TITLE PAGE

Protocol Title: A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function.

Protocol Number: 200231

Short Title: Daprodustat hepatic impairment study

Compound Number: GSK1278863

Sponsor Name and Legal Registered Address:

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1. SYNOPSIS

Protocol Title: A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function.

Short Title: Daprodustat hepatic impairment study

Rationale:

A recent study has shown that co-administration of daprodustat with a strong, irreversible inhibitor of the cytochrome (CYP) 2C8 enzyme (i.e., gemfibrozil) lead to marked increases in both daprodustat Cmax (4-fold) as well as AUC (19-fold). This suggests that the liver is primarily involved in the clearance of daprodustat through the CYP2C8 enzyme and, therefore hepatic impairment has the potential to affect daprodustat clearance and exposure. Thus, the intent of this study is to assess the effect of hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of daprodustat. The results of this study are planned to provide guidance on administration of daprodustat to patients with impaired hepatic function.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI)	Daprodustat and its metabolites plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-∞)], percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time zero (pre-dose) to last time of quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life (t½), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat
To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat in plasma	Unbound concentration and unbound fraction in plasma of daprodustat at 3, 12 and 24 h post dose (as data permit)
Secondary	
To characterize the effect of hepatic impairment on the pharmacodynamics effect of daprodustat	Maximum observed effect (Emax) and and area under the effect curve from administration to the last measureable erythropoietin concentration [AUC(E, last)]
To assess the safety and tolerability of a single 6 mg dose of daprodustat	Safety and tolerability parameters, including adverse events and clinical laboratory tests

Overall Design:

This will be a Phase 1, open-label, non-randomized, parallel group, single-dose, adaptive study in adults with moderate (Part 1) and potentially either mild or severe (Part 2) hepatic impairment and matched, healthy control participants with normal hepatic function.

All participants will undergo screening assessments within 28 days of enrolment. A decision to progress from Part 1 to 2 will be made based on the available study results, with the potential that Part 2 of the study will not be conducted.

In Part 1, healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (Child-Pugh score of 7-9). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state followed by pharmacokinetic and pharmacodynamic sampling for total concentrations of daprodustat in plasma. At sparse sampling times, unbound daprodustat concentrations will be assessed.

In Part 2, if the geometric mean total plasma AUC pharmacokinetic parameters of daprodustat is increased in Part 1 by ≥2-fold in moderately-impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with mild impairment (Child-Pugh score of 5-6; n=8) and matched, control participants (n=8). Alternatively, if the geometric mean total plasma AUC(0-∞) of daprodustat is increased by <2-fold in moderately impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with severe impairment (Child-Pugh score of 10-13; n=8) and matched, control participants (n=8). Similar to Part 1 of the study, all participants will receive 6 mg of daprodustat followed by pharmacokinetic and pharmacodynamic blood sampling.

Number of Participants:

A sufficient number of participants will be enrolled to ensure there are at least 8 participants comprising the pharmacokinetic population per cohort.

Recruitment of **Part 1** of this study will include the full range of participants with moderate hepatic impairment including at least one with a Child-Pugh score of 7, one with a score of 8 and one with a score of 9. The recruitment will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described.

Similar to the participants in Part 1, recruitment of **Part 2** of this study, if conducted, will include a range of participants as follows:

- If Part 2 is conducted, the study will recruit participants with mild hepatic impairment, recruitment will include at least one with a Child-Pugh score of 5 and one participant with a score of 6, and will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population.

- If Part 2 is conducted, the study will recruit participants with severe hepatic impairment, recruitment will include at least one with a Child-Pugh score of 10 or 11 and one with a score of 12 or 13, and will also include at least one female and at least one male participant in both the severe hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population.

Treatment Groups and Duration:

In both **Part 1**, and if conducted, **Part 2**, all participants will be administered 6 mg of daprodustat as a single oral dose, with assessments conducted for up to 48 h postdosing.

A follow-up visit will occur 10-14 days after the dose of study treatment.

A participant's total involvement with the study will be up to 7 weeks.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Informed Consent	X																	
Inclusion & Exclusion Criteria	X	X																
Demography	X																	
Full physical exam	X																	
Medical history	X																	
Past/current medications	X																	
Laboratory assessments [3]	X																X	X
Drug/Alcohol Screen	X	X																
12-lead ECG	X	X															X	X
Vital Signs and Weight	X	X															X	X
Pregnancy Test	X[4]	X[4]																
Females only: Estrogen and FSH[5]	X																	

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Admission to Unit		X																
Brief Physical Exam		X															X	X
Administration of daprodustat				X														
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Protein binding sample			X						X					X	X			
EPO blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X												X		X	X
Discharge from Unit																	X	

[1] All participants will undergo screening assessments within 28 days of enrolment.
[2] A follow-up visit will occur 10-14 days after the dose of study treatment.
[3] Laboratory assessment guidance can be found in Appendix 3.
[4] For women of childbearing potential that are not using an approved method of contraception (see Appendix 6), one negative pregnancy test between Day -7 and Day -4 AND another negative pregnancy test on Day -1 is required. Additional guidance can be found in Section 9.5.5.
[5] All females are to have estrogen and FSH measured at screening.

- The timing and number of planned study assessments, including safety, pharmacokinetic and pharmacodynamic assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) 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 hypoxia-inducible factor-prolyl hydroxylase enzymes inhibitor (HIF-PHI) currently in development for the treatment of anemia of chronic kidney disease (CKD). Daprodustat may present several important advantages over currently-available recombinant human erythropoietins (rhEPOs) and analogs used in the treatment of anemia. 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 daprodustat can effectively raise hemoglobin (Hgb) concentrations with lower erythropoietin (EPO) levels than those observed after administration of rhEPOs [Holdstock, 2016]. Because of the increased cardiovascular (CV) risk associated with raising Hgb concentrations through large increases in EPO levels [Pfeffer, 2009], daprodustat may be able to provide a safer treatment alternative for these patients than rhEPOs. Additional potential benefits include inproving iron availability for erythropoiesis, treating anemia without causing rhEPO-induced hypertension, and successfully treat rhEPO hypo-responders [Holdstock, 2016].

3.1. Study Rationale

A recent study has shown that co-administration of daprodustat with a strong, irreversible inhibitor of the cytochrome (CYP) 2C8 enzyme (i.e., gemfibrozil) lead to marked increases in both daprodustat Cmax (4-fold) as well as AUC (19-fold). This suggests that the liver is primarily involved in the clearance of daprodustat through the CYP2C8 enzyme and, therefore hepatic impairment has the potential to affect daprodustat clearance and exposure [Johnson, 2013]. Thus, the intent of this study is to assess the effect of hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of daprodustat. The results of this study are planned to provide guidance on administration of daprodustat to patients with impaired hepatic function.

This study will use an adaptive study design, comprising Part 1 and potentially Part 2. Recruitment of Part 1 of this study will include the full range of Child-Pugh scores within the moderate hepatic impairment category including at least one with a Child-Pugh score of 7, one with a score of 8 and one with a score of 9. The recruitment will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group. If the geometric mean total plasma AUC of daprodustat is increased in Part 1 by ≥2-fold in moderately-impaired participants relative to matched controls, Part 2 may potentially be conducted to evaluate daprodustat pharmacokinetics in participants with mild impairment (Child-Pugh scores of 5-6) and

matched, control participants. Alternatively, if the geometric mean total plasma AUC of daprodustat is increased by <2-fold in moderately-impaired participants relative to matched controls, Part 2 may potentially be conducted to evaluate daprodustat pharmacokinetics in participants with severe impairment (Child-Pugh scores of 10-13) and matched, control participants. These levels of change in exposure as decision points are based on regulatory agency guidances [FDA Guidance for Industry, 2003; Committee for medicinal products for human use (CHMP), 2005], and the consideration that daprodustat has not been observed to possess a narrow therapeutic index. A decision to progress from Part 1 to 2 will be made based on the available study results, with the potential that Part 2 of the study will not be conducted

3.2. Background

Daprodustat is currently in Phase 3 development for the treatment of anemia of CKD. The clinical efficacy of daprodustat has been demonstrated in two Phase 2 studies. In GSK study PHI113747 daprodustat achieved mean hemoglobin (Hgb) response in non-dialysis dependent (ND) participants with CKD within a target range over a 24-week treatment period. Participants in the daprodustat group achieved Hgb levels within the specific target range (8.0 to 11.0 g/dL; US only 8.0 to 10.0 g/dL), both in the recombinant, human (rh)-EPO naïve and rhEPO user groups. In study PHI113633 daprodustat achieved Hgb efficacy (maintenance of Hgb within the target range of 10.0 to 11.5 g/dL) in a similar fashion as did rhEPO in hemodialysis-dependent (HD) participants with CKD [Holdstock, 2016].

A detailed description of the chemistry, pharmacology, efficacy, and safety of daprodustat is provided in the Investigator's Brochure (IB) and associated IB Supplements, if applicable.

3.3. Benefit/Risk Assessment

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

3.3.1. Risk Assessment

The potential risks of clinical significance including AEs of special interest (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 2.

3.3.2. Benefit Assessment

As this is a single dose study, no clinical benefit is expected for participation.

3.3.3. Overall Benefit:Risk Conclusion

Overall, the available data from nonclinical and clinical studies has not identified prohibitive risks associated with daprodustat at the exposures planned for this study. While there are a number of important potential risks identified for daprodustat, these can

be addressed in clinical trials with proper participant selection, close safety monitoring, and specific risk characterization and mitigation.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI)	Daprodustat and its metabolites plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-∞)], percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time zero (pre-dose) to last time of quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life (t½), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat
To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat in plasma	Unbound concentration and unbound fraction in plasma of daprodustat at 3, 12 and 24 h post dose (as data permit)
Secondary	
To characterize the effect of hepatic impairment on the pharmacodynamics effect of daprodustat	Maximum observed effect (Emax) and and area under the effect curve from administration to the last measureable erythropoietin concentration [AUC(E, last)]
To assess the safety and tolerability of a single 6 mg dose of daprodustat	Safety and tolerability parameters, including adverse events and clinical laboratory tests

5. STUDY DESIGN

5.1. Overall Design

This will be a Phase 1, open-label, non-randomized, parallel group, single-dose, adaptive study in adults with moderate (**Part 1**) and potentially either mild or severe (**Part 2**) hepatic impairment and matched, healthy control participants with normal hepatic function.

All participants will undergo screening assessments within 28 days of enrolment. A decision to progress from Part 1 to 2 will be made based on the available study results, with the potential that Part 2 of the study will not be conducted.

In Part 1, healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (Child-Pugh score of 7-9). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state followed by pharmacokinetic and pharmacodynamic sampling for total concentrations of daprodustat in plasma. At sparse sampling times, unbound daprodustat concentrations will be assessed.

In Part 2, if the geometric mean total plasma AUC pharmacokinetic parameters of daprodustat is increased in Part 1 by ≥2-fold in moderately-impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with mild impairment (Child-Pugh score of 5-6; n=8) and matched, control participants (n=8). Alternatively, if the geometric mean total plasma AUC(0-∞) of daprodustat is increased by <2-fold in moderately impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with severe impairment (Child-Pugh score of 10-13; n=8) and matched, control participants (n=8). Similar to Part 1 of the study, all participants will receive 6 mg of daprodustat followed by pharmacokinetic and pharmacodynamic blood sampling.

A follow-up visit will occur 10-14 days after the dose of study treatment.

A participant's total involvement with the study will be up to 7 weeks.

Table 1 Study Cohorts

Study Part	Cohort	Sample Size	Treatment[1]
Part 1	1 (Moderate Hepatic Impairment)[2]	8	Daprodustat 6 mg
	2 (Matched Healthy Controls)[3]	8	
Part 2 (if conducted)[4]	3 (either Mild OR Severe Hepatic Impairment)[2]	8	
	4 (Matched Healthy Controls)[3]	8	

[1] All participants will receive a single 6 mg oral dose of daprodustat.
[2] Hepatic impairment categorized by Child-Pugh Classification system (See Table 2: Mild: Score 5-6; Moderate: Score 7-9; Severe: Score 10-13) in conjunction with the specifications listed in Section 6.
[3] Healthy control participants are matched to the hepatic impairment participants in gender, age (±10 years), and BMI (±15%).
[4] Part 2 of the study may be conducted dependent upon any observed difference in the geometric mean total plasma AUC(0-∞) of daprodustat in moderately impaired participants relative to matched controls as described in Section 10.3.2.

A participant is classified with hepatic impairment based on the Child-Pugh classification as described in Table 2:

- Mild hepatic impairment: Child-Pugh Class A, score of 5-6 points

- Moderate hepatic impairment: Child-Pugh Class B, score of 7-9
- Severe hepatic impairment: Child-Pugh Class C, score of 10-13

Table 2 Child-Pugh System of Hepatic Impairment Classification[1]

Parameter	Points Scored for Each Observed Finding		
	1 Point	2 Points	3 Points
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Prothrombin time INR (ratio)	<1.70	1.70 to 2.30	>2.30
Ascites	Absent	Slight or Participant on 1 medication to control ascites	Moderate or Participant on 2 medications to control ascites
Hepatic encephalopathy[2]	None	1 or 2 or Participant currently receiving treatment with lactulose, neomycin, or other acceptable treatments	3 or 4 or Continued encephalopathy while receiving treatment with lactulose, neomycin, and/or other acceptable treatments

[1] Child-Pugh System of Hepatic Impairment: adapted from Child, 1964; Pugh, 1973.
[2] A description of hepatic encephalopathy grades can be found in Appendix 8.

5.2. Number of Participants

A sufficient number of participants will be enrolled to ensure there are at least 8 participants comprising the pharmacokinetic population per cohort (See Section 10.3.1.3).

Recruitment of **Part 1** of this study will include the full range of participants with moderate hepatic impairment including at least one with a Child-Pugh score of 7, one with a score of 8 and one with a score of 9. The recruitment will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described (See Section 10.3.1.3).

Similar to the participants in Part 1, recruitment of **Part 2** of this study, if conducted, will include a range of participants as follows:

- If Part 2 is conducted, the study will recruit participants with mild hepatic impairment, recruitment will include at least one with a Child-Pugh score of 5 and one participant with a score of 6, and will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described (See Section 10.3.1.3).

- If Part 2 is conducted, the study will recruit participants with severe hepatic impairment, recruitment will include at least one with a Child-Pugh score of 10 or 11 and one with a score of 12 or 13, and will also include at least one female and at least one male participant in both the severe hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described (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 be an open label, single dose, parallel group, adaptive design for assessment of daprodustat PK and PD in participants with moderate hepatic impairment and matched control participants. The design will permit daprodustat and its metabolites PK parameters to be determined in participants with moderate hepatic impairment (Child-Pugh score 7-9), and compared to the PK parameters from matched healthy control participants with normal hepatic function. Additionally, the unbound fraction of daprodustat will be determined to assess the impact of hepatic impairment on daprodustat plasma protein binding. Finally, the effect of daprodustat on erythropoietin (EPO) levels will be described.

- This study will be open label since the primary endpoint (PK) is an objective measure and unlikely to be influenced by the participant's knowledge of the treatment received.

- A single dose of daprodustat will be used in this study as daprodustat PK exhibits linear and time-independent PK. Further, single-dose PK, as will be performed in this study, has consistently allowed reliable prediction of multiple-dose PK that would be observed with chronic administration. Finally, as daprodustat (as well as predominant circulating metabolites) has a short half-life, PK on Day 1 is similar to PK at steady state. Multiple-dose study designs are only recommended if the PK changes over time; i.e., in cases of auto-induction or accumulation due to a long half-life.

- The adaptive design of this study allows for subsequent study, if conducted, of participants with **either** mild (Child-Pugh score 5-6) **or** severe (Child-Pugh score 10-13) hepatic impairment to be implemented dependent upon the results from the participants with moderate hepatic impairment:

(i) If a <2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with severe hepatic impairment and a healthy, matched control group;

(ii) If a ≥2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

- The Child-Pugh scoring system for hepatic impairment will be used for the classification of hepatically-impaired participants. Currently, there are no well-established biochemical markers to estimate the effects of hepatic impairment on the PK/PD of a drug. Although the Child-Pugh classification system was not developed for the purpose of predicting drug elimination capacity, it is the most widely used and accepted method of categorizing the degree of hepatic impairment in participants included in a hepatic impairment PK study, and has been selected as the system to categorize the participants enrolled in this study [FDA Guidance for Industry, 2003; Pugh, 1973]. Because the clinical and biochemical criteria of the Child-Pugh classification system (i.e., encephalopathy, elevated bilirubin, increased INR, decreased albumin) are not specific only to liver disease, participants enrolled into the hepatic impairment cohorts must also exhibit clinical evidence of chronic liver disease and/or cirrhosis. This additional inclusion criteria will help to ensure the desired study population is recruited.

5.5. Dose Justification

A single, oral 6 mg dose of daprodustat is planned to be used in this study. This dose of daprodustat can be given by a single tablet, provides sufficient plasma levels for well-defined pharmacokinetics and margins for potential increases in daprodustat exposure in hepatic impaired population.

The 6 mg dose is currently being evaluated in Phase 3 trials as well as doses up to 24 mg. As the PK of daprodustat is linear with dose, effects of hepatic impairment observed at 6 mg can be extrapolated to the higher clinical doses.

Overall, single, oral doses of up to 150 mg administered to HD CKD participants and doses up to 500 mg administered to healthy participants has been generally well tolerated and no new safety concerns have been identified (GSK studies PHI112843 and PHI113635, respectively).

In the event that the 6 mg dose proves to be poorly tolerated by the study population, the dose of daprodustat may be reduced for participants yet to be enrolled.

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 of the following criteria apply:

6.1.1. Inclusion Criteria for All Participants

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

MEDICAL CONDITIONS
2. Hemoglobin values at screening ≤16.0 g/dL for males and ≤14.0 g/dL for females.

WEIGHT
3. Body weight ≥45 kg and body mass index (BMI) within the range 18-40 kg/m^2 (inclusive).

SEX
4. Male or female **Female participants:** A female participant is eligible to participate if she is not breastfeeding, and at least one of the following applies: (i) Not pregnant as confirmed by two pregnancy tests (see Section 9.5.5) (ii) Not a woman of childbearing potential (WOCBP) as defined in Appendix 6 (iii) For WOCBP that are currently utilizing a highly-effective contraceptive method prior to enrolment, agrees to follow the contraceptive guidance in Appendix 6 during the treatment period to the follow-up visit. (Additional guidance can be found in Section 9.5.5.)

INFORMED CONSENT
5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this

protocol.

6.1.1.1. Additional Inclusion Criteria for Hepatically-Impaired Participants

MEDICAL CONDITIONS

1. **Part 1 Participants with Moderate Hepatic Impairment Only (Cohort 1):** Is considered to have moderate hepatic impairment (of any etiology) and has been clinically stable for at least 1 month prior to screening. To be classified as having moderate hepatic impairment, participants must have a Child-Pugh (Class B) score of 7-9 **AND** previous confirmation of liver cirrhosis by liver biopsy or other medical imaging technique (including laparoscopy, computerized tomography (CT) scan, magnetic resonance imaging (MRI) or ultrasonography) associated with an unambiguous medical history (such as evidence of portal hypertension).
2. **Part 2 Participants with Mild OR Severe Hepatic Impairment Only (Cohort 3; if conducted):** Is considered to have mild or severe hepatic impairment (of any etiology) and has been clinically stable for at least 1 month prior to screening. To be classified as having mild **OR** severe hepatic impairment, participants must have:

(i) Be classified as having mild hepatic impairment, participants must have a Child-Pugh (Class A) score of 5-6 **AND** previous confirmation of chronic liver disease by liver biopsy or other medical imaging technique (including laparoscopy, CT scan, MRI or ultrasonography) associated with an unambiguous medical history (such as evidence of portal hypertension).

(ii) Be classified as having severe hepatic impairment, participants must have Child-Pugh (Class C) score of 10-13 **AND** previous confirmation of chronic liver disease by liver biopsy or other medical imaging technique (including laparoscopy, CT scan, MRI or ultrasonography) associated with an unambiguous medical history (such as evidence of portal hypertension).

3. **Supplemental inclusion criteria for ALL hepatically-impaired participants:** Chronic (>6 months), stable (no acute episodes of illness due to deterioration in hepatic function within the previous 1 month prior to screening) hepatic impairment due to any etiology. Participants must also remain stable throughout the Screening period. Assessment of the stability of the participant's hepatic function will be determined by the investigator.

6.1.1.2. Additional Inclusion Criteria for Healthy Control Participants

AGE

1. Healthy control participants will be matched for age ±10 years to participants in the respective hepatic impairment cohort but must also be at least 18 years of age inclusive, at the time of signing the informed consent.

MEDICAL CONDITIONS
2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. 3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator and/or the Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

WEIGHT
4. Healthy control participants will be matched for BMI ±15% to participants in the respective hepatic impairment cohort but must also remain in the range of body weight ≥45 kg and body mass index (BMI) within the range 18-38 kg/m^2 (inclusive).

6.2. Exclusion Criteria

6.2.1. Exclusion Criteria for All Participants

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

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. QTcF >500 msec **NOTES:** • The QTc must be the QT interval corrected for heart rate according to Fridericia's formula (QTcF). • For purposes of data analysis, QTcB will be used as specified in the Reporting and Analysis Plan (RAP). 2. Recent history of deep vein thrombosis, pulmonary embolism or other thrombosis related condition. Any prior medical history in these areas will be reviewed and approved by the PI and the sponsor's Medical Monitor on a case by case basis as needed. 3. Myocardial infarction or acute coronary syndrome, stroke or transient ischemic attack within the 12 weeks prior to enrollment. 4. Participants with a pre-existing condition (other than liver disease) interfering with normal gastrointestinal anatomy or motility that could interfere with the absorption, metabolism, and/or excretion of daprodustat. Examples of conditions

that could interfere with normal gastrointestinal anatomy or motility can be found in the SRM.

5. Participants that have undergone cholecystectomy within the past 3 months.
6. Participants with chronic inflammatory joint disease (e.g., scleroderma, systemic lupus erythematosis, rheumatoid arthritis).
7. History of malignancy within the prior 2 years or known kidney mass >3cm (end-stage renal disease patients only) **OR** currently receiving treatment for cancer, Note: ONLY exception is localized squamous cell or basal cell carcinoma of the skin definitively treated 12 weeks prior to enrollment.
8. Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

9. Current enrolment or past participation (i.e., administration of last dose of investigational study treatment) within the last 30 days (or 5 half-lives, whichever is longer) before Day 1 in this or any other clinical study involving an investigational study treatment or any other type of medical research.

6.2.1.1. Additional Exclusion Criteria for Hepatically-Impaired Participants

CONCURRENT CONDITIONS/MEDICAL HISTORY

1. Presence of 8 times ULN elevations in AST, ALT, or bilirubin.
2. Participants with any other medical condition which, in the judgment of the investigator and Medical Monitor, could jeopardize the integrity of the data derived from that participant or the safety of the participant.
3. Participants with advanced ascites (Grade 3).
4. Participants with refractory encephalopathy as judged by the investigator or significant Central Nervous System (CNS) disease (e.g., dementia, or seizures) which the investigator considers will interfere with the informed consent, conduct, completion, or results of this trial or constitutes an unacceptable risk to the participant.
5. Participants with functional Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement.
6. Presence of hepatopulmonary or hepatorenal syndrome.
7. Presence of primarily cholestatic liver diseases.
8. History of liver transplantation.
9. Participants with signs of active infection, including active spontaneous bacterial peritonitis.

10. Participants with unstable cardiac function or participants with hypertension whose blood pressure is not controlled (based on the investigator's discretion).
11. Diabetic participants whose diabetes is not controlled (based on the investigator`s discretion).

6.2.1.2. Additional Exclusion Criteria for Healthy Control Participants

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

1. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.

DIAGNOSTIC ASSESSMENTS

2. Presence of Hepatitis B surface antigen (HBsAg) at screening or Positive Hepatitis C antibody test result at screening or within 3 months before the first dose of study treatment.
3. Positive pre-study drug/alcohol screen.
4. Positive human immunodeficiency virus (HIV) antibody test.
5. Regular use of known drugs of abuse.
6. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >14 drinks. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will refrain from any food and drink (except water) at least 8 h before dosing and 4 h after dosing of any investigational product.

6.3.2. Caffeine, Alcohol, and Tobacco

- Participants will be instructed to limit ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 h prior to the start of dosing until collection of the final pharmacokinetic blood sample.

- Participants will abstain from alcohol for 24 h prior to the start of dosing until collection of the final pharmacokinetic blood sample.

- Participants will be instructed to limit use of nicotine and/or nicotine containing products. Up to 10 cigarettes/day is acceptable.

6.3.3. Activity

Participants will abstain from strenuous exercise for 48 h prior to each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watch television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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. Rescreening of individuals will be in consultation with the Medical Monitor.

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.

7.1. Treatments Administered

Product name:	**Daprodustat (GSK1278863)**
Dosage form:	Tablet
Unit dose strength(s)/Dosage level(s):	6 mg tablet strength/6 mg dosage level
Route of Administration:	Oral
Physical description:	9.0 mm round, compound radius, white film coated tablets
Packaging and Labelling:	Study Treatment will be provided in a bottle. Each bottle will be labelled as required per country requirement.
Manufacturer	GlaxoSmithKline

7.2. Dose Modification

As this is a single dose study, no dosage modification for a participant can occur. However, in the event that the 6 mg dose proves to be poorly tolerated by the study population, the dose of daprodustat may be reduced for participants yet to be enrolled.

7.3. Method of Treatment Assignment

All participants will receive the same treatment of a single oral 6 mg dose of daprodustat.

7.4. Blinding

This will be an open label study.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the 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. 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

As 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. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

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.

All concomitant medications will be reviewed by the GSK Medical Monitor and may be considered on a case by case basis. A concomitant medication may be permitted by the GSK Medical Monitor if it will not jeopardize the interpretation of the data derived from that participant or the safety of the participant.

7.7.1. Permitted Medications and Non-Drug Therapies

Acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor. See Appendix 7 for a list of permitted contraceptive methods for WOCBP.

7.7.2. Prohibited Medications and Non-Drug Therapies

Healthy matched control participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Use of any of the following prescription drugs from 28 days prior to Day 1 until 7 days after the last dose of study treatment is prohibited and will constitute a protocol violation:

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

7.8. Treatment after the End of the Study

Healthy control and hepatically-impaired participants will not receive any additional treatment from GSK after completion of the study.

For participants with hepatic impairment, 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

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 (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:

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

Discontinuation of study treatment for abnormal liver tests in the healthy control participant cohorts is required when:

- a participant meets one of the conditions outlined in the algorithm;

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.

The liver chemistry stopping criteria for healthy control participants can be found in Appendix 7.

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.

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

The following points must be noted:

- If assessments are scheduled for the same nominal time, **THEN** the procedures should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws

  NOTE: The timing of the assessments should allow the blood draw to occur as close as possible to the exact nominal time.
- The timing and number of planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time-points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this 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 Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- 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 (Section 2), is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

9.1. Efficacy Assessments

Efficacy is not assessed in this study.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 5.

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 (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 participant consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 h, as indicated in Section 12.5 Appendix 5. The investigator will submit any updated SAE data to the sponsor within 24 h 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 5.

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 recombinant, human erythropoietins (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, thromboembolic events, thrombosis of vascular access
- Cardiomyopathy
- Pulmonary artery hypertension
- Cancer-related mortality and tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

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 Investigator's Brochure 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 electronic CRF (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 CRF 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 will be collected after the start of study treatment and until the follow-up visit.

- If a pregnancy is reported, the investigator should inform GSK within 24 h of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

For this study, any dose of daprodustat greater than 6 mg within a 24-h 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. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).

9.5. Safety Assessments

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

9.5.1. 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.

9.5.2. 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 CRF.

9.5.3. Electrocardiograms

- ECG measurements will be obtained as outlined in the SoA (Section 2) Full 12-lead ECGs will be recorded with theparticipant in a supine position. Heart rate, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcF 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 QTcF value. The average QTcF value of all three ECGs will be used to determine eligibility.

9.5.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or at the follow-up visit 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 3, must be conducted in accordance with the laboratory manual and the SoA.

9.5.5. Pregnancy Testing

In this study, participants will have a drug exposure duration of <5 days including dosing plus 5 half-lives and dosing will occur in an inpatient setting. Given this scenario, pregnancy risks are effectively mitigated by adequately ruling out pregnancy at the time of dosing. Thus, it is not necessary to require participants to start a new contraceptive method if they are not already established on one. To ensure capture of women of childbearing potential in this category who may have conceived but are just shy of being able to identify the pregnancy with current detection methods, it is recommended that two pregnancy tests are done in a short time span.

Therefore, for WOCBP that are **not** currently utilizing a highly-effective contraceptive method listed in Appendix 6, a negative pregnancy test on or between Day -7 to Day -4 and again pre-dose (Day -1 or Day 0) is required. WOCBP who are already using a highly effective contraceptive method listed in Appendix 6 (<1% failure rate per year when used consistently and correctly) should continue this method until the follow-up visit at a minimum. In this case, a negative screening test within 28 days of dosing and again pre-dose (Day -1 to Day 0) is sufficient and the additional Day -7 to -4 test is not needed.

9.6. Pharmacokinetics

9.6.1. Blood sample collection

Blood samples for PK analysis of daprodustat and six predominant metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13) will be collected at the time points indicated in the SoA (Section 2). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Additional blood samples will be collected for the assessment of protein binding for daprodustat at the timepoints in the SoA (Section 2).

Details of PK and protein binding blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

9.6.2. Sample Analysis

Pharmacokinetic plasma analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, Platform Technology & Science (PTS) Drug Metabolism & Pharmacokinetics (DMPK), GSK. Concentrations and plasma protein binding of daprodustat and concentrations only of six predominant metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) will be determined in samples using the currently approved analytical methodology. Raw data will be stored in the archives at the site of bio-analysis.

9.7. Pharmacodynamics

Venous blood samples will be collected for measurement of plasma erythropoietin at the timepoints specified in the SoA (Section 2). Details of pharmacodynamics (PD) blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

9.8. Genetics

Genetics is not assessed in this study.

9.9. Biomarkers

Biomarkers are not assessed in this study.

9.10. 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

No formal hypotheses will be tested. An estimation approach will be used to evaluate the effect of hepatic impairment (i.e., moderate and potentially either mild or severe) on the PK of daprodustat. The comparisons of interest are the single dose PK parameters Cmax and AUC of daprodustat in each hepatic impaired cohort compared to the normal hepatic function cohort.

The point estimates of the geometric least squares (GLS) mean ratio for the PK parameters and associated 90% confidence intervals will be provided for cohort comparisons (hepatically impaired:healthy participants). The PK parameters will be log-transformed prior to analysis and cohort comparisons will be expressed as ratios on the original scale. %AUCex and tmax and will be summarized descriptively.

10.2. Sample Size Determination

10.2.1. Sample Size Assumptions

The FDA Guidance for Industry "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labelling" recommends that a sufficient number of participants should be enrolled to provide evaluable data from at least eight participants in the control and moderate impairment groups. A sample size of eight evaluable participants per cohort was selected based upon this recommendation.

Based on the recent GSK study PHI115573, the between participant CV (CVb) for AUC(0-inf) and Cmax of daprodustat (5 mg) is 41.9% (SD = 0.402) and 28.3% (SD = 0.278) respectively from proc mixed model. Based on these estimates of CVb and a sample size of 8 in each cohort, it is estimated that the half width of the 90% confidence interval will be 43% and 28% of the point estimates for AUC and Cmax, respectively. These calculations are based on the $\log_e$ scale. If the point estimate of the ratio of geometric means is 1, then the 90% confidence interval will be approximately (0.70, 1.43) and (0.78, 1.28) for AUC and Cmax, respectively.

10.2.2. Sample Size Sensitivity

Table 3 shows the precision and 90% CI for a sample size of 8 in each group based on the observed SD in studies conducted among healthy and renal impairment participants.

Table 3 Precision and 90% CI Estimates

Study	Dose	Population	Parameter	SD	Precision	90% CI
PHX111427	5 mg	Healthy	AUC(0-inf)	0.362	38%	(0.73, 1.38)
			Cmax	0.361	38%	(0.73, 1.38)
PHI112843	50 mg	Renal Impaired	AUC(0-inf)	0.294	30%	(0.77, 1.30)
			Cmax	0.159	15%	(0.87, 1.15)
PHI112843	50 mg	Healthy	AUC(0-inf)	0.148	14%	(0.88, 1.14)
			Cmax	0.109	11%	(0.90, 1.11)

10.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

10.3.1.1. Enrolled Population

All participants who were enrolled for the trial irrespective of whether they were randomized or not and for whom a record exist on the study database. This population will be used for summarizing screening failure reasons.

10.3.1.2. Safety Population

All participants who received at least one dose of study medication. This will be the primary population for the safety analyses.

10.3.1.3. Pharmacokinetic Population

All participants in the 'Safety' population for whom sufficient data are available to calculate the derived pharmacokinetic parameters on an as-treated basis. This will be the population used for all the pharmacokinetic displays.

10.3.2. Interim Analysis

An interim analysis of the primary endpoint will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

- If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with severe hepatic impairment and a healthy, matched control group.

- If a ≥ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10.4. Key Elements of Analysis Plan

Final analyses will be performed after the completion of the study and final dataset authorization.

Data will be listed and summarized separately for each part of the study according to GSK reporting standards where applicable. Listings will be sorted by participant, period, day, and time, noting treatment. Summaries will be presented by treatment, day and time.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), coefficient of variation for the mean (%CV), median, minimum, maximum, geometric mean with associated 95% confidence interval (CI), and the between-participant CV (%CVb) for the geometric mean; whereas, n and percent will be used as summary statistics for categorical variables.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.4 or higher of the SAS system will be used to analyze data as well as to generate tables, listings, and figures.

Complete details will be documented in the Reporting and Analysis Plan (RAP).

10.4.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed under the direct auspices of the Clinical Pharmacokinetics Modeling & Simulation department (CPMS), GlaxoSmithKline. Plasma concentration-time data for daprodustat and its six predominant metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) will be analyzed by non-compartmental methods with WinNonlin version 5.22 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], and apparent terminal phase half-life (t½).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Figures for individual plasma concentrations will be presented on both a linear and semi-log scale daprodustat and its six predominant metabolites. Linear and semi-log figures for mean and median plasma concentrations versus time will also be generated.

For each of the derived PK parameters of daprodustat and its six predominant metabolites, the following summary statistics will be calculated for each cohort: n (number of observations), arithmetic mean, standard deviation, median, minimum, maximum, and the 95% confidence interval of arithmetic mean.

In addition, summary statistics for log-transformed PK parameters of daprodustat and its six predominant metabolites [i.e., AUC(0-t), AUC(0-∞), Cmax, and t½],except tmax will include geometric mean, 95% confidence interval of the geometric mean, standard deviation of the logarithmically transformed data, and inter-participant coefficient of variation [CVb (%)].

The inter-participant CV [CVb (%)] will be calculated according to the following method:

$$\text{Log}_e \text{ Transformed Data:} \quad CVb(\%) = SQRT(\exp(SD^2) - 1) \times 100$$

where SD is the standard deviation on the $\log_e$ scale.

Unbound fraction (fu) will be calculated using the total and unbound plasma concentration of daprodustat generated at 3, 12 and 24 h post dose for both normal and hepatic impaired participants using the following formula:

$$fu = Cunbound/Ctotal$$

where Cunbound and Ctotal are the unbound and total concentrations of daprodustat in plasma, respectively.

Full details of the analysis will be provided in the RAP.

10.4.1.1. Statistical Analysis of Pharmacokinetic Parameters

Statistical analyses of the pharmacokinetic parameter data will be performed under the direct auspices of Quantitative Sciences India, GSK.

For each log-transformed PK parameter (expect %AUCex and tmax), point estimate and its associated 90% CI will be constructed for the cohort (hepatically impaired – healthy participants) difference. The results will be exponentiated to obtain the ratio of GLS means and its 90% CI.

As data permit, tmax will be analyzed non-parametrically using the Wilcoxon Rank Sum Test. The point estimates and 90% confidence intervals for the median differences will be calculated for the cohort difference (hepatically impaired – healthy participants). Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

A sensitivity analysis will be performed for log transformed PK parameters (except %AUCex and tmax) by analysis of covariance (ANCOVA) including terms cohort, gender, age and BMI. For each PK parameter, a point estimate and an associated 90% confidence interval (CI) will be constructed for the difference between participants with hepatic impairment and healthy participants. The results will be exponentiated to obtain the ratio of GLS means and its 90% CI.

Further details of analysis and reporting of PK data will be given in the RAP.

10.4.2. Pharmacodynamic Analyses

Pharmacodynamic data will be presented in graphical and/or tabular form and will be summarized descriptively.

Descriptive statistics, where appropriate, (n, arithmetic mean, geometric mean, standard deviation, minimum, median and maximum) will be calculated for the pharmacodynamic endpoints.

10.4.3. Safety Analyses

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

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Table 4 List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CKD	Chronic kidney disease
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum observed concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Clinical Pharmacokinetics Modeling & Simulation
CRF	Case Report Form
CPSR	Clinical study report
CT	Computerized tomography
Ctotal	Total concentration
Cunbound	Unbound concentration
CV	Cardiovascular
CVb	Between participant coefficient of variability
CYP	Cytochrome P450 enzyme
dL	decilitre
DMPK	Drug Metabolism & Pharmacokinetics
ECG	Electrocardiogram
ECHO	Echocardiographic
eCRF	Electronic Case Report Form
E,last	Last measurable concentration
Emax	Maximum observed effect
EPO	Erythropoietin
ex	Extrapolation
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
fu	Unbound fraction
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal

GLS	Geometric least squares
GSK	GlaxoSmithKline
h	Hour
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
HRT	Hormone replacement therapy
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
IDSL	Integrated Data Standards Library
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational new drug
INR	International normalization ratio
IP	Investigational product
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
IUS	Intrauterine system
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
mm	Millimeter
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Milliseconds
μM	Micromolar
n	Number
ND	Nondialysis dependent
NOAEL	No observed adverse effect level

NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
PAH	Pulmonary artery hypertension
PCI	Potential clinical importance
PD	Pharmacodynamic
%CV	Coefficient of variation of the mean
PHD	prolyl-4-hydroxylases
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development
PRVP	Peak right ventricular pressure
PSRAE	Possible Suicidality Related Adverse Events
PTS	Platform Technology & Science
QTc	Corrected QT interval
QTcB	QT duration corrected for heart rate by Bazett's formula
R&D	Research and development
RAP	Report and Analysis Plan
RBC	Red blood cells
rh	Recombinant human
RNA	Ribonucleic acid
SAE	Serious Adverse Event(s)
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of Activities
sPAP	systolic Pulmonary Artery Pressure
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t½	Half life
TIPS	Transjugular Intrahepatic Portosystemic Shunt
Tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
µM	Micromolar
VEGF	Vascular endothelial growth factor
WBC	White blood cells
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ADVAIR

Trademarks not owned by the GlaxoSmithKline group of companies
Chiron RIBA
SAS
WinNonlin

12.2. Appendix 2: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion, microthrombi, and tissue ischemia in a number of organs. 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. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 6.1.1 • Monitoring of emerging safety data by an internal GSK Safety Review Team.
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 rhEPOs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to CV risk are outlined in Section 6.2.1. • 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
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 were observed with intravenous and oral administration of daprodustat. Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat). In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported adverse event, however causal association has not been established. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	• Suspected GI bleeding or significant symptoms consistent with erosions or ulcers should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted. • 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
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 conducted to date , administration of daprodustat has been associated with: • In studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg. In studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. • Systemic EPO concentrations within the physiologic range Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 6.2.1. • 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 had no clinically significant effect on	• 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
	transthoracic Echocardiographic (ECHO) estimates of systolic pulmonary artery pressure (sPAP) under either normoxic or hypoxic conditions. ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically-meaningful changes in sPAP in participants not on dialysis for daprodustat. In hemodialysis participants, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (Daprodustat: 8 [7%]; Control 0) in participants reaching the sPAP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 participants with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study treatment; and there was no dose relationship for participants meeting the sPAP potential clinical importance (PCI) criterion. Overall, there is insufficient evidence to conclude a relationship to	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	treatment with daprodustat. 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. Small increases in cardiac troponin in 6 month rat study with daprodustat were consistent with the background finding of spontaneous rodent cardiomyopathy independent of exposure to daprodustat. 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.	• 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
	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 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	• 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
	duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization with daprodustat. Following review of clinical data with daprodustat received to date, this has not been identified as a safety concern for daprodustat.	
Exacerbation of rheumatoid arthritis	In inflamed rheumatic joints, activation of HIF-related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra 2010; Muz, 2009]. No abnormalities seen in non-clinical studies conducted to date for daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• 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	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. Daprodustat is an inhibitor of CYP2C8 in vitro, with an IC_{50} value of 21 µM. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with clopidogrel (a moderate CYP2C8 inhibitor) leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Co-administration of daprodustat with BCRP inhibitors has the potential to increase exposure of daprodustat. Use of BCRP inhibitors was not a significant covariate of daprodustat exposure, but was	• Co-administration of daprodustat with the strong CYP2C8 inhibitor, gemfibrozil and inducer, rifampin/rifampicin is not permitted as outlined in Section 7.7.2. • Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 7.7. • 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
	found to result in a small change in metabolite exposure (20% increase in AUC). Co-administration of daprodustat with BCRP inhibitors [e.g., cyclosporine, HIV antivirals (atazanavir, lopinavir, ritonavir, tipranavir), lapatanib and curcumin] is not expected to produce clinically relevant increases in daprodustat exposure. Daprodustat is an inhibitor of organic anion transporter polypeptide (OATP) 1B1/1B3 in vitro, with IC_{50} values of 6 µM and 11 µM, respectively. A clinical drug interaction study between 100 mg daprodustat with either a CYP2C8 substrate or an OATP1B1/1B3 substrate showed that there is no PK interaction at this dose of daprodustat.	

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12.3. Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the 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.
- 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 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin 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 (nonfasting)	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening	• Follicle-stimulating hormone and estradiol (as needed in women of			

Laboratory Assessments	**Parameters**
Tests	non-childbearing potential only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test[2] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) or specify other tests if applicable • PT/INR The results of each test must be entered into the CRF.

NOTES :

[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 and Appendix 7 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.

12.4. Appendix 4: 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 (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- 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.

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 participants, 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 (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Pharmacology Study Report (CPSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

12.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

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

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 (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

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

d. Results in 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 (eg, 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.

Recording AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

12.6. Appendix 6: 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 is to be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential that are **not** currently utilizing a highly-effective contraceptive method are eligible to participate if a pregnancy test conducted on or between Day -7 to Day -4 and again pre-dose (Day -1 or Day 0) is negative. It is not necessary to require participants to start a new contraceptive method if they are not already established on one.

Female participants of childbearing potential that are currently utilizing a highly-effective contraceptive method are eligible to participate if they agree to continue to use this method consistently and correctly as described in Table 6. In this instance a negative

pregnancy test on or between Day -7 to Day -4 and again pre-dose (Day -1 or Day 0) would not be required.

Table 6 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[b] • 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[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:
[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 for at least 48 h after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at the times listed in the SoA (Section 2)

- Additional pregnancy testing is not required during the treatment period and at 48 h after the last dose of study treatment
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 2 mIU/mL will be performed using the test kit provided by the central laboratory.

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 h 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 be withdrawn from the study.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

For the purposes of this protocol, please refer to the guidelines below for the required action, monitoring and follow-up assessments if a participant meets any of the criteria listed below, after dosing with the study medication.

Phase I liver chemistry stopping criteria and required follow up assessments for Healthy Volunteer Participants

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 h
• Complete the liver event CRF, 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, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 h
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained 48 h of last dose[4]
• 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</td></tr>
</table>

Liver Chemistry Stopping Criteria	
INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009] • Liver imaging (ultrasound, magnetic resonance, or 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 participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. 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
4. PK sample may not be required for participants 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 PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos.* 2009; 37:1779-1784.

12.8. Appendix 8: Grades of Hepatic Encephalopathy

Grade	Description
1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction
2	Lethargy; disorientation for time; obvious personality changes; inappropriate beharior
3	Somnolence to semistupor; responsive to stimuli; confused; gross disorientation; bizarre behavior
4	Coma; unable to test mental state

References

Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portalsystemic encephalopathy. A double-blind controlled trial. *Gastroenterology.* 1977; 72:573-583.

TITLE PAGE

Protocol Title: A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function.

Protocol Number: 200231

Short Title: Daprodustat hepatic impairment study

Compound Number: GSK1278863

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

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: 15-NOV-2017

SPONSOR SIGNATORY:

PPD

11/15/2017
Date

Alexander R. Cobitz, MD, PhD
Executive Director, Clinical Development
Metabolic Pathways and Cardiovascular Unit
GlaxoSmithKline

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	*15-NOV-2017*
Original Protocol	*23-May-2017*

Amendment 1 15-Nov-2017

Section # and Name	Description of Change	Brief Rationale
1 Synopsis	Chages as described in main protocol sections below	As below.
4. Objectives and Endpoints	Second primary objective and associate endpoint adds daprodustat AND its metabolites to plasma protein binding and unbound concentration in plasma Secondary PD enpoint is revised to say Cmax, EPO instead of Emax; and specifies AUC(0-t, EPO) instead of AUC(last)	For robustness of data in the hepatic impairment population, metabolite protein binding has been added Correction of PD endpoint to specify EPO
5.1 Overall Design	Part 1 adds metabolites to unbound daprodustat	For robustness of data in the hepatic impairment population, metabolite protein binding has been added.
5.4 Scientific Rationale for Study Design	Adds metabolites to unbound fraction of daprodustat, and also to plasma protein binding	For robustness of data in the hepatic impairment population, metabolite protein binding has been added.
9.6.1. Blood sample collection	Adds metabolites to protein binding assessement of daprodustat	For robustness of data in the hepatic impairment population, metabolite protein binding has been added.
9.6.2. Sample Analysis	Changes responsible GSK department name from Bioanalytical Science and Toxicokinetics and Drug Metabolism & Pharmacokinetics (DMPK) to Bioanalysis, Immunogenicity and Biomarkers and In Vitro/In Vivo Translation Remove “concentrations only of” six predominant metabolites…	Update of GSK responsible department names Updated to include protein binding of the six predominant metabolites
10.3.1. Analysis Populations	Enrolled and PK populations clarified; PD and Screened population descriptions added.	Additional and clarifying summarizations have been added to Enrolled and PK population descriptions; PD and Screened have population descriptions have been added (previously omitted in error).

Section # and Name	**Description of Change**	**Brief Rationale**
10.4.1. Pharmacokinetic Analyses	Metabolites added to unbound plasma concentration of daprodustat and calculations	For robustness of data in the hepatic impairment population, metabolite protein binding has been added
12.1. Appendix 1 Abbreviations and Trademarks	Cmax, EPO added	Clarification of abbreviation

TABLE OF CONTENTS

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1. SYNOPSIS

Protocol Title: A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function.

Short Title: Daprodustat hepatic impairment study

Rationale:

A recent study has shown that co-administration of daprodustat with a strong, irreversible inhibitor of the cytochrome (CYP) 2C8 enzyme (i.e., gemfibrozil) lead to marked increases in both daprodustat Cmax (4-fold) as well as AUC (19-fold). This suggests that the liver is primarily involved in the clearance of daprodustat through the CYP2C8 enzyme and, therefore hepatic impairment has the potential to affect daprodustat clearance and exposure. Thus, the intent of this study is to assess the effect of hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of daprodustat. The results of this study are planned to provide guidance on administration of daprodustat to patients with impaired hepatic function.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI)	Daprodustat and its metabolites plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-∞)], percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time zero (pre-dose) to last time of quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life (t½), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat
To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat and its metabolites in plasma	Unbound concentration and unbound fraction in plasma of daprodustat and its metabolites at 3, 12 and 24 h post dose (as data permit)
Secondary	
To characterize the effect of hepatic impairment on the pharmacodynamics effect of daprodustat	Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and erythropoietin area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable concentration [AUC (0-t, EPO)].
To assess the safety and tolerability of a single 6 mg	Safety and tolerability parameters, including adverse

Objective	Endpoint
dose of daprodustat	events and clinical laboratory tests

Overall Design:

This will be a Phase 1, open-label, non-randomized, parallel group, single-dose, adaptive study in adults with moderate (Part 1) and potentially either mild or severe (Part 2) hepatic impairment and matched, healthy control participants with normal hepatic function.

All participants will undergo screening assessments within 28 days of enrolment. A decision to progress from Part 1 to 2 will be made based on the available study results, with the potential that Part 2 of the study will not be conducted.

In Part 1, healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (Child-Pugh score of 7-9). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state followed by pharmacokinetic and pharmacodynamic sampling for total concentrations of daprodustat in plasma. At sparse sampling times, unbound daprodustat and its metabolites' concentrations will be assessed.

In Part 2, if the geometric mean total plasma AUC pharmacokinetic parameters of daprodustat is increased in Part 1 by ≥2-fold in moderately-impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with mild impairment (Child-Pugh score of 5-6; n=8) and matched, control participants (n=8). Alternatively, if the geometric mean total plasma AUC(0-∞) of daprodustat is increased by <2-fold in moderately impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with severe impairment (Child-Pugh score of 10-13; n=8) and matched, control participants (n=8). Similar to Part 1 of the study, all participants will receive 6 mg of daprodustat followed by pharmacokinetic and pharmacodynamic blood sampling.

Number of Participants:

A sufficient number of participants will be enrolled to ensure there are at least 8 participants comprising the pharmacokinetic population per cohort.

Recruitment of **Part 1** of this study will include the full range of participants with moderate hepatic impairment including at least one with a Child-Pugh score of 7, one with a score of 8 and one with a score of 9. The recruitment will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described.

Similar to the participants in Part 1, recruitment of **Part 2** of this study, if conducted, will include a range of participants as follows:

- If Part 2 is conducted, the study will recruit participants with mild hepatic impairment, recruitment will include at least one with a Child-Pugh score of 5 and

one participant with a score of 6, and will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population.

- If Part 2 is conducted, the study will recruit participants with severe hepatic impairment, recruitment will include at least one with a Child-Pugh score of 10 or 11 and one with a score of 12 or 13, and will also include at least one female and at least one male participant in both the severe hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population.

Treatment Groups and Duration:

In both **Part 1**, and if conducted, **Part 2**, all participants will be administered 6 mg of daprodustat as a single oral dose, with assessments conducted for up to 48 h postdosing.

A follow-up visit will occur 10-14 days after the dose of study treatment.

A participant's total involvement with the study will be up to 7 weeks.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Informed Consent	X																	
Inclusion & Exclusion Criteria	X	X																
Demography	X																	
Full physical exam	X																	
Medical history	X																	
Past/current medications	X																	
Laboratory assessments [3]	X																X	X
Drug/Alcohol Screen	X	X																
12-lead ECG	X	X															X	X
Vital Signs and Weight	X	X															X	X
Pregnancy Test	X[4]	X[4]																
Females only: Estrogen and FSH[5]	X																	

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Admission to Unit		X																
Brief Physical Exam		X															X	X
Administration of daprodustat				X														
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Protein binding sample			X						X					X	X			
EPO blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X												X		X	X
Discharge from Unit																	X	

[1] All participants will undergo screening assessments within 28 days of enrolment.
[2] A follow-up visit will occur 10-14 days after the dose of study treatment.
[3] Laboratory assessment guidance can be found in Appendix 3.
[4] For women of childbearing potential that are not using an approved method of contraception (see Appendix 6), one negative pregnancy test between Day -7 and Day -4 AND another negative pregnancy test on Day -1 is required. Additional guidance can be found in Section 9.5.5.
[5] All females are to have estrogen and FSH measured at screening.

- The timing and number of planned study assessments, including safety, pharmacokinetic and pharmacodynamic assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) 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 hypoxia-inducible factor-prolyl hydroxylase enzymes inhibitor (HIF-PHI) currently in development for the treatment of anemia of chronic kidney disease (CKD). Daprodustat may present several important advantages over currently-available recombinant human erythropoietins (rhEPOs) and analogs used in the treatment of anemia. 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 daprodustat can effectively raise hemoglobin (Hgb) concentrations with lower erythropoietin (EPO) levels than those observed after administration of rhEPOs [Holdstock, 2016]. Because of the increased cardiovascular (CV) risk associated with raising Hgb concentrations through large increases in EPO levels [Pfeffer, 2009], daprodustat may be able to provide a safer treatment alternative for these patients than rhEPOs. Additional potential benefits include inproving iron availability for erythropoiesis, treating anemia without causing rhEPO-induced hypertension, and successfully treat rhEPO hypo-responders [Holdstock, 2016].

3.1. Study Rationale

A recent study has shown that co-administration of daprodustat with a strong, irreversible inhibitor of the cytochrome (CYP) 2C8 enzyme (i.e., gemfibrozil) lead to marked increases in both daprodustat Cmax (4-fold) as well as AUC (19-fold). This suggests that the liver is primarily involved in the clearance of daprodustat through the CYP2C8 enzyme and, therefore hepatic impairment has the potential to affect daprodustat clearance and exposure [Johnson, 2013]. Thus, the intent of this study is to assess the effect of hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of daprodustat. The results of this study are planned to provide guidance on administration of daprodustat to patients with impaired hepatic function.

This study will use an adaptive study design, comprising Part 1 and potentially Part 2. Recruitment of Part 1 of this study will include the full range of Child-Pugh scores within the moderate hepatic impairment category including at least one with a Child-Pugh score of 7, one with a score of 8 and one with a score of 9. The recruitment will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group. If the geometric mean total plasma AUC of daprodustat is increased in Part 1 by ≥2-fold in moderately-impaired participants relative to matched controls, Part 2 may potentially be conducted to evaluate daprodustat pharmacokinetics in participants with mild impairment (Child-Pugh scores of 5-6) and

matched, control participants. Alternatively, if the geometric mean total plasma AUC of daprodustat is increased by <2-fold in moderately-impaired participants relative to matched controls, Part 2 may potentially be conducted to evaluate daprodustat pharmacokinetics in participants with severe impairment (Child-Pugh scores of 10-13) and matched, control participants. These levels of change in exposure as decision points are based on regulatory agency guidances [FDA Guidance for Industry, 2003; Committee for medicinal products for human use (CHMP), 2005], and the consideration that daprodustat has not been observed to possess a narrow therapeutic index. A decision to progress from Part 1 to 2 will be made based on the available study results, with the potential that Part 2 of the study will not be conducted

3.2. Background

Daprodustat is currently in Phase 3 development for the treatment of anemia of CKD. The clinical efficacy of daprodustat has been demonstrated in two Phase 2 studies. In GSK study PHI113747 daprodustat achieved mean hemoglobin (Hgb) response in non-dialysis dependent (ND) participants with CKD within a target range over a 24-week treatment period. Participants in the daprodustat group achieved Hgb levels within the specific target range (8.0 to 11.0 g/dL; US only 8.0 to 10.0 g/dL), both in the recombinant, human (rh)-EPO naïve and rhEPO user groups. In study PHI113633 daprodustat achieved Hgb efficacy (maintenance of Hgb within the target range of 10.0 to 11.5 g/dL) in a similar fashion as did rhEPO in hemodialysis-dependent (HD) participants with CKD [Holdstock, 2016].

A detailed description of the chemistry, pharmacology, efficacy, and safety of daprodustat is provided in the Investigator's Brochure (IB) and associated IB Supplements, if applicable.

3.3. Benefit/Risk Assessment

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

3.3.1. Risk Assessment

The potential risks of clinical significance including AEs of special interest (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 2.

3.3.2. Benefit Assessment

As this is a single dose study, no clinical benefit is expected for participation.

3.3.3. Overall Benefit:Risk Conclusion

Overall, the available data from nonclinical and clinical studies has not identified prohibitive risks associated with daprodustat at the exposures planned for this study. While there are a number of important potential risks identified for daprodustat, these can

be addressed in clinical trials with proper participant selection, close safety monitoring, and specific risk characterization and mitigation.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI)	Daprodustat and its metabolites plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-∞)], percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time zero (pre-dose) to last time of quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life (t½), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat
To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat and its metabolites in plasma	Unbound concentration and unbound fraction in plasma of daprodustat and its metabolites at 3, 12 and 24 h post dose (as data permit)
Secondary	
To characterize the effect of hepatic impairment on the pharmacodynamics effect of daprodustat	Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and erythropoietin area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable concentration [AUC (0-t, EPO)].
To assess the safety and tolerability of a single 6 mg dose of daprodustat	Safety and tolerability parameters, including adverse events and clinical laboratory tests

5. STUDY DESIGN

5.1. Overall Design

This will be a Phase 1, open-label, non-randomized, parallel group, single-dose, adaptive study in adults with moderate (**Part 1**) and potentially either mild or severe (**Part 2**) hepatic impairment and matched, healthy control participants with normal hepatic function.

All participants will undergo screening assessments within 28 days of enrolment. A decision to progress from Part 1 to 2 will be made based on the available study results, with the potential that Part 2 of the study will not be conducted.

In Part 1, healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (Child-Pugh score of 7-9). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state followed by pharmacokinetic and pharmacodynamic sampling for total concentrations of daprodustat in plasma. At sparse sampling times, unbound daprodustat and its metabolites' concentrations will be assessed.

In Part 2, if the geometric mean total plasma AUC pharmacokinetic parameters of daprodustat is increased in Part 1 by ≥2-fold in moderately-impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with mild impairment (Child-Pugh score of 5-6; n=8) and matched, control participants (n=8). Alternatively, if the geometric mean total plasma AUC(0-∞) of daprodustat is increased by <2-fold in moderately impaired participants relative to matched controls, Part 2 may be conducted to evaluate daprodustat pharmacokinetics in participants with severe impairment (Child-Pugh score of 10-13; n=8) and matched, control participants (n=8). Similar to Part 1 of the study, all participants will receive 6 mg of daprodustat followed by pharmacokinetic and pharmacodynamic blood sampling.

A follow-up visit will occur 10-14 days after the dose of study treatment.

A participant's total involvement with the study will be up to 7 weeks.

Table 1 Study Cohorts

Study Part	Cohort	Sample Size	Treatment[1]
Part 1	1 (Moderate Hepatic Impairment)[2]	8	Daprodustat 6 mg
	2 (Matched Healthy Controls)[3]	8	
Part 2 (if conducted)[4]	3 (either Mild OR Severe Hepatic Impairment)[2]	8	
	4 (Matched Healthy Controls)[3]	8	

[1] All participants will receive a single 6 mg oral dose of daprodustat.
[2] Hepatic impairment categorized by Child-Pugh Classification system (See Table 2: Mild: Score 5-6; Moderate: Score 7-9; Severe: Score 10-13) in conjunction with the specifications listed in Section 6.
[3] Healthy control participants are matched to the hepatic impairment participants in gender, age (±10 years), and BMI (±15%).
[4] Part 2 of the study may be conducted dependent upon any observed difference in the geometric mean total plasma AUC(0-∞) of daprodustat in moderately impaired participants relative to matched controls as described in Section 10.3.2.

A participant is classified with hepatic impairment based on the Child-Pugh classification as described in Table 2:

- Mild hepatic impairment: Child-Pugh Class A, score of 5-6 points

- Moderate hepatic impairment: Child-Pugh Class B, score of 7-9
- Severe hepatic impairment: Child-Pugh Class C, score of 10-13

Table 2 Child-Pugh System of Hepatic Impairment Classification[1]

Parameter	Points Scored for Each Observed Finding		
	1 Point	2 Points	3 Points
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Prothrombin time INR (ratio)	<1.70	1.70 to 2.30	>2.30
Ascites	Absent	Slight or Participant on 1 medication to control ascites	Moderate or Participant on 2 medications to control ascites
Hepatic encephalopathy[2]	None	1 or 2 or Participant currently receiving treatment with lactulose, neomycin, or other acceptable treatments	3 or 4 or Continued encephalopathy while receiving treatment with lactulose, neomycin, and/or other acceptable treatments

[1] Child-Pugh System of Hepatic Impairment: adapted from Child, 1964; Pugh, 1973.
[2] A description of hepatic encephalopathy grades can be found in Appendix 8.

5.2. Number of Participants

A sufficient number of participants will be enrolled to ensure there are at least 8 participants comprising the pharmacokinetic population per cohort (See Section 10.3.1.3).

Recruitment of **Part 1** of this study will include the full range of participants with moderate hepatic impairment including at least one with a Child-Pugh score of 7, one with a score of 8 and one with a score of 9. The recruitment will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described (See Section 10.3.1.3).

Similar to the participants in Part 1, recruitment of **Part 2** of this study, if conducted, will include a range of participants as follows:

- If Part 2 is conducted, the study will recruit participants with mild hepatic impairment, recruitment will include at least one with a Child-Pugh score of 5 and one participant with a score of 6, and will also include at least one female and at least one male participant in both the moderate hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described (See Section 10.3.1.3).

- If Part 2 is conducted, the study will recruit participants with severe hepatic impairment, recruitment will include at least one with a Child-Pugh score of 10 or 11 and one with a score of 12 or 13, and will also include at least one female and at least one male participant in both the severe hepatic impaired group and the healthy volunteer group to be part of the pharmacokinetic population as described (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 be an open label, single dose, parallel group, adaptive design for assessment of daprodustat PK and PD in participants with moderate hepatic impairment and matched control participants. The design will permit daprodustat and its metabolites PK parameters to be determined in participants with moderate hepatic impairment (Child-Pugh score 7-9), and compared to the PK parameters from matched healthy control participants with normal hepatic function. Additionally, the unbound fraction of daprodustat and its metabolites will be determined to assess the impact of hepatic impairment on daprodustat and its metabolites plasma protein binding. Finally, the effect of daprodustat on erythropoietin (EPO) levels will be described.

- This study will be open label since the primary endpoint (PK) is an objective measure and unlikely to be influenced by the participant's knowledge of the treatment received.

- A single dose of daprodustat will be used in this study as daprodustat PK exhibits linear and time-independent PK. Further, single-dose PK, as will be performed in this study, has consistently allowed reliable prediction of multiple-dose PK that would be observed with chronic administration. Finally, as daprodustat (as well as predominant circulating metabolites) has a short half-life, PK on Day 1 is similar to PK at steady state. Multiple-dose study designs are only recommended if the PK changes over time; i.e., in cases of auto-induction or accumulation due to a long half-life.

- The adaptive design of this study allows for subsequent study, if conducted, of participants with **either** mild (Child-Pugh score 5-6) **or** severe (Child-Pugh score 10-13) hepatic impairment to be implemented dependent upon the results from the participants with moderate hepatic impairment:

(i) If a <2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with severe hepatic impairment and a healthy, matched control group;

(ii) If a ≥2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

- The Child-Pugh scoring system for hepatic impairment will be used for the classification of hepatically-impaired participants. Currently, there are no well-established biochemical markers to estimate the effects of hepatic impairment on the PK/PD of a drug. Although the Child-Pugh classification system was not developed for the purpose of predicting drug elimination capacity, it is the most widely used and accepted method of categorizing the degree of hepatic impairment in participants included in a hepatic impairment PK study, and has been selected as the system to categorize the participants enrolled in this study [FDA Guidance for Industry, 2003; Pugh, 1973]. Because the clinical and biochemical criteria of the Child-Pugh classification system (i.e., encephalopathy, elevated bilirubin, increased INR, decreased albumin) are not specific only to liver disease, participants enrolled into the hepatic impairment cohorts must also exhibit clinical evidence of chronic liver disease and/or cirrhosis. This additional inclusion criteria will help to ensure the desired study population is recruited.

5.5. Dose Justification

A single, oral 6 mg dose of daprodustat is planned to be used in this study. This dose of daprodustat can be given by a single tablet, provides sufficient plasma levels for well-defined pharmacokinetics and margins for potential increases in daprodustat exposure in hepatic impaired population.

The 6 mg dose is currently being evaluated in Phase 3 trials as well as doses up to 24 mg. As the PK of daprodustat is linear with dose, effects of hepatic impairment observed at 6 mg can be extrapolated to the higher clinical doses.

Overall, single, oral doses of up to 150 mg administered to HD CKD participants and doses up to 500 mg administered to healthy participants has been generally well tolerated and no new safety concerns have been identified (GSK studies PHI112843 and PHI113635, respectively).

In the event that the 6 mg dose proves to be poorly tolerated by the study population, the dose of daprodustat may be reduced for participants yet to be enrolled.

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 of the following criteria apply:

6.1.1. Inclusion Criteria for All Participants

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

MEDICAL CONDITIONS
2. Hemoglobin values at screening ≤16.0 g/dL for males and ≤14.0 g/dL for females.

WEIGHT
3. Body weight ≥45 kg and body mass index (BMI) within the range 18-40 kg/m^2 (inclusive).

SEX
4. Male or female **Female participants:** A female participant is eligible to participate if she is not breastfeeding, and at least one of the following applies: (i) Not pregnant as confirmed by two pregnancy tests (see Section 9.5.5) (ii) Not a woman of childbearing potential (WOCBP) as defined in Appendix 6 (iii) For WOCBP that are currently utilizing a highly-effective contraceptive method prior to enrolment, agrees to follow the contraceptive guidance in Appendix 6 during the treatment period to the follow-up visit. (Additional guidance can be found in Section 9.5.5.)

INFORMED CONSENT
5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this

protocol.

6.1.1.1. Additional Inclusion Criteria for Hepatically-Impaired Participants

MEDICAL CONDITIONS

1. **Part 1 Participants with Moderate Hepatic Impairment Only (Cohort 1):** Is considered to have moderate hepatic impairment (of any etiology) and has been clinically stable for at least 1 month prior to screening. To be classified as having moderate hepatic impairment, participants must have a Child-Pugh (Class B) score of 7-9 **AND** previous confirmation of liver cirrhosis by liver biopsy or other medical imaging technique (including laparoscopy, computerized tomography (CT) scan, magnetic resonance imaging (MRI) or ultrasonography) associated with an unambiguous medical history (such as evidence of portal hypertension).
2. **Part 2 Participants with Mild OR Severe Hepatic Impairment Only (Cohort 3; if conducted):** Is considered to have mild or severe hepatic impairment (of any etiology) and has been clinically stable for at least 1 month prior to screening. To be classified as having mild **OR** severe hepatic impairment, participants must have:

(i) Be classified as having mild hepatic impairment, participants must have a Child-Pugh (Class A) score of 5-6 **AND** previous confirmation of chronic liver disease by liver biopsy or other medical imaging technique (including laparoscopy, CT scan, MRI or ultrasonography) associated with an unambiguous medical history (such as evidence of portal hypertension).

(ii) Be classified as having severe hepatic impairment, participants must have Child-Pugh (Class C) score of 10-13 **AND** previous confirmation of chronic liver disease by liver biopsy or other medical imaging technique (including laparoscopy, CT scan, MRI or ultrasonography) associated with an unambiguous medical history (such as evidence of portal hypertension).

3. **Supplemental inclusion criteria for ALL hepatically-impaired participants:** Chronic (>6 months), stable (no acute episodes of illness due to deterioration in hepatic function within the previous 1 month prior to screening) hepatic impairment due to any etiology. Participants must also remain stable throughout the Screening period. Assessment of the stability of the participant's hepatic function will be determined by the investigator.

6.1.1.2. Additional Inclusion Criteria for Healthy Control Participants

AGE

1. Healthy control participants will be matched for age ±10 years to participants in the respective hepatic impairment cohort but must also be at least 18 years of age inclusive, at the time of signing the informed consent.

MEDICAL CONDITIONS
2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. 3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator and/or the Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

WEIGHT
4. Healthy control participants will be matched for BMI ±15% to participants in the respective hepatic impairment cohort but must also remain in the range of body weight ≥45 kg and body mass index (BMI) within the range 18-38 kg/m^2 (inclusive).

6.2. Exclusion Criteria

6.2.1. Exclusion Criteria for All Participants

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

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. QTcF >500 msec **NOTES:** • The QTc must be the QT interval corrected for heart rate according to Fridericia's formula (QTcF). • For purposes of data analysis, QTcB will be used as specified in the Reporting and Analysis Plan (RAP). 2. Recent history of deep vein thrombosis, pulmonary embolism or other thrombosis related condition. Any prior medical history in these areas will be reviewed and approved by the PI and the sponsor's Medical Monitor on a case by case basis as needed. 3. Myocardial infarction or acute coronary syndrome, stroke or transient ischemic attack within the 12 weeks prior to enrollment. 4. Participants with a pre-existing condition (other than liver disease) interfering with normal gastrointestinal anatomy or motility that could interfere with the absorption, metabolism, and/or excretion of daprodustat. Examples of conditions that could interfere with normal gastrointestinal anatomy or motility can be found

in the SRM.

5. Participants that have undergone cholecystectomy within the past 3 months.
6. Participants with chronic inflammatory joint disease (e.g., scleroderma, systemic lupus erythematosis, rheumatoid arthritis).
7. History of malignancy within the prior 2 years or known kidney mass >3cm (end-stage renal disease patients only) **OR** currently receiving treatment for cancer, Note: ONLY exception is localized squamous cell or basal cell carcinoma of the skin definitively treated 12 weeks prior to enrollment.
8. Class IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

9. Current enrolment or past participation (i.e., administration of last dose of investigational study treatment) within the last 30 days (or 5 half-lives, whichever is longer) before Day 1 in this or any other clinical study involving an investigational study treatment or any other type of medical research.

6.2.1.1. Additional Exclusion Criteria for Hepatically-Impaired Participants

CONCURRENT CONDITIONS/MEDICAL HISTORY

1. Presence of 8 times ULN elevations in AST, ALT, or bilirubin.
2. Participants with any other medical condition which, in the judgment of the investigator and Medical Monitor, could jeopardize the integrity of the data derived from that participant or the safety of the participant.
3. Participants with advanced ascites (Grade 3).
4. Participants with refractory encephalopathy as judged by the investigator or significant Central Nervous System (CNS) disease (e.g., dementia, or seizures) which the investigator considers will interfere with the informed consent, conduct, completion, or results of this trial or constitutes an unacceptable risk to the participant.
5. Participants with functional Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement.
6. Presence of hepatopulmonary or hepatorenal syndrome.
7. Presence of primarily cholestatic liver diseases.
8. History of liver transplantation.
9. Participants with signs of active infection, including active spontaneous bacterial peritonitis.
10. Participants with unstable cardiac function or participants with hypertension

whose blood pressure is not controlled (based on the investigator's discretion).

11. Diabetic participants whose diabetes is not controlled (based on the investigator`s discretion).

6.2.1.2. Additional Exclusion Criteria for Healthy Control Participants

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

1. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.

DIAGNOSTIC ASSESSMENTS

2. Presence of Hepatitis B surface antigen (HBsAg) at screening or Positive Hepatitis C antibody test result at screening or within 3 months before the first dose of study treatment.
3. Positive pre-study drug/alcohol screen.
4. Positive human immunodeficiency virus (HIV) antibody test.
5. Regular use of known drugs of abuse.
6. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >14 drinks. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will refrain from any food and drink (except water) at least 8 h before dosing and 4 h after dosing of any investigational product.

6.3.2. Caffeine, Alcohol, and Tobacco

- Participants will be instructed to limit ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, chocolate) for 24 h prior to the start of dosing until collection of the final pharmacokinetic blood sample.

- Participants will abstain from alcohol for 24 h prior to the start of dosing until collection of the final pharmacokinetic blood sample.

- Participants will be instructed to limit use of nicotine and/or nicotine containing products. Up to 10 cigarettes/day is acceptable.

6.3.3. Activity

Participants will abstain from strenuous exercise for 48 h prior to each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watch television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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. Rescreening of individuals will be in consultation with the Medical Monitor.

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.

7.1. Treatments Administered

Product name:	**Daprodustat (GSK1278863)**
Dosage form:	Tablet
Unit dose strength(s)/Dosage level(s):	6 mg tablet strength/6 mg dosage level
Route of Administration:	Oral
Physical description:	9.0 mm round, compound radius, white film coated tablets
Packaging and Labelling:	Study Treatment will be provided in a bottle. Each bottle will be labelled as required per country requirement.
Manufacturer	GlaxoSmithKline

7.2. Dose Modification

As this is a single dose study, no dosage modification for a participant can occur. However, in the event that the 6 mg dose proves to be poorly tolerated by the study population, the dose of daprodustat may be reduced for participants yet to be enrolled.

7.3. Method of Treatment Assignment

All participants will receive the same treatment of a single oral 6 mg dose of daprodustat.

7.4. Blinding

This will be an open label study.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the 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. 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

As 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. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

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.

All concomitant medications will be reviewed by the GSK Medical Monitor and may be considered on a case by case basis. A concomitant medication may be permitted by the GSK Medical Monitor if it will not jeopardize the interpretation of the data derived from that participant or the safety of the participant.

7.7.1. Permitted Medications and Non-Drug Therapies

Acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor. See Appendix 7 for a list of permitted contraceptive methods for WOCBP.

7.7.2. Prohibited Medications and Non-Drug Therapies

Healthy matched control participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Use of any of the following prescription drugs from 28 days prior to Day 1 until 7 days after the last dose of study treatment is prohibited and will constitute a protocol violation:

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

7.8. Treatment after the End of the Study

Healthy control and hepatically-impaired participants will not receive any additional treatment from GSK after completion of the study.

For participants with hepatic impairment, 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

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 (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:

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

Discontinuation of study treatment for abnormal liver tests in the healthy control participant cohorts is required when:

- a participant meets one of the conditions outlined in the algorithm;

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.

The liver chemistry stopping criteria for healthy control participants can be found in Appendix 7.

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.

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

The following points must be noted:

- If assessments are scheduled for the same nominal time, **THEN** the procedures should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws

  NOTE: The timing of the assessments should allow the blood draw to occur as close as possible to the exact nominal time.
- The timing and number of planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time-points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this 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 Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- 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 (Section 2), is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

9.1. Efficacy Assessments

Efficacy is not assessed in this study.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 5.

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 (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 participant consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 h, as indicated in Section 12.5 Appendix 5. The investigator will submit any updated SAE data to the sponsor within 24 h 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 5.

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 recombinant, human erythropoietins (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, thromboembolic events, thrombosis of vascular access
- Cardiomyopathy
- Pulmonary artery hypertension
- Cancer-related mortality and tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

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 Investigator's Brochure 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 electronic CRF (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 CRF 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 will be collected after the start of study treatment and until the follow-up visit.

- If a pregnancy is reported, the investigator should inform GSK within 24 h of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

For this study, any dose of daprodustat greater than 6 mg within a 24-h 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. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).

9.5. Safety Assessments

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

9.5.1. 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.

9.5.2. 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 CRF.

9.5.3. Electrocardiograms

- ECG measurements will be obtained as outlined in the SoA (Section 2) Full 12-lead ECGs will be recorded with theparticipant in a supine position. Heart rate, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcF 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 QTcF value. The average QTcF value of all three ECGs will be used to determine eligibility.

9.5.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or at the follow-up visit 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 3, must be conducted in accordance with the laboratory manual and the SoA.

9.5.5. Pregnancy Testing

In this study, participants will have a drug exposure duration of <5 days including dosing plus 5 half-lives and dosing will occur in an inpatient setting. Given this scenario, pregnancy risks are effectively mitigated by adequately ruling out pregnancy at the time of dosing. Thus, it is not necessary to require participants to start a new contraceptive method if they are not already established on one. To ensure capture of women of childbearing potential in this category who may have conceived but are just shy of being able to identify the pregnancy with current detection methods, it is recommended that two pregnancy tests are done in a short time span.

Therefore, for WOCBP that are **not** currently utilizing a highly-effective contraceptive method listed in Appendix 6, a negative pregnancy test on or between Day -7 to Day -4 and again pre-dose (Day -1 or Day 0) is required. WOCBP who are already using a highly effective contraceptive method listed in Appendix 6 (<1% failure rate per year when used consistently and correctly) should continue this method until the follow-up visit at a minimum. In this case, a negative screening test within 28 days of dosing and again pre-dose (Day -1 to Day 0) is sufficient and the additional Day -7 to -4 test is not needed.

9.6. Pharmacokinetics

9.6.1. Blood sample collection

Blood samples for PK analysis of daprodustat and its six predominant metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13) will be collected at the time points indicated in the SoA (Section 2). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Additional blood samples will be collected for the assessment of protein binding for daprodustat and metabolites at the timepoints in the SoA (Section 2).

Details of PK and protein binding blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

9.6.2. Sample Analysis

Pharmacokinetic plasma analysis will be performed under the management of Bioanalysis, Immunogenicity and Biomarkers, Platform Technology & Science (PTS) In Vitro/In Vivo Translation, GSK. Concentrations and plasma protein binding of daprodustat six predominant metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) will be determined in samples using the currently approved analytical methodology. Raw data will be stored in the archives at the site of bio-analysis.

9.7. Pharmacodynamics

Venous blood samples will be collected for measurement of plasma erythropoietin at the timepoints specified in the SoA (Section 2). Details of pharmacodynamics (PD) blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

9.8. Genetics

Genetics is not assessed in this study.

9.9. Biomarkers

Biomarkers are not assessed in this study.

9.10. 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

No formal hypotheses will be tested. An estimation approach will be used to evaluate the effect of hepatic impairment (i.e., moderate and potentially either mild or severe) on the PK of daprodustat. The comparisons of interest are the single dose PK parameters Cmax and AUC of daprodustat in each hepatic impaired cohort compared to the normal hepatic function cohort.

The point estimates of the geometric least squares (GLS) mean ratio for the PK parameters and associated 90% confidence intervals will be provided for cohort comparisons (hepatically impaired:healthy participants). The PK parameters will be log-transformed prior to analysis and cohort comparisons will be expressed as ratios on the original scale. %AUCex and tmax and will be summarized descriptively.

10.2. Sample Size Determination

10.2.1. Sample Size Assumptions

The FDA Guidance for Industry "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labelling" recommends that a sufficient number of participants should be enrolled to provide evaluable data from at least eight participants in the control and moderate impairment groups. A sample size of eight evaluable participants per cohort was selected based upon this recommendation.

Based on the recent GSK study PHI115573, the between participant CV (CVb) for AUC(0-inf) and Cmax of daprodustat (5 mg) is 41.9% (SD = 0.402) and 28.3% (SD = 0.278) respectively from proc mixed model. Based on these estimates of CVb and a sample size of 8 in each cohort, it is estimated that the half width of the 90% confidence interval will be 43% and 28% of the point estimates for AUC and Cmax, respectively. These calculations are based on the $\log_e$ scale. If the point estimate of the ratio of geometric means is 1, then the 90% confidence interval will be approximately (0.70, 1.43) and (0.78, 1.28) for AUC and Cmax, respectively.

10.2.2. Sample Size Sensitivity

Table 3 shows the precision and 90% CI for a sample size of 8 in each group based on the observed SD in studies conducted among healthy and renal impairment participants.

Table 3 Precision and 90% CI Estimates

Study	Dose	Population	Parameter	SD	Precision	90% CI
PHX111427	5 mg	Healthy	AUC(0-inf)	0.362	38%	(0.73, 1.38)
			Cmax	0.361	38%	(0.73, 1.38)
PHI112843	50 mg	Renal Impaired	AUC(0-inf)	0.294	30%	(0.77, 1.30)
			Cmax	0.159	15%	(0.87, 1.15)
PHI112843	50 mg	Healthy	AUC(0-inf)	0.148	14%	(0.88, 1.14)
			Cmax	0.109	11%	(0.90, 1.11)

10.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

10.3.1.1. Enrolled Population

All participants who were successfully screened and enrolled for the trial and for whom a record exists on the study database. This population will be used for summarize number of subjects by Country and Site ID and age ranges.

10.3.1.2. Safety Population

All participants who received at least one dose of study medication. This will be the primary population for the safety analyses.

10.3.1.3. Pharmacokinetic Population

All participants in the 'Safety Population' for whom a PK sample has been obtained and analyzed will be included in the PK population. This population will be used in the evaluation of PK data. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PK data.

10.3.1.4. Pharmacodynamic Population

All participants in the 'Safety Population' who had at least 1 PD assessment. PD samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PD data.

10.3.1.5. Screened Population

All participants who were screened will be considered for this population. This population will be used for summarizing screening status.

10.3.2. Interim Analysis

An interim analysis of the primary endpoint will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

- If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with severe hepatic impairment and a healthy, matched control group.

- If a ≥ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

10.4. Key Elements of Analysis Plan

Final analyses will be performed after the completion of the study and final dataset authorization.

Data will be listed and summarized separately for each part of the study according to GSK reporting standards where applicable. Listings will be sorted by participant, period, day, and time, noting treatment. Summaries will be presented by treatment, day and time.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), coefficient of variation for the mean (%CV), median, minimum, maximum, geometric mean with associated 95% confidence interval (CI), and the between-participant CV (%CVb) for the geometric mean; whereas, n and percent will be used as summary statistics for categorical variables.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.4 or higher of the SAS system will be used to analyze data as well as to generate tables, listings, and figures.

Complete details will be documented in the Reporting and Analysis Plan (RAP).

10.4.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed under the direct auspices of the Clinical Pharmacokinetics Modeling & Simulation department (CPMS), GlaxoSmithKline. Plasma concentration-time data for daprodustat and its six predominant metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) will be analyzed by non-compartmental methods with WinNonlin version 5.22 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], and apparent terminal phase half-life (t½).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Figures for individual plasma concentrations will be presented on both a linear and semi-log scale daprodustat and its six predominant metabolites. Linear and semi-log figures for mean and median plasma concentrations versus time will also be generated.

For each of the derived PK parameters of daprodustat and its six predominant metabolites, the following summary statistics will be calculated for each cohort: n (number of observations), arithmetic mean, standard deviation, median, minimum, maximum, and the 95% confidence interval of arithmetic mean.

In addition, summary statistics for log-transformed PK parameters of daprodustat and its six predominant metabolites [i.e., AUC(0-t), AUC(0-∞), Cmax, and t½],except tmax will include geometric mean, 95% confidence interval of the geometric mean, standard deviation of the logarithmically transformed data, and inter-participant coefficient of variation [CVb (%)].

The inter-participant CV [CVb (%)] will be calculated according to the following method:

$$\text{Log}_e \text{ Transformed Data:} \quad CVb(\%) = SQRT(\exp(SD^2) - 1) \times 100$$

where SD is the standard deviation on the $\log_e$ scale.

Unbound fraction (fu) will be calculated using the total and unbound plasma concentration of daprodustat and its metabolites generated at 3, 12 and 24 h post dose for both normal and hepatic impaired participants using the following formula:

$$fu = Cunbound/Ctotal$$

where Cunbound and Ctotal are the unbound and total concentrations of daprodustat and its metabolites in plasma, respectively.

Full details of the analysis will be provided in the RAP.

10.4.1.1. Statistical Analysis of Pharmacokinetic Parameters

Statistical analyses of the pharmacokinetic parameter data will be performed under the direct auspices of Quantitative Sciences India, GSK.

For each log-transformed PK parameter (expect %AUCex and tmax), point estimate and its associated 90% CI will be constructed for the cohort (hepatically impaired – healthy participants) difference. The results will be exponentiated to obtain the ratio of GLS means and its 90% CI.

As data permit, tmax will be analyzed non-parametrically using the Wilcoxon Rank Sum Test. The point estimates and 90% confidence intervals for the median differences will be calculated for the cohort difference (hepatically impaired – healthy participants). Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

A sensitivity analysis will be performed for log transformed PK parameters (except %AUCex and tmax) by analysis of covariance (ANCOVA) including terms cohort, gender, age and BMI. For each PK parameter, a point estimate and an associated 90% confidence interval (CI) will be constructed for the difference between participants with hepatic impairment and healthy participants. The results will be exponentiated to obtain the ratio of GLS means and its 90% CI.

Further details of analysis and reporting of PK data will be given in the RAP.

10.4.2. Pharmacodynamic Analyses

Pharmacodynamic data will be presented in graphical and/or tabular form and will be summarized descriptively.

Descriptive statistics, where appropriate, (n, arithmetic mean, geometric mean, standard deviation, minimum, median and maximum) will be calculated for the pharmacodynamic endpoints.

10.4.3. Safety Analyses

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

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Table 4 List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CKD	Chronic kidney disease
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum observed concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Clinical Pharmacokinetics Modeling & Simulation
CRF	Case Report Form
CPSR	Clinical study report
CT	Computerized tomography
Ctotal	Total concentration
Cunbound	Unbound concentration
CV	Cardiovascular
CVb	Between participant coefficient of variability
CYP	Cytochrome P450 enzyme
dL	decilitre
DMPK	Drug Metabolism & Pharmacokinetics
ECG	Electrocardiogram
ECHO	Echocardiographic
eCRF	Electronic Case Report Form
E,last	Last measurable concentration
Cmax, EPO	Maximum observed EPO concetration
EPO	Erythropoietin
ex	Extrapolation
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
fu	Unbound fraction
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal

GLS	Geometric least squares
GSK	GlaxoSmithKline
h	Hour
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
HRT	Hormone replacement therapy
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
IDSL	Integrated Data Standards Library
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational new drug
INR	International normalization ratio
IP	Investigational product
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
IUS	Intrauterine system
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
mm	Millimeter
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Milliseconds
µM	Micromolar
n	Number
ND	Nondialysis dependent
NOAEL	No observed adverse effect level

NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
PAH	Pulmonary artery hypertension
PCI	Potential clinical importance
PD	Pharmacodynamic
%CV	Coefficient of variation of the mean
PHD	prolyl-4-hydroxylases
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development
PRVP	Peak right ventricular pressure
PSRAE	Possible Suicidality Related Adverse Events
PTS	Platform Technology & Science
QTc	Corrected QT interval
QTcB	QT duration corrected for heart rate by Bazett's formula
R&D	Research and development
RAP	Report and Analysis Plan
RBC	Red blood cells
rh	Recombinant human
RNA	Ribonucleic acid
SAE	Serious Adverse Event(s)
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of Activities
sPAP	systolic Pulmonary Artery Pressure
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t½	Half life
TIPS	Transjugular Intrahepatic Portosystemic Shunt
Tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
µM	Micromolar
VEGF	Vascular endothelial growth factor
WBC	White blood cells
WOCBP	Woman of childbearing potential

Trademark Information

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12.2. Appendix 2: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Excessive erythropoiesis (polycythemia) leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis attributed to daprodustat was associated with vascular congestion, microthrombi, and tissue ischemia in a number of organs. 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. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 6.1.1 • Monitoring of emerging safety data by an internal GSK Safety Review Team.
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 rhEPOs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to CV risk are outlined in Section 6.2.1. • 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
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 were observed with intravenous and oral administration of daprodustat. Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat). In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported adverse event, however causal association has not been established. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	• Suspected GI bleeding or significant symptoms consistent with erosions or ulcers should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted. • 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
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 conducted to date , administration of daprodustat has been associated with: • In studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg. In studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. • Systemic EPO concentrations within the physiologic range Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 6.2.1. • 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 had no clinically significant effect on	• 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
	transthoracic Echocardiographic (ECHO) estimates of systolic pulmonary artery pressure (sPAP) under either normoxic or hypoxic conditions. ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically-meaningful changes in sPAP in participants not on dialysis for daprodustat. In hemodialysis participants, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (Daprodustat: 8 [7%]; Control 0) in participants reaching the sPAP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 participants with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study treatment; and there was no dose relationship for participants meeting the sPAP potential clinical importance (PCI) criterion. Overall, there is insufficient evidence to conclude a relationship to	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	treatment with daprodustat. 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. Small increases in cardiac troponin in 6 month rat study with daprodustat were consistent with the background finding of spontaneous rodent cardiomyopathy independent of exposure to daprodustat. 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.	• 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
	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 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	• 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
	duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization with daprodustat. Following review of clinical data with daprodustat received to date, this has not been identified as a safety concern for daprodustat.	
Exacerbation of rheumatoid arthritis	In inflamed rheumatic joints, activation of HIF-related genes secondary to decreased oxygen and pro-inflammatory cytokines has been postulated to contribute to the neo-angiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra 2010; Muz, 2009]. No abnormalities seen in non-clinical studies conducted to date for daprodustat. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• 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	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. Daprodustat is an inhibitor of CYP2C8 in vitro, with an IC_{50} value of 21 µM. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with clopidogrel (a moderate CYP2C8 inhibitor) leads to a ~ 2-fold increase in AUC, with no clinically-significant increase in the measured Hgb response. Co-administration of daprodustat with BCRP inhibitors has the potential to increase exposure of daprodustat. Use of BCRP inhibitors was not a significant covariate of daprodustat exposure, but was	• Co-administration of daprodustat with the strong CYP2C8 inhibitor, gemfibrozil and inducer, rifampin/rifampicin is not permitted as outlined in Section 7.7.2. • Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 7.7. • 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
	found to result in a small change in metabolite exposure (20% increase in AUC). Co-administration of daprodustat with BCRP inhibitors [e.g., cyclosporine, HIV antivirals (atazanavir, lopinavir, ritonavir, tipranavir), lapatanib and curcumin] is not expected to produce clinically relevant increases in daprodustat exposure. Daprodustat is an inhibitor of organic anion transporter polypeptide (OATP) 1B1/1B3 in vitro, with IC_{50} values of 6 µM and 11 µM, respectively. A clinical drug interaction study between 100 mg daprodustat with either a CYP2C8 substrate or an OATP1B1/1B3 substrate showed that there is no PK interaction at this dose of daprodustat.	

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12.3. Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the 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.
- 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 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin 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 (nonfasting)	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening	• Follicle-stimulating hormone and estradiol (as needed in women of			

Laboratory Assessments	**Parameters**
Tests	non-childbearing potential only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test[2] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) or specify other tests if applicable • PT/INR The results of each test must be entered into the CRF.

NOTES :

[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 and Appendix 7 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.

12.4. Appendix 4: 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 (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- 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.

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 participants, 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 (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Pharmacology Study Report (CPSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

12.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

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

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 (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

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

d. Results in 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 (eg, 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.

Recording AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

12.6. Appendix 6: 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 is to be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential that are **not** currently utilizing a highly-effective contraceptive method are eligible to participate if a pregnancy test conducted on or between Day -7 to Day -4 and again pre-dose (Day -1 or Day 0) is negative. It is not necessary to require participants to start a new contraceptive method if they are not already established on one.

Female participants of childbearing potential that are currently utilizing a highly-effective contraceptive method are eligible to participate if they agree to continue to use this method consistently and correctly as described in Table 6. In this instance a negative

pregnancy test on or between Day -7 to Day -4 and again pre-dose (Day -1 or Day 0) would not be required.

Table 6 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[b] • 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[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:
[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 for at least 48 h after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at the times listed in the SoA (Section 2)

- Additional pregnancy testing is not required during the treatment period and at 48 h after the last dose of study treatment
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 2 mIU/mL will be performed using the test kit provided by the central laboratory.

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 h 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 be withdrawn from the study.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

For the purposes of this protocol, please refer to the guidelines below for the required action, monitoring and follow-up assessments if a participant meets any of the criteria listed below, after dosing with the study medication.

Phase I liver chemistry stopping criteria and required follow up assessments for Healthy Volunteer Participants

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 h
• Complete the liver event CRF, 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, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 h
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained 48 h of last dose[4]
• 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</td></tr>
</table>

Liver Chemistry Stopping Criteria	
INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009] • Liver imaging (ultrasound, magnetic resonance, or 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 participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. 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
4. PK sample may not be required for participants 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 PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos*. 2009; 37:1779-1784.

12.8. Appendix 8: Grades of Hepatic Encephalopathy

Grade	Description
1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction
2	Lethargy; disorientation for time; obvious personality changes; inappropriate beharior
3	Somnolence to semistupor; responsive to stimuli; confused; gross disorientation; bizarre behavior
4	Coma; unable to test mental state

References

Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portalsystemic encephalopathy. A double-blind controlled trial. *Gastroenterology.* 1977; 72:573-583.

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).