TITLE PAGE

Protocol Title: An open-label study in healthy male participants to determine the mass balance, absolute bioavailability and pharmacokinetics of daprodustat, administered as a single intravenous microtracer (concomitant with an oral dose of non-radiolabelled daprodustat) and a single, oral radiolabelled dose

Protocol Number: 200232

Short Title: Absorption and elimination of radiolabelled daprodustat

Compound Number: GSK1278863 (daprodustat)

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	*01-Sep-2017*
Original Protocol	*30-May-2017*

Amendment 01 01-SEP-2017

Overall Rationale for the Amendment: This amendment is required by regulatory authority.

Section # and Name	**Description of Change**	**Brief Rationale**
9.2.1. Time Period and Frequency for Collecting AE and SAE Information	"Promptly" has been changed to "within 24 hours following knowledge of the SAE."	Clarification of "promptly."
9.2.5. Regulatory Reporting Requirements for SAEs	"Prompt" has been changed to "within 24 hours following knowledge of an SAE."	Clarification of "prompt."

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1. SYNOPSIS

Protocol Title: An open-label study in healthy male participants to determine the mass balance, absolute bioavailability and pharmacokinetics of daprodustat, administered as a single intravenous microtracer (concomitant with an oral dose of non-radiolabelled daprodustat) and a single, oral radiolabelled dose.

Short Title: Absorption and elimination of radiolabelled daprodustat

Rationale:

Absorption, metabolism and excretion of daprodustat (GSK1278863) have been studied in pre-clinical animals models, *in vitro*, and in previous clinical trials; however, the elimination routes and metabolic pathways of daprodustat have not been fully elucidated in humans. The absorption, metabolism and excretion of daprodustat must be adequately described in human subjects as part of the clinical development of this compound.

This study will use the Entero-Test (HDC Corp., Mountain View, CA; or alternative source, subject to commercial availability) for sampling of duodenal bile to conduct qualitative assessment of drug metabolites in this matrix in order to characterise biliary elimination pathways. Samples from this study will also be transferred to a separate study to characterise and quantify the metabolites of daprodustat in plasma, urine, faeces, and duodenal bile.

Objectives and Endpoints:

Objectives	Endpoints[1]
Primary	
• To determine total radioactivity (drug related material) in blood and plasma following a single IV microtracer dose of [^{14}C]-GSK1278863[1] (concomitant with an oral dose of non-radiolabelled daprodustat[1]) and a single, oral dose of [^{14}C]-GSK1278863.	• AUC(0–inf), AUC(0–t), C_{max}, t_{max} and $t_{1/2}$ of total drug-related material (radioactivity) in blood and plasma. • Volume (Vss) and clearance (CL) of total drug-related material (radioactivity) after IV dose only (Period 1).
• To determine the rate and extent of excretion of total radioactivity in urine and faeces and the total recovery of radioactivity following a single, oral dose of [^{14}C]-GSK1278863.	• Urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time (Treatment Period 2 only).

Objectives	Endpoints[1]
Secondary	
• To determine parent daprodustat and metabolite concentrations in plasma following a single IV microtracer dose of [^{14}C]-GSK1278863 and both oral doses of daprodustat.	• AUC(0–inf), AUC(0–t), C_{max}, t_{max} and $t_{1/2}$ of daprodustat parent and metabolite in plasma from the IV dose and both oral doses. • Volume (Vss) and clearance (CL) of daprodustat parent and metabolite (if possible) after IV dose only (Period 1).
• To estimate the absolute bioavailability of daprodustat following oral administration.	• F (absolute bioavailability) after oral dosing.
• To generate samples that will be used to characterize the metabolite profile of daprodustat following a single IV microtracer dose of [^{14}C]-GSK1278863 concomitant with an oral dose of non-radiolabelled daprodustat (plasma and duodenal bile) and a single, oral dose of [^{14}C]-GSK1278863 (plasma, urine and faeces).	• Characterization and quantification of metabolites in plasma, urine, faeces, and duodenal bile (these analytical investigations will be conducted and the results reported under a separate GSK protocol).
• To evaluate the safety and tolerability of daprodustat after single IV and oral doses in healthy participants.	• Incidence and severity of adverse events. • Laboratory safety, 12-lead ECG, and vital signs parameters.

[1] For measured concentrations of daprodustat in blood and plasma, the nomenclature [^{14}C]-GSK1278863 describes the parent daprodustat concentration derived via analysis by liquid chromatography (LC) + Accelerator Mass Spectrometry (AMS), whereas daprodustat describes the parent daprodustat concentration derived via liquid chromatography-tandem mass spectrometry (LC/MS).

Overall Design:

This is an open-label, single-centre, non-randomised, 2-period, single-sequence, crossover, mass balance study in 6 healthy male participants. The aim of the study is to assess the excretion balance of daprodustat (GSK1278863) using [^{14}C]-radiolabelled drug substance administered orally, and as an IV infusion, administered as a microtracer dose (concomitant with an oral, non-radiolabelled dose). Absolute bioavailability of an oral dose will also be assessed.

Safety data will include AE reporting, 12-lead ECG, vital signs, and laboratory safety tests. Blood will be sampled extensively on the day of dosing, and daily until Day 7, for assessing the PK of daprodustat and metabolites.

Number of Participants:

6 healthy male participants will be enrolled.

If one or more participants prematurely discontinue the study, replacement participants may be enrolled at the discretion of the sponsor and in consultation with the investigator.

Replacement subjects may be required to complete one or both treatment periods, at the discretion of the sponsor.

Treatment Periods and Duration:

Each participant will be involved in the study for up to 10 weeks. He will have a screening visit, two treatment periods (Treatment Periods 1 and 2), separated by about 7 days (at least 14 days between oral doses), and a follow up visit 1-2 weeks after the last assessment in Treatment Period 2. During both treatment periods, participants will reside in the unit from the afternoon before Day 1 (Day -1) until all procedures are completed on Day 7. Participants may be asked to stay for up to 1 week longer in Treatment Period 2, if excretion of drug-related material takes longer than anticipated.

Treatment Period 1 (oral tablet and intravenous infusion)

On Day 1 of Treatment Period 1, after an overnight fast of at least 8 h, each participant will take a single 6 mg oral dose of daprodustat; participants will continue to fast for 4 h after dosing. After approximately 1 h, participants will receive 50 µg of [^{14}C]-GSK1278863 (approximately 4.63 kBq; 125 nCi) by IV infusion over 1 h. Blood samples will be collected for 144 h after oral dosing (until Day 7), while duodenal bile will be collected by Entero-Test as described below. Participants will be discharged on study Day 7 after completion of the 144 h sample collection.

The Entero-Test to collect duodenal bile will be used only in Treatment Period 1. The Entero-Test will be swallowed about 3.5 h before the oral dose, a duration recommended to allow transit of the Entero-Test to the duodenum, while participants are in a fasted state. It will be removed about 3 h after the oral dose (about 1 h after the end of the IV infusion), a time when the oral dose is expected to have transitioned from the stomach to the duodenum. At about 0.5 h after the start of IV infusion (i.e., 1.5 h before string withdrawal) a food cue will be used to stimulate gall bladder emptying.

Treatment Period 2 (oral solution)

On Day 1 of Treatment Period 2, after an overnight fast of at least 8 h, each participant will receive 25 mg [^{14}C]-GSK1278863 (approximately 2.31 MBq; 62.5 µCi) as an oral solution; participants will continue to fast for 4 h after dosing. Blood, urine and faecal samples will be collected for a minimum of 144 h (up to Day 7) after dosing, depending on the amount of radioactivity excreted by each participant. Radioactivity quantification using liquid scintillation counting (LSC) will be performed daily on the 24-h urine collections and 24-h faecal homogenates on Day 6 (96–120 h) and Day 7 (120–144 h).

Based on the radioquantitification results on Days 6 and 7, participants will be asked to do the following:

- If $\geq$ 90% of the administered radioactivity has been recovered and less than 1% of the dose is excreted on both Day 6 (96–120 h) and Day 7 (120–144 h) for a given participant, he may be discharged on Day 8 (after the LSC results are available), and no further samples will be collected. Drug Metabolism and

Pharmacokinetics (DMPK) at GSK should be consulted to agree with release of a participant.

- If excretion is higher than 1% in the 96–144 h (Day 6–7) collection period, or if the results are inconclusive, the participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals for up to 7 additional days (until the morning of Day 14). Once less than 1% of the dose is excreted in 2 consecutive 24-h periods where samples are provided, or ≥ 90% of the radioactivity has been recovered, the participant will be discharged. All remaining participants will be discharged from the unit no later than Day 15.
- In the unlikely event that excretion is still higher than 1% in the 24-h collection period prior to discharge on Day 15, the participant will continue to collect faecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2 to 3 days for analysis.

2. SCHEDULE OF ACTIVITIES (SOA)

The SoA for Treatment Period 1 and Treatment Period 2 is presented in Table 1 and Table 2, respectively.

The timing and number of planned study assessments, including safety and pharmacokinetic 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent (ICF).

Table 1 SoA: Treatment Period 1 (oral tablet and intravenous infusion)

Visit	Screening[1]		Treatment Period 1																				
Day	-30 to -1	-1	1														2		3	4	5	6	7
Procedure		*hour*	*Pre-dose*	*0*	*0.5*	*1*	*1.25*	*1.5*	*2*	*3*	*4*	*6*	*8*	*10*	*12*	*24*	*36*	*48*	*72*	*96*	*120*	*144*
Informed consent	X																						
Medical history (including drug/alcohol use)	X																						
Demography	X																						
Admission to unit		X																					
Discharge from unit[2]																							X
Full physical exam, including height,weight and BMI	X																						
Brief physical exam		X																					X
Drugs of abuse screen	X	X																					
Alcohol and cotinine tests, CO breath tests	X	X																					
HIV and hepatitis B and C screen	X																						
Laboratory safety tests (including LFTs)	X	X																					X
12-lead ECG[3]	X																						X
Vital signs[3,4]	X		X							X													X
[^{14}C]-GSK1278863 IV infusion						←				→													
Oral daprodustat[5]				X																			
Blood samples for drug assay and radioactivity[6]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection[7]			X																				

Visit	Screening[1]		Treatment Period 1																			
Day	-30 to -1	-1	1												2		3	4	5	6	7	
Procedure		*hour*	*Pre-dose*	*0*	*0.5*	*1*	*1.25*	*1.5*	*2*	*3*	*4*	*6*	*8*	*10*	*12*	*24*	*36*	*48*	*72*	*96*	*120*	*144*
Faecal collection[7]			X																			
Entero-Test (duodenal bile)[8]			←							→												
Meals[8,9]								X			X			X								
AE/SAE/concomitant medication review[10]	←																					→

Abbreviations: AE: adverse event; ECG: electrocardiogram; HIV: human immunodeficiency virus; IV: intravenous; LFTs: liver function tests; SAE: serious adverse event.

Notes:

[1] Screening will be within 30 days before Day 1.

[2] Participants will be discharged for a washout period prior to dosing in Treatment Period 2; there will be at least 14 days between a participant's oral doses. Participants who withdraw from the study early should be subject to those assessments that would be required at discharge in that treatment period, if participants agree to that.

[3] Single ECG measurements will be taken at at all time points. If any measurement is considered abnormal, triplicate measurements will be taken and the mean of the triplicate measurements used. The pre-dose measurement on Day 1 will be used as baseline.

[4] Triplicate measurements of systolic and diastolic blood pressure; single measurements of oral temperature and respiratory rate.

[5] Participants will fast for at least 8 h before oral dosing.

[6] Samples will be taken for background radiation at screening, Day –1 and pre-dose only, while total radioactivity, [^{14}C]-GSK1278863 analysis, cold daprodustat analysis, and metabolite profiling will include predose and all post-dosing samples. Sampling times are relative to the oral dose on Day 1, unless otherwise indicated.

[7] Urine and faeces will be collected at pre-dose (up to 3 h pre-dose for the urine sample; up to 48 h pre-dose for the faecal sample).

[8] The Entero-Test will be swallowed about 3.5 h before the oral dose, while participants are in a fasted state. It will be removed 3 h after the oral dose (about 1 h after the end of the IV infusion). At about 0.5 h after the start of IV infusion (i.e., 1.5 h before string withdrawal) a food cue will be used to stimulate gall bladder emptying.

[9] Meal times are specified for Day 1 only. On all other days, meals will be served at the unit's standard times.

[10] AEs and SAEs will be collected from the start of oral dosing until the final follow-up visit. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.

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

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

Table 2 SoA: Treatment Period 2 (oral solution)

Visit	Treatment Period 2																					FU[1]
Day	-1	1												2		3	4	5	6	7[2]	8–15[2,3]	
Procedure	*hour*	*Pre-dose*	*0*	*0.5*	*1*	*1.5*	*2*	*3*	*4*	*6*	*8*	*10*	*12*	*24*	*36*	*48*	*72*	*96*	*120*	*144*		
Admission to unit	X																					
Discharge from unit[4]																				X	X	
Brief physical exam	X																			X	X	X
Drugs of abuse screen	X																					
Alcohol and cotinine tests, CO breath tests	X																					
Laboratory safety tests (including LFTs)	X																			X	X	X
12-lead ECG[5]		X																			X	X
Vital signs[5,6]		X						X												X	X	X
[^{14}C]-GSK1278863 oral solution[7]			X																			
Blood samples for drug assay and radioactivity[8]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine collection[9]		X	←																		→	
Faecal collection[9]		X	←																		→	
Meals[10]									X			X										
AE/SAE/concomitant medication review[11]	←																				→	

Abbreviations: AE: adverse event; ECG: electrocardiogram; FU: follow-up; HIV: human immunodeficiency virus; LFTs: liver function tests; SAE: serious adverse event.

Notes:

[1] Follow-up will be 7–14 days after the participant's last assessment.

[2] Urine and faecal samples will be collected for a minimum of 144 h (up to Day 7) after dosing, depending on the amount of radioactivity excreted by each participant. Liquid scintillation counting (LSC) will be performed daily on 24-h urine collections and 24-h faecal homogenates on Day 6 (96–120 h) and Day 7 (120–144 h). If less than 1% of the dose is excreted in each of those 24-h periods for a given participant, he may be discharged on Day 8 (after the LSC results from Days 6 and 7 are available), and no further samples will be collected. If excretion is higher than 1% in the 96–144 h (Day 6–7) collection period, or if the results are inconclusive, the participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals, for up to 7 additional days (until the morning of Day 14). Once less than 1% of the dose is excreted in a 24-h period, or ≥ 90% of the radioactivity has been recovered, that participant will be discharged. Any remaining participants will be discharged from the unit on Day 15. In the unlikely event that excretion is still higher than 1% in the 24-h collection period prior to discharge on Day 15, the participant will continue to collect faecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2 to 3 days for analysis.

[3] Brief physical exam, laboratory safety tests, 12-lead ECG and vital signs to be done only on the day of discharge. Blood samples for drug assay and radioactivity to be taken each morning (at the time of dosing on Day 1) until Day 7.

[4] Participants withdrawing from the study early should be subject to those assessments that would be required at discharge.

[5] Single ECG measurements will be taken at at all time points. If any measurement is considered abnormal, triplicate measurements will be taken and the mean of the triplicate measurmements used. The pre-dose measurement on Day 1 will be used as baseline.

[6] Triplicate measurements of systolic and diastolic blood pressure; single measurements of oral temperature and respiratory rate.

[7] Participants will fast for at least 8 h before oral dosing.

[8] Samples will be taken for background radiation pre-dose only, while total radioactivity, [^{14}C]-GSK1278863 analysis, cold GSK1278863 analysis, and metabolite profiling will include predose and all post-dosing samples.

[9] Urine and faeces will be collected at pre-dose (up to 3 h pre-dose for the urine sample; up to 48 h pre-dose for the faecal sample), then over 24 h collection periods as follows: 0–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h and 120–144 h. If participants are required to stay after Day 7, collections will continue at 24-h intervals. An aliquot from each collection period will be taken for metabolic profiling (separate study).

[10] Meal times are specified for Day 1 only. On all other days, meals will be served at the unit's standard times.

[11] AEs and SAEs will be collected until the final follow-up visit.

If assessments are scheduled for the same nominal time, the assessments should occur in the following order:

1. 12-lead ECG
2. vital signs
3. blood draws
4. other assessments

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

3. INTRODUCTION

Daprodustat (GSK1278863) is an orally-available, small molecule which inhibits hypoxia-inducible factor (HIF) prolyl-4-hydroxylases (PHDs), and is being studied for treatment of anaemia of chronic kidney disease (CKD).

3.1. Study Rationale

Absorption, metabolism and excretion of daprodustat (GSK1278863) have been studied in pre-clinical animals models, *in vitro*, and in previous clinical trials; however, the elimination routes and metabolic pathways of daprodustat have not been fully elucidated in humans. The absorption, metabolism and excretion of daprodustat must be adequately described in human subjects as part of the clinical development of this compound.

This open-label study in 6 healthy male participants will assess the excretion balance of daprodustat in humans using [^{14}C]-radiolabelled drug substance administered as an intravenous (IV) infusion and orally. [^{14}C]-GSK1278863 administered by IV infusion will be a microtracer; therefore, it will be administered concomitant to an oral non-radiolabelled dose, to ensure that the pharmacokinetics (PK) are representative of a clinically-relevant dose. The study will also provide an assessment of bioavailability of daprodustat following administration of a [^{14}C]-radiolabelled oral solution.

Since biliary excretion has been shown as a predominant elimination route in preclinical species for daprodustat, this study will use the Entero-Test (HDC Corp., Mountain View, CA; or alternative source, subject to commercial availability) for sampling of duodenal bile to conduct qualitative assessment of drug metabolites in this matrix in order to characterise biliary elimination pathways. Samples from this study will also be transferred to a separate study to characterise and quantify the metabolites of daprodustat in plasma, urine, faeces, and duodenal bile.

3.2. Background

3.2.1. Anaemia of CKD

Anaemia is a common complication of CKD. The causes of anaemia in this population is multi-factorial, including relative or absolute deficiency of erythropoietin (EPO) and reduced iron availability related to chronic inflammation.

Current treatments for anaemia of CKD include supplemental iron therapy (IV and/or oral), the use of recombinant human EPO (rhEPO) and blood transfusions. However, each of these treatments has significant limitations, including poor compliance, gastrointestinal intolerability and increased risk of cardiovascular (CV) complications (e.g., stroke and myocardial infarction) and cancer-related morbidity and mortality (FDA Drug Safety Communication, 2011).

HIF prolyl hydroxylase inhibitors (PHIs), such as daprodustat, are an emerging new class of agent under investigation for the treatment of anaemia of CKD. Both pre-clinical and clinical data show that daprodustat can increase endogenous EPO levels and erythropoiesis with a resultant increase in haemoglobin (Hgb) levels.

Daprodustat may present several important advantages over rhEPO. It is an oral medication and does not require cold-chain storage as does rhEPO, thus increasing ease of use for patients. After administration of daprodustat, data suggest that increases in Hgb are achieved with EPO exposures lower than that observed with rhEPO. Treatment of anaemia of CKD with rhEPO is associated with increased CV risk which is postulated to be related to the associated increases in EPO exposure with rhEPO [Szczech, 2008]; therefore, daprodustat has the potential to raise Hgb without increasing CV risk.

3.2.2. Daprodustat (GSK1278863)

Daprodustat stimulates erythropoiesis through inhibition of HIF-PHDs: PHD1, PHD2 and PHD3. This activity results in the accumulation of HIFα transcription factors which leads to increased transcription of HIF-responsive genes. This biological activity simulates components of the natural response to hypoxia. During hypoxia, the PHDs are inhibited, resulting in the accumulation of unhydroxylated HIFα subunits, which dimerize with HIFβ subunits to induce transcription of HIF-responsive genes, including EPO and others involved in increasing oxygen utilisation (transferrin, haem oxygenase 1 (HO-1)).

Other functions regulated by HIFs include iron metabolism and utilization (haemojuvelin, and ferroportin), angiogenesis (VEGF), extracellular matrix metabolism, apoptosis, energy and glucose metabolism, vascular tone, cell adhesion, and motility.

To date, a total of eleven Clinical Pharmacology studies have been completed. In all of the completed studies daprodustat has been generally well tolerated and no new safety concerns have been identified which would preclude further development. In the Clinical Pharmacology program oral daprodustat has been administered to 332 healthy subjects (subjects with normal renal function), and 26 subjects with CKD. In this program, single doses of daprodustat between 2 mg and 500 mg and repeat doses between 5 mg and 100 mg once daily for up to 15 days have been administered. Daprodustat has not been administered IV to human participants in any study conducted to date.

Detailed information relating to non-clinical pharmacology, safety pharmacology, PK and metabolism, toxicology and other pre-clinical data can be found in the daprodustat Investigator's Brochure (IB) and supplements.

3.3. Benefit/Risk Assessment

The potential risks of study treatment and trial procedures, and their mitigation, are given in Appendix 2.

More detailed information about the known and expected benefits and risks of daprodustat may be found in the IB and supplements.

3.3.1. Benefit Assessment

As this is a study in healthy volunteers, they will receive no clinical benefit for participation in this study.

3.3.2. Overall Benefit:Risk Conclusion

Overall, the available data from non-clinical 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 and the study procedures, these can be addressed in clinical trials with proper participant selection, close safety monitoring, and specific risk characterisation and mitigation (see Appendix 2).

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints[1]
Primary	
• To determine total radioactivity (drug related material) in blood and plasma following a single IV microtracer dose of [^{14}C]-GSK1278863[1] (concomitant with an oral dose of non-radiolabelled daprodustat[1]) and a single, oral dose of [^{14}C]-GSK1278863.	• AUC(0–inf), AUC(0–t), C_{max}, t_{max} and $t_{1/2}$ of total drug-related material (radioactivity) in blood and plasma. • Volume (Vss) and clearance (CL) of total drug-related material (radioactivity) after IV dose only (Treatment Period 1).
• To determine the rate and extent of excretion of total radioactivity in urine and faeces and the total recovery of radioactivity following a single, oral dose of [^{14}C]-GSK1278863.	• Urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time (Treatment Period 2 only).
Secondary	
• To determine parent daprodustat and metabolite concentrations in plasma following a single IV microtracer dose of [^{14}C]-GSK1278863 and both oral doses of daprodustat.	• AUC(0–inf), AUC(0–t), C_{max}, t_{max} and $t_{1/2}$ of daprodustat parent and metabolite in plasma from the IV dose and both oral doses. • Volume (Vss) and clearance (CL) of daprodustat parent and metabolite (if possible) after IV dose only (Treatment Period 1).
• To estimate the absolute bioavailability of daprodustat following oral administration.	• F (absolute bioavailability) after oral dosing.
• To generate samples that will be used to characterise the metabolite profile of daprodustat following a single IV microtracer dose of [^{14}C]-GSK1278863 concomitant with an oral dose of non-radiolabelled daprodustat (plasma and duodenal bile) and a single, oral dose of [^{14}C]-GSK1278863 (plasma, urine and faeces).	• Characterisation and quantification of metabolites in plasma, urine, faeces, and duodenal bile (these analytical investigations will be conducted and the results reported under a separate GSK protocol).
• To evaluate the safety and tolerability of daprodustat after single IV and oral doses in healthy participants.	• Incidence and severity of adverse events. • Laboratory safety, 12-lead ECG, and vital sign parameters.

[1] For measured concentrations of daprodustat in blood and plasma, the nomenclature [^{14}C]-GSK1278863 describes the parent daprodustat concentration derived via analysis by liquid chromatography (LC) + Accelerator Mass Spectrometry (AMS), whereas daprodustat describes the parent daprodustat concentration derived via liquid chromatography-tandem mass spectrometry (LC/MS).

5. STUDY DESIGN

5.1. Overall Design

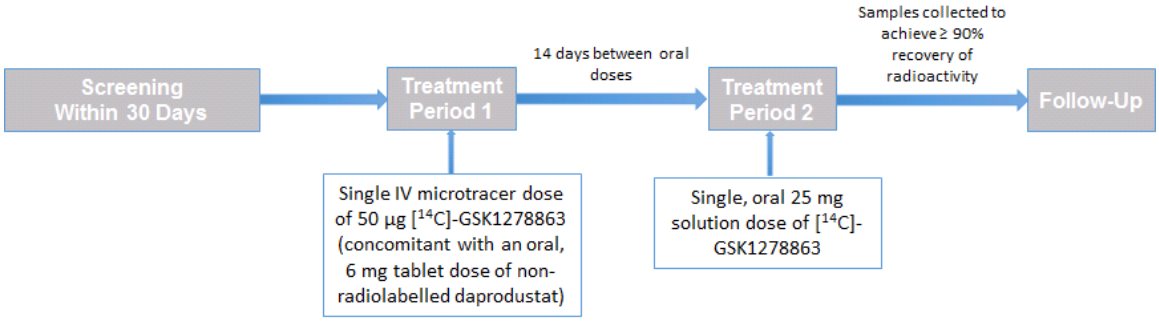
This is an open-label, single-centre, non-randomised, 2-period, single-sequence, crossover, mass balance study in 6 healthy male participants. The aim of the study is to assess the excretion balance of daprodustat (GSK1278863) using [^{14}C]-radiolabelled drug substance administered orally, and as an IV infusion, administered as a microtracer dose (concomitant with an oral, non-radiolabelled dose). Absolute bioavailability of an oral dose will also be assessed.

No formal sample size calculation has been performed for this study; 4 to 6 participants are deemed sufficient for this purpose. In order to minimise the number of participants exposed to radiation, those participants that discontinue early will not be replaced unless the total number of participants who complete dosing and all critical assessments drops below 4.

Each participant will be involved in the study for up to 10 weeks. He will have a screening visit, two treatment periods (Treatment Periods 1 and 2), separated by about 7 days (at least 14 days between oral doses), and a follow up visit 1-2 weeks after the last assessment in Treatment Period 2. During both treatment periods, participants will reside in the unit from the afternoon before Day 1 (Day -1) until all procedures are completed on Day 7. Participants may be asked to stay for up to 1 week longer in Treatment Period 2, if excretion of drug-related material takes longer than anticipated. A schematic of the study design is presented in Figure 1.

Safety data will include AE reporting, 12-lead ECG, vital signs, and laboratory safety tests. Blood will be sampled extensively on the day of dosing, and daily until Day 7, for assessing the PK of daprodustat and metabolites.

Figure 1 Study Treatment Schematic



Screening Period

Participants must be screened within 30 days before the first dose of daprodustat, and must meet all eligibility criteria.

Treatment Period 1 (oral tablet and intravenous infusion)

On Day 1 of Treatment Period 1, after an overnight fast of at least 8 h, each participant will take a single 6 mg oral dose of daprodustat. After approximately 1 h, participants will receive 50 µg of [^{14}C]-GSK1278863 (approximately 4.63 kBq; 125 nCi) by IV infusion over 1 h. Blood samples will be collected for 144 h after oral dosing (until Day 7), while duodenal bile will be collected by Entero-Test as described below. Participants will be discharged on study Day 7 after completion of the 144 h sample collection.

The Entero-Test to collect duodenal bile will be used only in Treatment Period 1. The Entero-Test will be swallowed about 3.5 h before the oral dose, a duration recommended to allow transit of the Entero-Test to the duodenum, while participants are in a fasted state. It will be removed about 3 h after the oral dose (about 1 h after the end of the IV infusion), a time when the oral dose is expected to have transitioned from the stomach to the duodenum [Guiney, 2011]. At about 0.5 h after the start of IV infusion (i.e., 1.5 h before string withdrawal) a food cue will be used to stimulate gall bladder emptying.

Treatment Period 2 (oral solution)

On Day 1 of Treatment Period 2, after an overnight fast of at least 8 h, each participant will receive 25 mg [^{14}C]-GSK1278863 (approximately 2.31 MBq; 62.5 µCi) as an oral solution; participants will continue to fast for 4 h after dosing. Blood, urine and faecal samples will be collected for a minimum of 144 h (up to Day 7) after dosing, depending on the amount of radioactivity excreted by each participant. Radioactivity quantification using liquid scintillation counting (LSC) will be performed daily on the 24-h urine collections and 24-h faecal homogenates on Day 6 (96–120 h) and Day 7 (120–144 h).

Based on the radioquantitification results on Days 6 and 7, participants will be asked to do the following:

- If $\geq$ 90% of the administered radioactivity has been recovered and less than 1% of the dose is excreted on both Day 6 (96–120 h) and Day 7 (120–144 h) for a given participant, he may be discharged on Day 8 (after the LSC results are available), and no further samples will be collected. Drug Metabolism and Pharmacokinetics (DMPK) at GSK should be consulted to agree with release of a participant.

- If excretion is higher than 1% in the 96-144 h (Day 6-7) collection period, or if the results are inconclusive, the participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals for up to 7 additional days (until the morning of Day 14). Once less than 1% of the dose is excreted in 2 consecutive 24-h periods where samples are provided, or $\geq$ 90% of the radioactivity has been recovered, the participant will be discharged. All remaining participants will be discharged from the unit no later than Day 15.
- In the unlikely event that excretion is still higher than 1% in the 24-h collection period prior to discharge on Day 15, the participant will continue to collect faecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2 to 3 days for analysis.

Follow-up

Follow-up procedures will be done 7-14 days after the participant's last assessment in Treatment Period 2. The follow-up period may be extended if:

(i) radioactivity excretion is still higher than 1%;
(ii) a participant has an unresolved AE at the follow-up visit, which, in the opinion of the investigator, merits further follow-up; or
(iii) new information becomes available that supports an extended follow-up period.

The investigator will decide on the nature of the extended follow-up. For example, participants may have a telephone follow-up at which they are asked about AEs, or participants may be asked to attend extra outpatient visits for additional monitoring of blood levels and/or for extra safety tests. The extra safety tests might include tests that are not described in this protocol. The investigator reserves the right, during or after the study, to repeat safety tests or to do any extra safety tests that are in the best interest of the participants. Those extra tests may or may not be described in this protocol.

5.2. Number of Participants

6 healthy male participants will be enrolled.

If one or more participants prematurely discontinue the study, replacement participants may be enrolled at the discretion of the sponsor and in consultation with the investigator. Replacement subjects may be required to complete one or both treatment periods, at the discretion of the sponsor.

5.3. Participant and Study Completion

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

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

5.4. Scientific Rationale for Study Design

In the first treatment period of this study, an IV microtracer dose of [^{14}C]-GSK1278863 will be infused over 1 h. The infusion will be administered after an oral dose of non-radiolabelled daprodustat. The non-radiolabelled dose of daprodustat is to ensure that the PK of the microdose represents a therapeutically-relevant dose. In the second treatment period, an oral solution of [^{14}C]-GSK1278863 will be used for comparison.

Metabolic elimination pathways will be characterised after the IV dose by the planned inclusion of duodenal bile collection. Complexities in human faecal sample analysis such as extraction, stability in the gastrointestinal tract, and endogenous contamination are minimised through assessment of the metabolic profile in duodenal bile.

5.5. Dose Justification

Daprodustat (GSK1278863) Dose

The dose of [^{14}C]-GSK1278863 to be administered intravenously is a microdose of 50 µg, which will be infused over 1 h. A microdose was selected because daprodustat has not previously been administered by IV infusion to humans. That dose level meets the criterion for a microdose, for the following reasons:

- It is ≤ 100 µg
- It is ≤ 1/100th of the lowest pharmacologically-active oral dose in healthy participants with normal renal function (i.e., 15 mg single, oral dose) based on an increase in plasma erythropoietin (GSK study PHX111427)
- It is ≤ 1/100th the no observed adverse effect level (NOAEL) of 3 mg/kg/day in the 39-week monkey where gastric erosions were observed at doses of ≥10 mg/kg/day

In an *in vitro* hemolysis assay using human erythrocytes, daprodustat formulations at concentrations ≤ 181.8 µg/mL (containing ethanol/tromethamine buffer) did not produce hemolysis when added to human blood. Additionally, a 50 µg total dose of [^{14}C]-GSK1278863 will be formulated as a 5 µg/mL solution in 0.9% phosphate-buffered saline (pH adjusted between 7 and 8, with a target of 7.5; 10 mL total volume).

To ensure clinically-relevant systemic exposure during the microdose, the IV infusion of [^{14}C]-GSK1278863 will be administered concomitant to an oral non-radiolabelled dose. Following oral administration, daprodustat is rapidly absorbed (t_{max}: 1.5 to 2 h) and exhibits a dose-proportional increase in exposure over the range 2 mg to 300 mg. The terminal half-life of daprodustat is 2.4 to 4 h, and it did not accumulate upon repeated-dose administration of doses up to 100 mg, once daily, in healthy participants.

The oral non-radiolabelled daprodustat dose is within the therapeutic range for the treatment of anaemia of CKD. The 6 mg dose was identified as the dose most likely to be administered to haemodialysis-dependent CKD patients based on a longitudinal dose Hgb-response model [GSK Document Number 2015N248947_00]. The 6 mg dose is lower than the highest once-daily dose currently under investigation in the ongoing Phase 3 studies (24 mg), and is substantially lower than current single, oral dose clinical experience (500 mg; GSK study PHI113635).

The planned dose of the oral solution of [^{14}C]-GSK1278863 is 25 mg. That dose is similar to the maximum once-daily dose currently under investigation in the ongoing Phase 3 studies (24 mg; GSK studies 200807 &200808); it is approximately one-half the potentially highest three-times weekly dose (48 mg; GSK study 204837). Therefore, a single dose of 25 mg [^{14}C]-GSK1278863 oral solution bridges both the once-daily and three-times weekly dosing paradigms.

In summary, the doses selected are suitable to meet the objectives of the study whilst minimising exposure of participants to daprodustat.

Radiolabel Dose

The effective dose of radiolabelled drug administered in human mass balance studies is calculated from data on the distribution and elimination of the radioactive drug from laboratory animals, taking into account the nature of the isotope, the concentration of radioactivity in individual tissues/organs and the residence or elimination half-life of the radioactivity from those tissues/organs.

In this study, each participant will receive the following doses of radioactivity:

- approximately 4.63 kBq (125 nCi) in Treatment Period 1.
- approximately 2.31 MBq (62.5 μCi) in Treatment Period 2.

It is estimated that the combined total effective dose for the two treatment periods will be <1mSv. On this basis, the maximum administered activity would comply with the ICRP 1992 recommendation of a 1 mSv maximum for Category IIa projects (further details are in Appendix 3).

6. STUDY POPULATION

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

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product is provided in the IB and IB supplements, if applicable.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Aged 30 to 55 years, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Healthy, as determined by the investigator or medically qualified designee, based on a medical evaluation including medical history, physical examination, vital signs, laboratory tests, and ECG. A participant with a clinical abnormality or laboratory parameter (i.e., outside the reference range for the population being studied), which is not specifically listed in the eligibility criteria, may be included only if the

investigator agrees and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

3. Haemoglobin value at screening greater than the lower limit of the laboratory reference range and less than or equal to 16.0 g/dL.
4. History of regular bowel movements (averaging one or more bowel movements per day).
5. Non-smoker, or ex-smoker who hasn't regularly smoked for the 6 months before screening.

Weight

6. Body weight of 50 kg and above, and body mass index (BMI) within the range 19.0–31 kg/m^2 (inclusive).

Sex

7. Male only.

   Participants must agree to use contraception as follows: participants with female partners of childbearing potential must agree to use a condom from the time of first dose of study treatment until 1 month after their last dose. Further details are given in Appendix 7.

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 5 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
9. Willingness to give written consent to have data entered into The Overvolunteering Prevention System.

6.2. Exclusion Criteria

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

Medical Conditions

1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Participants with a history of cholecystectomy must be excluded.
2. Any clinically relevant abnormality identified at the screening medical assessment (physical examination/medical history), clinical laboratory tests, or 12-lead ECG.
3. Miocardial infarction or acute coronary syndrome ≤ 12 weeks prior to screening through to enrollment (Day 1, Treatment Period 1).
4. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs, or which could constitute a risk when taking the study treatment, or interfere with the interpretation of data.

5. Evidence of actively bleeding gastric, duodenal or esophageal ulcer disease OR clinically significant GI bleeding ≤ 12 weeks prior to screening through to enrollment (Day 1, Treatment Period 1).
6. History of malignancy within the two years before dosing, with the exception of localized squamous cell or basal cell carcinoma of the skin that has been definitively treated prior to screening; currently receiving treatment for cancer; has a strong family history of cancer (e.g., familial cancer disorders).
7. Mentally or legally incapacitated.
8. Heart Failure: Class II, III or IV heart failure, as defined by the New York Heart Association (NYHA) functional classification system.
9. Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study.

Prior/Concomitant Therapy

10. Daprodustat is a substrate of CYP2C8. Co-administration of drugs that are inhibitors of this enzyme are prohibited (see Section 7.7).
11. Past or intended use of over-the-counter or prescription medication including herbal medications prior to dosing except occasional use of paracetamol (acetaminophen), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study treatment until completion of the follow-up visit, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study.

Prior/Concurrent Clinical Study Experience

12. Current enrolment in a clinical trial; recent participation in a clinical trial and has received an investigational product within 3 months before their first dose in the current study.
13. Exposure to more than 4 new chemical entities within 12 months before their first dose in the current study.
14. Participation in a clinical trial involving administration of ^{14}C-labelled compound(s) within the last 12 months. A participant's previous effective dose will be reviewed by the medical investigator to ensure there is no risk of contamination/carryover into the current study.
15. Received a total body radiation dose of greater than 10.0 mSv (upper limit of WHO category II) or exposure to significant radiation (e.g., serial x-ray or computed tomography [CT] scans, barium meal, etc.) in the 3 years before this study. Further details in Appendix 2.

Diagnostic assessments

16. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
17. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
18. QTc >500 msec

    NOTES:

    - The QTc must be the QT interval corrected for heart rate according to Bazett's formula (QTcB).
    - The specific formula that will be used to determine eligibility for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include the participant from the trial.
    - For purposes of data analysis, QTcB will be used as specified in the Reporting and Analysis Plan (RAP).
19. 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.
20. Positive pre-study drug/alcohol screen.
21. Positive human immunodeficiency virus (HIV) antibody test.
22. Regular use of known drugs of abuse.
23. Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >21 units. One unit is equivalent to 8 g of alcohol: a glass (~240 mL) of beer, 1 small glass (~100 mL) of wine or 1 (~25 mL) measure of spirits.
24. At screening, a supine blood pressure BP that is persistently higher than 140/90 millimeters of mercury (mmHg) taken in triplicate, unless deemed not clinically significant by the investigator.
25. At screening, a supine mean heart rate (HR) outside the range of 40–100 beats per minute, unless deemed not clinically significant by the investigator.

Other Exclusions

26. Has had an occupation which requires monitoring for radiation exposure, nuclear medicine procedures, or excessive x-rays within the past 12 months.
27. Unable to refrain from consumption of prohibited food and drinks (Section 6.3.1) from 7 days before the first dose of study medication until the follow up visit.
28. Participation in the study would result in donation of blood or blood products in excess of 550 mL within a 90 day period.

29. Unwillingness or inability to follow the procedures outlines in the protocol, including the use of the Entero-Test capsule.
30. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products in the 6 months prior to screening.
31. History of drug abuse or dependence within 6 months of the study.
32. History of sensitivity to daprodustat, or their components thereof, or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will be required to fast for at least 5 h before laboratory safety tests, and for at least 8 h before dosing in both treatment periods. In both treatment periods, participants will also be required to fast for 4 h after dosing.
- Meal times are specified in both treatment periods for Day 1 (please refer to the SoA, Section 2); on all other days, meals will be served at the standard times of the clinical site.
- Participants will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, nuts, seeds or fruit juices from 7 days before the start of study treatment until the follow-up visit.
- Adequate hydration should be encouraged to help facilitate stool sample production. If needed, participants may consume prunes or prune juice to facilitate stool samples.
- No water is allowed until 1.5 h after oral dosing (apart from rinsing the oral solution dose of [^{14}C]-GSK1278863); water is allowed *ad libitum* at all other times.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each treatment period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) from 24 h before admission until discharge from the unit.
- Participants will abstain from alcohol for 24 h before the screening visit until the follow-up visit.
- Use of tobacco- or nicotine-containing products will not be allowed from screening until after the final follow-up visit; only non-smokers will be enrolled in the study.

6.3.3. Activity

Participants will abstain from strenuous exercise from 3 days before screening and until their final follow-up visit. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled 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 not be rescreened.

7. TREATMENTS

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

7.1. Treatments Administered

Table 3 Treatments administered during the study

Study Treatment Name:	[^{14}C]-GSK1278863 solution for IV infusion	[^{14}C]-GSK1278863 oral solution	Daprodustat
Dosage formulation:	IV solution	Oral solution	Oral tablet
Unit dose strengths:	Strength: 5 µg/mL Dosage Level: 50 µg	Strength: 200 µg/mL Dosage Level: 25 mg	Strength: 6 mg tablet Dosage Level: 6 mg
Route of Administration:	IV	Oral	Oral
Dosing instructions:	Administer 10 mL intravenously over 1 h approximately 1 h post oral dose	Administer 125 mL in the fasted state in the morning. Follow with 125 mL of room temperature water while rinsing dosing container.	One tablet taken in the fasted state in the morning with 240 mL of room temperature water
Manufacturer:	Drug product: HMR	Drug product: HMR	GSK
Physical Description:	A clear, colourless solution free from visible particulate matter	A clear, colorless solution	9.0 mm round, white film coated tablet

For more information on the preparation of the oral and IV dosing solutions, please refer to the Study Reference Manual (SRM) and/or Technical Agreement (TA).

7.2. Dose Modification

There will be no deviation from the treatments listed in Section 7.1 in this study.

7.3. Method of Treatment Assignment

This is an open-label study; each participant will be assigned to each of the following treatments in a non-randomised manner:

- Treatment Period 1 (IV infusion concomitant with a solid oral dose of daprodustat), first;
- Treatment Period 2 (oral solution), second.

7.4. Blinding

This is an open-label study.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorised 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 authorised 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).
- A description of the methods and materials required for preparation of [^{14}C]-GSK1278863 solution for IV infusion and oral administration is provided in the SRM and/or TA and will be accompanied by a Quality Agreement.
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
- Dose administrators must follow site-specific procedures for handling radiolabelled GSK1278863.

7.6. Treatment Compliance

- Any individual dose for a participant prepared from a bulk supply will be confirmed by a second member of the study site staff.
- All participants will receive their doses 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. For oral doses, 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.

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 GSK Medical Monitor, the medication will not interfere with the study.

Paracetamol (acetaminophen) at doses of ≤ 2 grams/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 GSK Medical Monitor.

Special warnings and precautions for use of daprodustat are given in the IB, Section 6 (Development Core Safety Information (DCSI)).

7.8. Treatment of Study Treatment Overdose

For this study, any dose of daprodustat greater than those listed in this protocol given within a 24-hour time period will be considered an overdose.

There is no specific antidote for overdose with daprodustat. The expected manifestations of daprodustat overdosage include signs and symptoms associated with an excessive and/or rapid increase in Hgb concentration.

In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted, as dictated by the participant's clinical status. Additionally, subjects should be monitored closely for CV events, increased heart rate and hematologic abnormalities.

7.9. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

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

- Haemoglobin value greater than or equal to 16.0 g/dL.
- Severe pain, redness, bleeding or swelling at the infusion site.
- Liver chemistry abnormalities exceeding the threshold criteria (Section 8.1.1).
- Diagnosis of cancer (new or recurrent), with the exception of localized squamous cell or basal cell carcinoma of the skin.

In all cases, the reason for study treatment discontinuation and the date of the last dose will be recorded in the participant's case report form (CRF) and the participant will be withdrawn from the study as described in Section 8.2.

8.1.1. Liver Chemistry Stopping Criteria

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

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

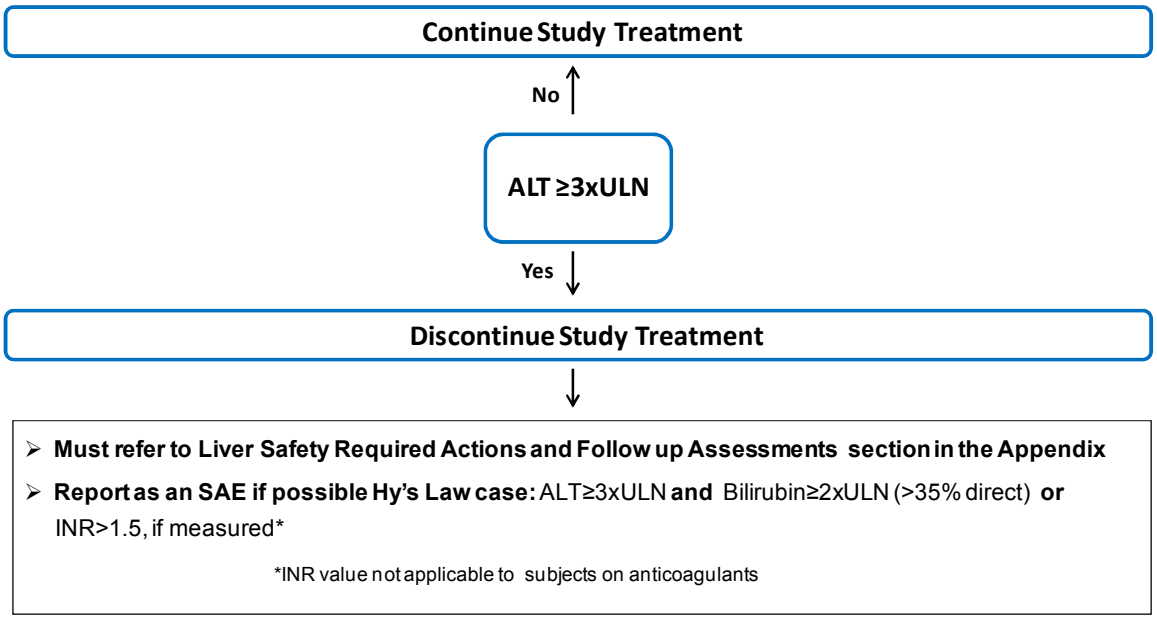
- a participant meets one of the conditions outlined in the algorithm

  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.

Study treatment will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Figure 2 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 8.

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, 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 may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Refer to the SoA (see Section 2) for data to be collected at the time of study discontinuation. The investigator will record in the source documents the results of follow-up examination of withdrawn participants, if the participant gives their consent.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he 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). Those contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, only then will he be considered to have withdrawn from the study with a primary reason of "lost to follow-up".

8.4. Study Stopping Criteria

The trial will be stopped if either of the following occurs:

- one or more serious adverse event that is considered to be at least possibly related to study treatment.
- 2 or more severe, clinically significant adverse events that are considered to be at least possibly related to study treatment.

If, after an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the Medicines and Healthcare Products Regulatory Agency (MHRA) and Independent Ethics Committee (IEC). The trial will not restart until the amendment has been approved by the MHRA and IEC.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (see Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the GSK Medical Monitor 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 (see Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (see Section 2).

- The timing and number of planned study assessments, including safety, and pharmacokinetic 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 ICF.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 550 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Screening and Critical Baseline Assessments

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.

9.2. Adverse Events

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

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 (see Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from start of treatment until the follow-up visit at the time points specified in the SoA (see 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 Appendix 6. 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 notify the sponsor within 24 hours following knowledge of the SAE.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of Special Interest (as defined in Section 9.2.4) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 6.

9.2.4. Adverse Events of Special Interest (AESI)

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

- Thrombosis and tissue ischemia secondary to excessive erythropoiesis
- Risk of death, MI, stroke, venous thromboembolism, thrombosis of vascular access
- Cardiomyopathy
- Pulmonary artery hypertension
- Increased cancer-related mortality and tumor progression and recurrence

- Manifestations of gastric erosions (e.g., upper GI bleeding, severe abdominal pain, upper GI perforations)
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

9.2.5. Regulatory Reporting Requirements for SAEs

- Notification by the investigator to the sponsor within 24 hours following knowledge of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the 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, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the participant's final 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 SAE.

9.3. Safety Assessments

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

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the eyes, skin, joints, and the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded, and BMI calculated.

- 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.

9.3.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- For time points where vital signs are collected in triplicate, there should be about a 2 minute interval between readings.
- Baseline will be defined as the mean of the 3 pre-dose measurements taken on Day 1 in each treatment period.

9.3.3. Electrocardiograms

- ECG measurements will be obtained as outlined in the SoA (see Section 2) Full 12-lead ECGs will be recorded with the participant in a supine position. Heart rate, PR interval, QRS duration, and QT (uncorrected) interval will be measured. QTcB will be calculated (machine read or manually).
- At each time point at which ECGs are required, single ECG measurments are appropriate; however, two additional ECGs are required if the initial ECG measurement indicates prolonged QTc (i.e., QTcB $\geq$ 500 msec) using the automated or manually calculated QTcB value. The average QTcB value of all three ECGs will be used to determine eligibility.

9.3.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 4 for the list of clinical laboratory tests to be performed and to the SoA (see 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.
- All laboratory tests with values considered clinically-significantly abnormal during participation in the study or within 14 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 4, must be conducted in accordance with the laboratory manual and the SoA (see Section 2).

9.4. Pharmacokinetics

- Separate whole blood samples will be collected for measurement of each of the following as specified in the SoA (see Section 2): blood and plasma total radioactivity, [^{14}C]-GSK1278863, plasma concentrations of daprodustat and predominant circulating metabolites and metabolite profiling. A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The actual date and time (24-h clock time) of each sample 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.
- Details of PK blood sample collection (including the volumes to be collected), processing, storage and shipping procedures are provided in the SRM.
- Plasma samples for metabolite profiling will be analysed under a separate GSK protocol. The results of these analyses will be reported separately.
- For samples used to evaluate the PK of daprodustat and predominant circulating metabolites, each plasma sample will be divided into 2 aliquots (1 each for PK, and a back-up). Samples collected for analyses of daprodustat plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be stored for no longer than 15 years after the end of the trial.

9.5. Urine Sample collection

Urine samples to measure total radioactivity excreted in urine and for metabolite profiling (to be conducted in a separate study) will be collected over the time periods specified in the SoA (Treatment Period 2 only; see Section 2). All participants will be asked to void their bladders before study treatment administration. A blank urine sample will be collected pre-dose (up to 3 h before oral dosing) in Treatment Periods 1 and 2. Details of urine sample collection, processing, storage and shipping procedures are provided in the SRM.

9.6. Faecal Sample Collection

Faecal samples to measure total radioactivity excreted in faeces and for metabolite profiling (to be conducted in a separate study) will be collected over the time periods specified in the SoA (Treatment Period 2 only; see Section 2). A faecal sample will be collected from each participant before dosing in Treatment Periods 1 and 2 (the pre-dose sample can be collected up to 48 h before oral dosing). Details of faecal sample collection, processing, storage and shipping procedures are provided in the SRM.

9.7. Bile Sample Collection

Bile samples for analysis of metabolites (to be conducted in a separate GSK study) will be collected via the Entero-Test in Treatment Period 1 only, as specified in the SoA (see Section 2). The Entero-Test comprises a gelatine capsule which contains 90 cm or 140 cm of nylon string attached to a 1 g steel weight. One end of the string is attached to the outside of the mouth before swallowing the capsule, so that it can still be retrieved. The gelatine capsule dissolves in the stomach whilst the string and weight continue to the duodenum via peristalsis. Following a food cue to stimulate gall bladder emptying the string is withdrawn. On withdrawal of the string through the mouth the steel weight separates from the string at the pyloric sphincter and is excreted in the faeces. Once the string has been removed from the participant it will be frozen and shipped for metabolite profiling (to be conducted in a separate study). Full details of the Entero-Test sample collection, processing, storage and shipping procedures are provided in the SRM.

9.8. Sample Analysis

Total radioactivity measurements in urine samples and faecal homogenates will be determined by LSC and by accelerator mass spectrometry (AMS). Total radioactivity measurements from blood and plasma derived from blood will be analysed, as appropriate, by LSC and if required AMS, for Treatment Period 1 and Treatment Period 2, as detailed in the SRM.

[^{14}C]-GSK1278863 and daprodustat plasma concentrations and predominant circulating metabolites will be analysed, as appropriate, as detailed in the SRM.

Plasma and aliquots of urine and faecal homogenates will be analysed in a separate GSK study for metabolite profiling investigations. Duodenal bile samples collected via the Entero-Test will similarly be analysed in a separate GSK study. The results of these analyses will be reported separately.

Analysis of all samples (blood, plasma, urine, faeces, and duodenal bile) will be performed under the control of Platform Technology and Science (PTS) - BIB (Bioanalysis, Immunogenicity and Biomarkers) and Mechanistic Safety and Disposition (MSD), GlaxoSmithKline, the details of which will be included in the SRM. Raw data will be archived at the bioanalytical site (detailed in the SRM).

9.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.10. Genetics

Genetics are not evaluated in this study.

9.11. Biomarkers

Biomarkers are not evaluated in this study.

10. DATA MANAGEMENT

- For this study data will be double-entered into a clinical database management system (ClinPlus Version 3.3).
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug by GSK.
- Original CRFs will be retained by GSK, while the investigator will retain a copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size Assumptions

No formal sample size calculation has been performed for this study. The primary objective of the study is to gain a better understanding of the compound's excretory and metabolic profile and 4 to 6 participants are deemed sufficient for this purpose.
6 participants will be enrolled into the study. In order to minimise the number of participants exposed to radiation, those participants that discontinue early will not be replaced unless the total number of participants who complete dosing and all critical assessments drops below 4.

11.1.1. Sample Size Sensitivity

Not applicable.

11.1.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

11.2. Data Analysis Considerations

11.2.1. Analysis Populations

11.2.1.1. Screened Population

All participants who sign the ICF. This will be the population for reporting screened population data.

11.2.1.2. All Subjects Population

All participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received. This will be the population for reporting safety and study population data.

11.2.1.3. 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.

11.2.2. Interim Analysis

No interim analyses will be performed.

11.3. Key Elements of Analysis Plan

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

11.3.1. Pharmacokinetic Analyses

Plasma daprodustat and metabolite concentration-time data will be listed for each participant and summarised by treatment and planned sampling time. [^{14}C]-GSK1278863 and radioactivity concentrations in plasma will be reported similarly. Individual participant, mean and median plasma daprodustat, [^{14}C]-GSK1278863 and total radioactivity concentration–time profiles will be plotted for each treatment on both a linear and semi-log scale.

Pharmacokinetic analysis will be performed by or under the direct auspices of Clinical Pharmacology Modelling & Simulation, GSK. Plasma daprodustat, [^{14}C]-GSK1278863 and total radioactivity concentration–time data will be analysed by non-compartmental methods with WinNonlin Version 6.3 or above. 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, for daprodustat, [^{14}C]-GSK1278863 and total radioactivity, as data permits: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve [AUC(0–t) and AUC(0-inf)], terminal phase rate constant (λ_z), and apparent terminal phase half-life ($t_{1/2}$) following oral and IV dosing. Additionally, volume of distribution at steady state (Vss) and total systemic clearance (CL) will be derived following IV dosing. These parameters will be summarised descriptively.

Absolute bioavailability will be estimated from the oral and IV doses administered in Period 1 with Equation 1.

Equation 1

$$F = \frac{AUC_{po}}{AUC_{IV}} \cdot \frac{\text{dose}_{IV}}{\text{dose}_{po}}$$

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

Derivation of the urine and faecal radioactivity parameters will be the responsibility, or under the direct auspices, of the BIB department within GSK. The following parameters will be determined from the urine and faecal radiolabelled drug-related material (total radioactivity) data, and will be listed and summarised by treatment:

- Absolute amount excreted and percentage excreted in urine (Ae[urine] and Fe%[urine]) within each collection period and cumulative urinary recovery and fraction excreted over the total collection period.
- Absolute amount excreted and percentage excreted in faeces (Ae[faecal] and Fe%[faecal]) with each collection period and cumulative faecal recovery and fraction excreted over the total collection period and cumulatively over the collection period.
- Total excretion (sum of urine and faecal excretion), Ae [total] and Fe% [total] will be calculated by collection interval for each participant.

The urine, faecal and total radioactivity parameters will be listed, summarised and plotted.

All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D. Production of the summaries, listings and figures of the plasma, urine and faeces data will be performed under the direct auspices of Clinical Statistics, GSK.

Further details regarding the tables, figures and listings to be produced for the study report will be given in the RAP.

11.3.2. Metabolite profiling

The metabolic profiling/structural characterisation aspect of this work will be performed by GSK in a separate GSK study and reported separately.

11.3.3. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Further details will be given in the RAP.

12. REFERENCES

FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease. (Available at http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm; Posted June 24, 2011).

Guiney, W.J; Beaumont, C; Thomas, S.R; Robertson, D.C; McHugh, S.M; Koch, A; Richards, D; Use of Entero-Test, a simple approach for non-invasive clinical evaluation of the biliary disposition of drugs. *Br J Clin Pharmacol.* 2011; 72:133-142.

Szczech, L. A.; Barnhart, H. X.; Inrig, J. K.; Reddan, D. N.; Sapp, S.; Califf, R. M.; Patel, U. D.; Singh, A. K. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 2008, 74, 791-8.

13. APPENDICES

13.1. Appendix 1: Abbreviations and Trademarks

Table 4 Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AMS	Accelerator Mass Spectrometry
AUC	Area under concentration-time curve
AUC(0–inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0–t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
BCRP	Breast cancer resistant protein
BIB	Bioanalysis, Immunogenicity and Biomarkers
BID	Bis In Die (Twice A Day)
BMI	Body mass index
BP	Blood Pressure
Bq	Becquerel
CKD	Chronic Kidney Disease
C_{max}	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CV	Cardiovascular
CYP	Cytochrome P450
DCSI	Development Core Safety Information
DMPK	Drug Metabolism and Pharmacokinetics
ECHO	Echocardiogram
ECG	Electrocardiogram
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agent
F	Absolute bioavailability
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour(s)
HBsAg, Hep B, Hep C	Hepatitis Surface Antigen, Hepatitis B and C
HIF	Hypoxia inducible factor
Hgb	Haemoglobin

HIV	Human Immunodeficiency Virus
HMR	Hammersmith Medicines Research
HO-1	Heme Oxygenase-1
IB	Investigator's Brochure
ICF	Information Consent Form
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LC	Liquid Chromatography
LC/MS	Liquid Chromatography–Mass Spectrometry
LSC	Liquid Scintillation Counting
LFTs	Liver Function Tests
LVEF	Left Ventricular Ejection Fraction
µCi	Micro Curie
µg	Microgram
µSv	Microsievert
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MHRA	Medicines and Healthcare Regulatory Agency
mL	Millilitre
MSDS	Material Safety Data Sheet
mSv	Millisievert
nCi	Nano Curie
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
OATP	Organic Anion-Transporting Polypeptide
PHDs	Prolyl-4-hydroxylase
PK	Pharmacokinetic(s)
PRVP	Peak Right Ventricular Pressure
PTS	Platform Technology Services
QD	Quaque Die (Once A Day)
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SoA	Schedule of Activities
sPAP	Systolic Pulmonary Artery Pressure
SRM	Study Reference Manual
t_{max}	Time of occurrence of C_{max}
UK	United Kingdom

ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation
λz	Lambda-z (Terminal Phase Rate Constant)

Table 5 Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Entero-Test
SAS
WinNonlin

13.2. 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. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat. 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.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Section 6 • Specific guidance for discontinuation of daprodustat based on Hgb is provided in Section 8.1 • 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 rhEPO/ESAs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anaemia 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. • Monitoring of emerging safety data by an internal GSK Safety Review Team.
Oesophageal and gastric erosions	In animal studies, undesirable gastrointestinal effects including emesis, abnormal faeces and/or decreased food consumption/body weight loss and stomach erosions/ulcers with haemorrhage were observed with daprodustat. In rodents stomach erosions observed with intravenous and oral administration of daprodustat. Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3 -fold (monkeys) and 737 -fold (rats) above human exposure (25 mg daprodustat). In clinical trials to date with daprodustat, mild-moderate gastrointestinal signs and symptoms represent the most frequently reported adverse event, however causal association has not been established.	• Suspected GI bleeding or significant symptoms consistent with erosion 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
	Following review of clinical data received to date, gastrointestinal erosions have not been identified as a safety concern for daprodustat.	
Cancer-related mortality and tumour 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, an angiogenic factor that has been implicated in tumour growth, was observed at doses ranging from 10 to 150 mg. In clinical studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. • 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 or participants with complex kidney cyst are outlined in Section 6. • Stopping criteria for participants with treatment emergent malignancy are outlined in Section 8.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team.
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	• 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
	13 weeks duration in mice and dog, up to 26 weeks in rat, and up to 39 weeks in monkeys. Acute hypoxic challenge (rats): Daprodustat produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. These hypoxia-induced PRVP changes fall within the range of PRVP differences noted among non-treated rats. Results from a clinical study of acute hypoxic challenge in healthy volunteers demonstrated that short-term (5 days) therapy with daprodustat 5 mg or 100 mg has no clinically significant effect on echocardiographically-estimated systolic pulmonary artery pressure (sPAP) under either normoxic or hypoxic conditions. ECHO assessments performed in Phase 2b studies (24 weeks treatment duration) did not identify any clinically-meaningful changes in sPAP in participants not on dialysis for daprodustat. In haemodialysis participants, mean absolute change from baseline in sPAP was similar for both treatment groups; however, there was a numeric imbalance (Daprodustat: 8 [7%]; Control 0) in participants reaching the sPAP PCI (>20 mmHg increase from baseline). Regarding this imbalance, there were a number of confounding factors in the study, most notably a 4.5:1 randomization scheme and inconsistency in timing of ECHOs relative to dialysis day. Additionally, 2 of 3 participants with resolution of sPAP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study treatment; and there was no dose relationship for participants meeting the sPAP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. 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. 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
Proliferative retinopathy, macular oedema, choroidal neovascularization	Increases in local (ocular) VEGF production with retinal neovascularization and macular oedema observed in diabetic retinopathy and to choroidal leakage, oedema 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	• Suspected proliferative retinopathy, macular oedema, 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
	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 duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular oedema, 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. Due to the known time delay in enhancing erythropoiesis by daprodustat, co-administration with strong CYP2C8 inhibitors for up to 14 days is not anticipated to lead to immediate marked increases in hemoglobin levels. Therefore, there is adequate time to change to alternate therapy that does not inhibit CYP2C8. Additionally, as the time for maximum induction of CYP2C8 occurs approximately 10-14 days of dosing with rifampin [Brodie, 2013 and Ohnhaus, 1989], daprodustat systemic exposure will decrease over time which will result in a lag period before an effect on Hgb is recognized and is of clinical concern. 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 IC50 value of 21 µM. Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. Co-administration of daprodustat with potent BCRP inhibitors has the potential to increase exposure of daprodustat. Use of BCRP inhibitors (mostly weak) was	• Chronic co-administration of daprodustat with the strong CYP2C8 inhibitor, gemfibrozil and inducers, rifampin/rifampicin is not permitted as outlined in Section 7.7. Short duration (i.e., less than or equal to 14 days) is permitted. • Co-administration of daprodustat with moderate CYP2C8 inhibitors (i.e., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, Hgb should be monitored every 4 weeks for 12 weeks as outlined in Section 7.7 and the IB. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 7.7 and the IB. • 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). Daprodustat is an inhibitor of OATP1B1/1B3 in vitro, with IC50 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.	
Radioactivity exposure risk	The total effective dose associated with IV and oral administrations of [^{14}C]-GSK1278863 is <1 mSv. That effective dose is within WHO recommendation of a <5 mSv maximum for Category 2 projects, which is considered to be within dose limits for members of the public with a minor risk. The total effective dose is also below the GlaxoSmithKline Global Safety Board level of radiation which would require specific additional justification and exemption (10 mSv).	• Participants will be monitored for recovery of radioactivity throughout the study • To avoid recruitment of radiation worker or serial study volunteers, participants who have been exposed to ionising radiation in excess of 10mSv above background over the previous 3 year period as a result of occupational exposure to radiation or as a result of research studies are excluded. Clinically justified (therapeutic or diagnostic) exposures are not included in the exposure calculation. Participants are asked about any occupational exposure or previous participation in research studies at screening so that dose estimates can be obtained where necessary.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Intravenous dosing of daprodustat (GSK1278863)	This is the first time daprodustat will be administered IV to humans. The total systemic exposure of daprodustat from the combined IV microtracer (50 µg) and oral dose (6 mg), as well as the single oral dose of 25 mg is well below exposures observed in previous trials in healthy participants. IV administration can be associated with pain at the injection site. Non-clinical IV irritancy studies have been performed in a number of species (refer to the IB); those studies did not show significant dermal irritation.	• In addition to taking samples for pharmacokinetic analysis of daprodustat, routine safety tests, including vital signs, 12-lead ECG, and a panel of laboratory safety tests, will be done whilst participants are resident at the unit. • Participants will be monitored for signs of pain at the injection site. Paracetamol (acetaminophen), at doses of ≤ 2 g/day can be taken if required. • Stopping criteria for participants with severe pain, redness, bleeding or swelling at the infusion site are outlined in Section 8.1.
Study Procedures		
Entero-Test for bile collection risk	The use of the Entero-Test has been approved by the European regulatory authorities (ISO 9001 and CE Mark Certification; European Union Medical Devices Directive (MDD)). • Streaks of blood on the string due to local irritation have been infrequently noted. • Rarely, a participant will be unable to swallow the capsule because of gagging or will vomit after doing so. • Gagging upon retrieval of the string can occur. • On a few occasions, an entire string has been swallowed without ill effects and passes out from the body in the faeces.	• The string will be securely taped in place (to the cheek of each individual) during the collection time to minimise risk of swallowing the entire string.

References

Campochiaro PA and the first ARVO/Pfizer Institute Working Group *et al.* Ocular versus extraocular neovascularization: Mirror images or vague resemblances. *Invest Ophthalmol & Vis Sci.* 2006; 47:462-474.

Formenti F, Beer PA, Croft QPP, Dorrington KL, Gale DP, Lappin TRJ, Lucas GS, Maher ER, Maxwell PH, McMullin MF, O'Connor DF, Percy MJ, Pugh CW, Ratcliffe PJ, Smith TG, Talbot NP, Robbins PA. Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2α gain-of-function mutation. *FASEB J*. 2011; 25:2001-2011.

Muz B, Khan MN, Kiriakidis S, Paleolog EM. The role of hypoxia and HIF-dependent signalling events in rheumatoid arthritis. *Arthritis Research & Therapy* 2009; 11:201-209.

Smith TG, Brooks JT, Balanos GM, Lappin TR, Layton DM, Leedham DL, Liu C, Maxwell PH, Treacy M, Robbins PA. Mutations of von Hippel-Lindau tumour suppressor and heman cardiopulmonary physiology. *PLos Med.* 2006; 3:3290.

Westra J, Molema G, Kallenberg CG. Hypoxia-inducible factor-1 as regulator of angiogenesis in rheumatoid arthritis - therapeutic implications. *Curr Med Chem.* 2010; 17:254-63.

13.3. Appendix 3: An assessment of the radiation dose to male volunteers from the oral and IV administration of the study treatment

OFFICIAL-SENSITIVE [COMMERCIAL] Contract Report

CRCE-RHE-24-2016

Assessment of the Radiation Dose to Male Volunteers from the Oral Administration of [^{14}C]GSK1278863

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through advocacy, partnerships, world-class science, knowledge and intelligence, and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

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This report has been produced by Public Health England's Centre for Radiation, Chemical and Environmental Hazards under contract to GlaxoSmithKline plc., 980 Great West Road, Brentford, Middlesex TW8 9GS

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Public Health England
Chilton, Didcot
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CRCE-RHE-24-2016

Assessment of the Radiation Dose to Male Volunteers from the Oral Administration of [^{14}C]GSK1278863

PPD

This work was undertaken under contract to GlaxoSmithKline plc., 980 Great West Road, Brentford, Middlesex TW8 9GS

Centre for Radiation, Chemical and Environmental Hazards
Public Health England
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1 Introduction

GlaxoSmithKline has provided experimental data on the biokinetics of [^{14}C]GSK1278863 following its oral administration to pigmented and albino rats and dogs. The data have been used to determine the likely dose to male volunteers from a single administration of the radio-labelled compound. The assumption is made that the levels of uptake and retention by tissues will be the same in man as in the experimental animals. Committed equivalent doses to tissues and organs and committed effective dose (E(50)) have been calculated according to the 1990 Recommendations of the International Commission on Radiological Protection (ICRP)[1] as implemented in The Ionising Radiations Regulations 1999[2] in response to EU Council Directive 96/29/Euratom[3]. The E(50) is compared with the dose categories proposed for research projects involving human volunteers by the World Health Organization (WHO)[4] and ICRP[5].

2 Data used in calculations

Results were provided for the urinary and faecal excretion of ^{14}C following the oral administration of [^{14}C]GSK1278863 to albino rats and dogs. Expressed as percentages of total excretion, the values were 11% urinary and 89% faecal excretion for rats and 2% urinary and 98% faecal excretion for dogs. The calculations were performed using the values for dogs: the assumption of greater faecal excretion results in greater dose estimates.

Data were provided for the tissue distribution of ^{14}C after oral administration of [^{14}C]GSK1278863 to pigmented rats. Concentrations of radio-labelled compound retained in the tissues were expressed as microgram equivalents per gram (µg eq/g) of tissue. These concentrations were converted to values for the percentage of administered activity retained in individual tissues or organs using standard organ weights[6]. Doses were calculated using values for 21 tissues at 7 time-points between 1 and 840 hours after administration.

3 Method of calculation

The initial step is the calculation of the number of transformations (U) in each source region from 1 Bq of administered drug. These values were calculated for the period for which data were supplied by the trapezoidal method of integration. Any fraction of the ^{14}C remaining in tissues or organs at the last time point was assumed, conservatively, to be lost with a half-time of 100 days.

The values of U for the contents of the gut compartments, gall bladder and urinary bladder were calculated, as recommended by Dolphin and Eve[7], from the fraction of the administered activity passing through their contents and their mean residence time in each compartment. Calculations were made assuming that 100% of the faecally excreted activity was released into the gut in bile.

In order to calculate committed equivalent doses, $H_T(50)$ (Sv), to the target organs, the values of U are combined with a set of values known as Specific Effective Energies (SEEs)[8]. In short, the SEEs give the dose to each target region, T, per transformation in each source organ, S.

$$H_T(50) = \sum_S U(S,50) \times SEE(T,S)$$

The SEEs are calculated using data on absorbed fractions, (Φ) derived from a mathematical phantom[8], with additional data for the prostate taken from Stabin[9]. Absorbed fractions represent the fraction of energy emitted in each source that is absorbed in each target. In simple cases where S and T are the same, e.g. liver, the absorbed fraction for non-penetrating radiations is equal to one. The expression for SEE can be simply written

$$SEE(T,S) = \frac{\varepsilon}{m_T}$$

where ε is the mean energy of the emission (J) and m_T is the mass of the target organ (kg). The source organ masses used for the calculations are those specified by the ICRP[10].

The committed effective dose, E(50), is the sum of the committed equivalent doses to individual tissues or organs, each weighted to allow for the relative contributions of tissues and organs to the total detriment; taking account of the probability of attributable fatal cancer, the weighted probability of attributable non-fatal cancer, the weighted probability of severe hereditary effects and the relative length of life lost[1]. Thus:

$$E(50) = \sum_T w_T \cdot H_T(50)$$

where $H_T(50)$ is the committed equivalent dose in tissue or organ T and w_T is the tissue weighting factor.

Weighting factors are specified for testes (0.2); colon, lung, red bone marrow and stomach (each 0.12); bladder, breast, liver, oesophagus and thyroid (each 0.05) and bone surfaces and skin (each 0.01)[1]. A complication is that the current dosimetric model of the gastrointestinal tract does not consider doses to the oesophagus, and divides the colon into upper and lower large intestine[11]. Until a revised model is available, doses to the oesophagus have been calculated using the thymus data (this is a standard dosimetric procedure justified for penetrating photon radiation on the basis of the proximity of the oesophagus and thymus). The dose to the colon is taken to be the mass weighted mean of the doses to the upper large intestine and lower large intestine. Doses from ^{14}C in transit through the gut were calculated separately from doses from activity retained in the gut wall. The dose received by bone surfaces was calculated using data for retention in bone marrow, assuming uniform distribution of activity throughout marrow. Where information is not provided for retention in soft tissues with specific tissue weighting factors, but information is provided for retention in muscle tissue, the equivalent dose to muscle is assumed to apply; in this case, for the breasts. The mass weighted average of the dose to remainder tissues is given a total weighting factor

of 0.05 unless any one tissue exceeds the highest equivalent dose to named tissues when it is attributed a weighting factor of 0.025; the weighting factor for the remainder becomes 0.025.

4 Results

The results of the calculation of committed effective dose, E(50), from the oral administration of [^{14}C]GSK1278863, based on the animal data supplied, are given in Table 1. The E(50) is the sum of the weighted equivalent doses to named tissues and the remainder tissues. The E(50) to a male volunteer following the oral administration of [^{14}C]GSK1278863 was calculated as 2.7 x 10^{-10} Sv Bq^{-1}. The doses to the colon and gonads contributed 73% and 20% of the E(50), respectively.

5 Conclusions

The E(50) value obtained for oral administration of [^{14}C]GSK1278863 to male volunteers was 2.7 x 10^{-10} Sv Bq^{-1} (Table 1). On this basis, the maximum administered activity that would comply with the WHO[4] recommendation of a 0.5 mSv maximum for Category 1 projects (see Table 2) would be 1.9 MBq (51.1 µCi). To comply with the ICRP[5] Category 1 limit of 0.1 mSv (see Table 2), the maximum activity would be 0.37 MBq (10.2 µCi).

6 Table 1

Estimated radiation doses to human tissues after oral administration of [^{14}C]GSK1278863 (Based on animal data)

Tissues	w_T	Equivalent Dose (Sv Bq^{-1})	Equivalent Dose x w_T (Sv Bq^{-1})	Contribution to effective dose (%)
Gonads	0.2	2.61E-10	5.22E-11	19.57
Red bone marrow	0.12	1.49E-11	1.79E-12	0.67
Colon	0.12	1.62E-09	1.94E-10	72.76
Lungs	0.12	1.15E-11	1.38E-12	0.52
Stomach	0.12	8.54E-11	1.02E-11	3.84
Urinary Bladder	0.05	4.82E-12	2.41E-13	0.09
Breasts	0.05	1.15E-11	5.77E-13	0.22
Liver	0.05	3.23E-11	1.61E-12	0.60
Oesophagus	0.05	5.62E-11	2.81E-12	1.05
Thyroid	0.05	2.61E-12	1.30E-13	0.05
Skin	0.01	9.95E-11	9.95E-13	0.37
Bone surfaces	0.01	7.41E-12	7.41E-14	0.03
Remainder	0.05	1.24E-11	6.21E-13	0.23
Highest remainder tissue	0.00	0.00E+00	0.00E+00	0.00
Effective dose			**2.67E-10**	**100.00**
	Mass (g)		**Equivalent Dose x Mass**	
Adrenals	14	2.63E-11	3.68E-10	
Brain	1450	2.09E-12	3.02E-09	
Eyes (pigmented region)	1.5	1.36E-10	2.04E-10	
Heart	330	4.88E-12	1.61E-09	
Kidneys	310	3.46E-11	1.07E-08	
Muscle	29000	1.15E-11	3.35E-07	
Pancreas	140	3.27E-11	4.58E-09	
Pituitary	0.6	4.02E-11	2.41E-11	
Prostate	17	3.88E-11	6.60E-10	
Spleen	150	9.72E-12	1.46E-09	
Small intestine	650	4.10E-11	2.66E-08	
Gall bladder	10	1.35E-09	1.35E-08	
Thymus	25	4.50E-11	1.12E-09	

Category 1 Limits:	WHO 1977 <0.5 mSv	**1.87 MBq (51.1 µCi)**
	ICRP 1992 <0.1 mSv	**0.37 MBq (10.2 µCi)**

8 References

1 ICRP, 1991. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication **60**. Ann. ICRP, Vol. **21** (1-3).

2 The Ionising Radiations Regulations 1999. UK Parliament Statutory Instruments. No.3232. HMSO, London.

3 EURATOM. Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation. Official Journal of the European Communities **39**, L159/1114 (1996).

4 World Health Organization, 1977. Use of ionising radiation and radionuclides on human beings for medical research, training and nonmedical purposes. Technical report series No. **611**, Geneva.

5 ICRP, 1992. Radiological Protection in Biomedical Research. ICRP Publication **62**. Ann. ICRP, Vol. **22** (3).

6 Physiological Parameter Values for PBPK models. A Report Prepared by the International Life Sciences Institute Risk Science Institute. Under a cooperative agreement with the U.S. Environmental Protection Agency Office of Health and Environmental Assessment. Dec. 1994.

7 Dolphin, G.W. and Eve, I.S., 1966. Dosimetry of the gastrointestinal tract. Health Physics **12**, 163-172.

8 Cristy, M., and Eckerman, K.F., 1987. Specific absorbed fractions of energy at various ages from internal photon sources. Oak Ridge, Tennessee. Oak Ridge National Laboratory. ORNL/TM-8381/v1-7.

9 Stabin, M.G., 1994. A model of the prostate gland for use in internal dosimetry. J. Nucl. Med. Technol. **35** (3).

10 ICRP, 2002. Basic Anatomical and Physiological Data for Use in Radiological Protection Reference Values. ICRP Publication **89**. Ann. ICRP, Vol. **32** (3-4).

11 ICRP, 1972. Limits for Intakes of Radionuclides by Workers. ICRP Publication **30** (Part 1). Ann. ICRP, Vol. **2** (3-4).

7 Table 2

Categories of risk and corresponding level of benefit for human exposure in biomedical research

WHO 1977

Category	Effective dose equivalent	Level of risk
I	Less than 0.5 mSv	Within variations of natural background
II	More than 0.5 mSv but less than 5 mSv	Within dose limits for members of the public
III	More than 5 mSv but less than 50 mSv	Within dose limits for persons occupationally exposed to radiation

ICRP 1992

Level of risk	Risk category	Corresponding effective dose range (adults) (mSv)	Level of societal benefit
Trivial	Category I ($\approx 10^{-6}$ or less)	<0.1	Minor
Minor to intermediate	Category II IIa ($\approx 10^{-5}$) IIb ($\approx 10^{-4}$)	0.1 - 1 1 – 10	Intermediate to moderate
Moderate	Category III ($\approx 10^{-3}$ or greater)	>10	Substantial

13.4. Appendix 4: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- 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 6 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count RBC Count Hemoglobin Haematocrit	RBC Indices: MCV MCH Absolute and % 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
	Fasting glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if leukocyte esterase, nitrites, blood or protein is abnormal)			
Other Screening Tests	• Alcohol breath test, urine cotinine test • Carbon Monoxide (CO) breath test • Drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

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 8.1.1 and Section 13.8. 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).

13.5. Appendix 5: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of AE/SAE/protocol deviations 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 legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised 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 centre.

- 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 authorised 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 authorised representative.
- Participants who are rescreened are required to sign a new ICF.

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

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his 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 hi medical records may be examined by Clinical Quality Assurance auditors or other authorised 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 multicentre 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 (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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 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 SPM.

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

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

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (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 NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

Events NOT Meeting the AE Definition
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 fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, 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

A SAE is defined as any untoward medical occurrence that, at any dose:
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.
g. Is associated with liver injury and impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Section 13.8 (Appendix 8) for the required liver chemistry follow-up instructions.

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 Paper CRF
• Facsimile transmission or email of the SAE paper CRF are the preferred methods to transmit this information to the Sponsor/medical monitor/SAE coordinator. Fax number and email address can be found in the SRM. • In rare circumstances and in the absence of facsimile equipment or email, 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 at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

13.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- In addition, male participants must refrain from donating sperm for during the protocol-defined time frame.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 h of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

13.8. Appendix 8: Liver Safety: Required Actions and Follow-up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology.

These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance.

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

Table 7 Phase I liver chemistry stopping criteria and required follow up assessments

<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>• Immediately discontinue study treatment
• 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</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• 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.</td></tr>
</table>

Liver Chemistry Stopping Criteria	
chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **If ALT≥3xULN AND bilirubin < 2xULN and 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	• Record alcohol use on the liver event alcohol intake case report form **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] 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

Brodie MJ, et.al. Enzyme induction with antiepileptic drugs: Cause for concern?. *Epilepsia.* 2013;54(1):11-27.

GlaxoSmithKline Document Number 2015N248947_00. Phase 2 Population Pharmacodynamic Analyses of GSK1278863 in Anemic Subjects with Chronic Kidney Disease. Report Date 22-APR-2016.

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.

Ohnhaus EE, Breckenridge AM, Park BK. Urinary Excretion of 6-Beta-Hydroxycortisol and the Time Course Measurement of Enzyme Induction in Man. *Eur J Clin Pharmacol.* 1989;36:39-48.

13.9. Appendix 9: Protocol Amendment 01

Where the Amendment Applies

This amendment applies to all sites participating in this clinical trial.

Summary of Amendment Changes

In the List of Specific Changes below, except minor format changes, the previous protocol version text is shown with ~~strikethrough~~ revision marks denoting removed text; **bold** text denotes text that has been added.

Rational for Changes:

The changes noted in the List of Specific Changes Protocol Section 9.2.5.: Regulatory Reporting Requirements for SAEs, Bullet 1, are made by requirement of the Regulatory Authority: Medicines and Healthcare Products Regulatory Agency (United Kingdom). The changes noted in the List of Specific Changes Protocol Section 9.2.1.: Time Period and Frequency for Collecting AE and SAE Information, Bullet 5, are made because the time requirement for reporting is the same, therefore, "promptly" has also been clarified in this section.

List of Specific Changes

Section 9.2.1. Time Period and Frequency for Collecting AE and SAE Information, Bullet 5:

PREVIOUS TEXT

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 **within 24 hours following knowledge of the SAE**.

REVISED TEXT

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 notify the sponsor within 24 hours following knowledge of the SAE.

Section 9.2.5. Regulatory Reporting Requirements for SAEs, Bullet 1:

PREVIOUS TEXT

~~Prompt notification~~ **Notification** by the investigator to the sponsor **within 24 hours following knowledge** of a**n** SAE is essential so that legal obligations and ethical

responsibilities towards the safety of participants and the safety of the a study treatment under clinical investigation are met.

REVISED TEXT

Notification by the investigator to the sponsor within 24 hours following knowledge of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the a study treatment under clinical investigation are met.