clear distinction between assessment of the Hgb and resultant action(s).
9.2 Adverse Events	Updated GSK standard language.	For consistency among GSK protocols.
9.2.8 Pregnancy	Text was updated to reflect guidance given in Appendix 5.	Correction of error .
10.3.2 Interim Analysis	The potential for an interim analysis was removed.	GSK deemed the interim analysis was no longer necessary in support of the daprodustat program.
12.3 Appendix 3: Risk Assessment	Several updates were made to the risk assessment table.	The benefit-risk table was recently updated.
12.6 Appendix 6: Definition of Cardiovascular Events	The table with definitions of cardiovascular events was added.	For consistency among GSK protocols.
12.6 Appendix 6: Reporting of SAE to GSK	Additional text surrounding the requirement for the PI to review SAEs and to provide causality within 72 hours of the SAE entry into the eCRF was added.	For consistency among GSK protocols.

Amendment 1 30-Nov-2017

Overall Rationale for the Amendment: It was noted that one exclusion criterion was incorrect. This amendment serves to revise that as well as streamline the study procedures, as noted from investigators. Lastly, minor spelling and context errors were corrected.

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria	Changed criterion to high sensitivity CRP; Corrected value for hsCRP exclusionary criterion	To have clear exclusion criteria; ensure consistency with other program protocols
6.2 Exclusion Criteria	Changed the prior clinical study experience criteria from 120 days to 30 days	Ensure consistency with other program protocols; re-evaluation determined this duration is not necessary; improve recruitment.
2 Schedule of Assessments	Updated pregnancy testing time points.	More complete pregnancy testing throughout the study; better compliance with GSK standards.
2 Schedule of Assessments	Changed routine urinalysis to coincide with urine pregnancy testing.	Ease of procedural parameters for the sites.
2 Schedule of Assessments	Added in one time point for isotopic iron blood sampling	Affords more robust analysis of absorption of one isotope vs the other
2 Schedule of Assessments	Added/changed various time points for vital signs	More complete monitoring throughout study; better compliance with GSK standards.
2 Schedule of Assessments; Appendix 4	Ferritin included in a footnote for the iron status markers and added to the Laboratory Assessments Table	Initial intention was to include ferritin in the iron status markers. Adds consistency throughout the document as ferritin is listed in the Objectives and Endpoints as well as the Iron Status Markers Section (9.8.2)
Appendix 4	Clinical Laboratory Assessments Table 8 and Table 9 were combined	The two tables were combined for a more clear understanding of the laboratory assessments for the study.
Section 9.4.1	Table 4 was updated to reflect the changes in the Schedule of Assessments.	For consistency.
2 Schedule of Assessments, Section 9.8.2	Iron status markers collection	Additional guidance given for blood draw relative to IP dosing
Section 12.4, Table 8	Fasting Glucose	Removed the fasting requirement for this lab value; determined to be unnecessary for this study.