TITLE PAGE

Protocol Title: A single centre, single dose, open-label, randomised, 2-way crossover study in healthy Japanese male subjects to evaluate the bioequivalence of daprodustat tablets (2 mg tablet vs. 4 mg tablet) (Part 1) and the food effect on the pharmacokinetics of daprodustat (Part 2).

Protocol Number: 207727

Compound Number: GSK1278863

Study Phase: Phase I

Short Title: Daprodustat bioequivalence and food effect study

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A single centre, single dose, open-label, randomised, 2-way crossover study in healthy Japanese male subjects to evaluate the bioequivalence of daprodustat tablets (2 mg tablet vs. 4 mg tablet) (Part 1) and the food effect on the pharmacokinetics of daprodustat (Part 2).

Short Title: Daprodustat bioequivalence and food effect study

Rationale:

This study is composed of two parts. Part 1 aims to evaluate the bioequivalence of daprodustat tablets (2 mg tablet vs. 4 mg tablet), and Part 2 aims to evaluate the food effect on the pharmacokinetics (PK) of daprodustat.

Objectives and Endpoints:

Objective	Endpoint
Primary	
Part 1 • To determine the bioequivalence of daprodustat 2 mg tablet vs. 4 mg tablet in healthy Japanese male subjects. Part 2 • To investigate the food effect on PK of daprodustat following a single dose of daprodustat in the fed and fasted state in healthy Japanese male subjects.	Parts 1 and 2 • Plasma PK parameters for daprodustat: AUC(0-t), Cmax, and the other parameters [AUC(0-inf), Tmax, t1/2, %AUCex, CL/F, Vz/F, kel and MRT]
Secondary	
Parts 1 and 2 • To assess the safety and tolerability of single dose of daprodustat following administration of daprodustat in healthy Japanese male subjects.	Parts 1 and 2 • Safety: Adverse events (AEs), clinical laboratory tests, vital signs (blood pressure, pulse and body temperature), and 12-lead electrocardiogram (ECG) parameters.

Overall Design:

This study consists of two parts; Part 1 is a single centre, single dose, open-label, randomised, 2-way crossover study in healthy Japanese male subjects. Part 2 is a single

centre, single dose in the fed and fasted state, open-label, randomised, 2-way crossover study in healthy Japanese male subjects.

In both parts (Part 1 and Part 2), healthy subjects will have a screening visit within 30 days prior to the first dose of study intervention, two intervention periods, and re-visit 7 (±1) days after the second dose for follow-up. All subjects will be administered daprodustat as a single oral dose, with assessments conducted for up to 24 hours post-dose. Subjects will be housed in the clinical research unit from Day -1 through Day 2 of each period. At least 5-day wash-out period will occur between each intervention period.

Disclosure Statement: This is an open-label, 2 parts, 2-way crossover study.

Number of Participants:

Sufficient participants will be randomised such that approximately 52 and 12 (a total of 64 participants) evaluable participants complete the study of Part 1 and Part 2, respectively. The definition of the study complete is described in the section 4.4.

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

If PK parameters are not within the bioequivalence acceptance criterion because of an insufficient number of participants, one add-on participant study can be performed using not less than half the number of participants with the same methodology as the initial study according to the "Guideline for bioequivalence studies for different strengths of oral solid dosage forms [MHLW, 2012]" (Japanese BE guideline).

Intervention Groups and Duration:

Subjects will be divided into the study of Parts 1 and 2, and will be randomized to one of two groups (Part 1: A or B, Part 2: C or D) in the following table;

Part 1 (Bioequivalence part)

- Daprodustat 2 mg tablet x 2, single dose, in the fasted state
- Daprodustat 4 mg tablet x 1, single dose, in the fasted state

Group	n	Period 1	Period 2
A	26	2 mg tablet x 2	4 mg tablet x 1
B	26	4 mg tablet x 1	2 mg tablet x 2

Part 2 (Food effect part)

- Daprodustat 4 mg tablet, single dose, in the fed state
- Daprodustat 4 mg tablet, single dose, in the fasted state

Group	n	Period 1	Period 2
C	6	4 mg tablet x 1 (fed)	4 mg tablet x 1 (fasted)
D	6	4 mg tablet x 1 (fasted)	4 mg tablet x 1 (fed)

Blood sampling for PK analysis will be performed prior to dosing and until 24 hours post-dose following each dose. The duration of each subject's participation will be approximately 6 weeks from screening to the follow-up.

Data Monitoring Committee: No

1.2. Schedule of Activities (SoA)

Time and Events Table for both Part 1 and Part 2 of the study.

Procedure	Screening[1]	Intervention period (Period 1-2)													Follow-up [7]
		Day -1	Day 1											Day 2	
			Pre-dose	0 h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	4 h	6 h	8 h	12 h	24 h	
Informed consent	X															
Demography/Medical history	X															
Height, Weight, Body mass index (BMI)	X															
Urine drug screen	X															
Serology test[2]	X															
Physical examination	X	X	X							X					X	X
12-lead ECG	X		X							X					X	X
Vital signs[3]	X		X							X					X	X
Clinical laboratory test[4]	X	X													X	X
Study intervention dosing[5]				X												
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	
AE[6]/Serious adverse events (SAE)[6]	<==========															==========>
Concomitant medication review	<==========															==========>
Admission to unit		X														
Discharge															X	
Outpatient visit	X															X

1: Within 30 days prior to Day 1 of Period 1.

2: Serology tests for syphilis [RPR & TP], Human immunodeficiency virus (HIV) antigen/antibody, Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) antibody and Human T-cell lymphotropic virus type 1 (HTLV-1) antibody.

3: Body temperature (axillary), systolic and diastolic blood pressure and pulse (supine).

4: Haematology, clinical chemistry and urinalysis.

5: Subjects will remain in a sitting or semi-supine position for approximately 4 hours if possible after dosing on Day 1. In Part 2, study subjects who are in fed state should take a standard meal as recommended for chronic kidney disease (CKD) by the Japanese Society of Nephrology in Japan [Jpn J Nephrol, 2014] in 20 minutes or less and the drug product should be administered 30 minutes after the end of the meal.

6: AEs and SAEs will be collected from the start of intervention until the follow-up visit at the time points specified. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, or invasive tests) will be recorded from the time a subject consents to participate in the study.

7: 7(±1) days post-dose of Period 2.

- The timing and number of planned study assessments, including safety, or PK 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 as the result of emerging PK data from this study 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) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the IRB before implementation.

2. INTRODUCTION

Daprodustat (GSK1278863) is a prolyl hydroxylase inhibitor that stimulates erythropoiesis in a manner similar to the natural response to hypoxia, whereby inhibition of hypoxia inducible factor (HIF) prolyl-4-hydroxylases (PHD1, PHD2, PHD3) by daprodustat ultimately results in increased levels of HIF-responsive genes. Daprodustat is currently under development in oral dose as an emerging new class of agent for treatment of anaemia associated with chronic kidney disease (CKD).

2.1. Study Rationale

Daprodustat is formulated as immediate release tablets with dose strengths of 1 mg, 2 mg, 4 mg and 6 mg. For the commercial formulation coloured film coats will be used for the 1 mg, 2 mg and 6 mg tablets and white film coat will be remained for 4 mg tablet for the Japanese market. The dissolution profiles of these tablets have been evaluated according to the Japanese BE guideline, and the dissolution test results across strengths demonstrated equivalence with the exception of the 2 mg vs 4 mg test using water. The result of the 2 mg vs 4 mg dissolution test using water was considered due to properties of the drug substance and the drug products of daprodustat. Considering the administration manner for the renal anaemia patients in Japan, the risk that water has any effects following administration of daprodustat in humans is low. This study is planned according to Japanese Guideline as follows:

Part 1

The purpose of Part 1 is to evaluate the bioequivalence between daprodustat tablet strengths (2 mg vs. 4 mg) in healthy Japanese male subjects according to the Japanese BE guideline.

Part 2

The purpose of Part 2 is to evaluate the food effect on the PK of daprodustat in healthy Japanese male subjects with reference to Japanese Notification for Clinical Pharmacokinetic Studies of Pharmaceuticals [MHLW, 2001]. This part will assess the PK of a single oral dose of daprodustat under fasted state and following a standard meal with reference to the Dietary recommendations for chronic kidney disease in Japan [Jpn J Nephrol, 2014].

2.2. Background

As of June 2017, more than 1700 patients and healthy subjects have received daprodustat in domestic and overseas clinical trials. For Japanese subjects, a global Phase I study including 19 Japanese subjects (dose: 10 - 100 mg single dose) and three Phase II studies which are domestic and multinational (dose: up to 12 mg daily including 163 Japanese patients) have completed, and three Phase III studies (dose: 1 - 24 mg daily) are ongoing.

Administration of daprodustat in development with a high fat/calorie breakfast led to a 1.0 hr delay in Tmax and 29% decrease in Cmax, and an 8% decrease in AUC in healthy

South Asian subjects resident in India (Study PHI113634). These data suggest that daprodustat may be administered without regard to food.

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

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

The potential risks of clinical significance including adverse events of special interest (AESI)(Section 8.3.4), and the mitigation strategies for this protocol taking into account the results of completed clinical and non-clinical studies with daprodustat, are outlined in the table below. These sentences are included in the interests of transparency. However, the risks of following events after the single lower dose (up to 4 mg) administration in this study are considered very low.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [Daprodustat]		
Excessive erythropoiesis (polycythaemia) leading to thrombosis and/or tissue ischaemia	In animal studies, excessive erythropoiesis (haemoglobin (Hgb) /haematocrit (Hct) > upper limit normal) attributed to daprodustat was associated with vascular congestion, inflammation, microthrombi, and tissue ischaemia in a number of organs. Phase II dose-ranging studies, and associated statistical and dose response modelling has informed Phase III dose rationale, starting doses, dose steps, and dose adjustment scheme to optimize Hgb management. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat at clinically relevant doses.	• Specific eligibility criteria related to requirements for entry Hgb are detailed in Exclusion Criteria. • Hgb will be closely monitored throughout the dosing period as outlined in the SoA (Section 1.2). • Specific guidance for discontinuation of daprodustat based on Hgb is provided in Section 7.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team.
Death, Myocardial infarction (MI), stroke, heart failure, thromboembolic events, thrombosis of vascular access at Hgb levels which are within the normal range (i.e. not polycythaemic conditions)	Marketed recombinant human erythropoietin (rhEPO) and its analogues have been associated with an increased risk for death and serious cardiovascular (CV) events when used in patients with anaemia of CKD. In non-clinical studies conducted to date, not observed at tolerated doses when Hgb/Hct within normal range for species. The clinical data received to date are insufficient to conclude or refute this risk.	• Specific eligibility criteria related to CV risk are outlined in Section 5.2. • Hgb will be closely monitored throughout the dosing period as outlined in the SoA (Section 1.2). • Monitoring of emerging safety data by an internal GSK Safety Review Team.
Oesophageal and gastric erosions (e.g. upper gastrointestinal (GI) bleeding, severe abdominal pain, upper GI perforations)	In animal studies, undesirable GI effects including emesis, abnormal faeces and/or decreased food consumption/body weight loss and stomach erosions/ulcers with haemorrhage were observed with daprodustat. In rats, stomach erosions were observed with intravenous and oral administration of daprodustat. Stomach erosions/ulcers also reported in rats with some marketed rhEPO	• Suspected GI bleeding or significant symptoms consistent with erosions or ulcers should be investigated diagnostically (i.e. endoscopic examination) as clinically warranted. • Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and its analogues. In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported AE, however causal association has not been established. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	
Cancer-related mortality and tumour progression and recurrence	In clinical trials, use of rhEPO and its analogues in patients with cancer has been associated with increased risk of cancer related morbidity and mortality. Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating vascular endothelial growth factor (VEGF) while significant erythropoietin (EPO) increases were observed. There were no test article-related neoplastic findings in 2-year rat (oral daprodustat) or mouse (daprodustat + subcutaneous injection of the 3 major human metabolites; M2, M3 and M13) carcinogenicity studies. In clinical studies conducted to date, administration of daprodustat has been associated with: Once daily administration: • In studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg. In studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. • Systemic EPO concentrations within the physiologic range. Three times weekly administration: In studies up to 4 weeks duration at doses of 10 to 30 mg: • Dose dependent increases in plasma VEGF and EPO concentrations were observed. • Pre-dose concentrations of EPO and VEGF were near or below baseline indicating no accumulation of EPO or VEGF after three times weekly dosing. Following review of clinical data received to date, this has not been identified as a safety concern for daprodustat.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 5.2. • Stopping criteria for subjects with treatment emergent malignancy are outlined in Section 7.1. • 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	• Monitoring of emerging safety data by an

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 (up to 13-weeks duration in dogs, up to 2-years in rats and mice, and up to 39-weeks in monkeys.) Acute hypoxic challenge (rats): Daprodustat produced increases in peak right ventricular pressure (PRVP) during acute hypoxia that were slightly higher than the vehicle control group. However, these hypoxia-induced PRVP changes were within the range of PRVP changes noted among untreated rats. Results from a clinical study of acute hypoxic challenge in patients demonstrated that short-term (5 days) therapy with daprodustat 5 mg or 100 mg had no clinically significant effect on transthoracic echocardiographic estimates of pulmonary artery systolic pressure (PASP) under either normoxic or hypoxic conditions. Echocardiograph (ECHO) assessments performed in Phase IIb studies (24weeks treatment duration) did not identify any clinically meaningful changes in PASP in subjects not on dialysis. In haemodialysis subjects, mean absolute change from baseline in PASP was similar for both treatment groups; however, there was a numeric imbalance (GSK Total: 8 [7%]; Control 0) in subjects reaching the PASP potential clinical importance (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 subjects with resolution of PASP on safety follow-up ECHOs had confounding conditions that could contribute to resolution other than discontinuation of study drug; and there was no dose relationship for subjects meeting the PASP PCI criterion. Overall, there is insufficient evidence to conclude a relationship to treatment with daprodustat. Following review of clinical data received to date, this has not been	internal GSK Safety Review Team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	identified as a safety concern for daprodustat.	
Cardiomyopathy	Published data suggest that cardiac effects of HIF stabilization are likely a function of the mechanism, extent, and duration of the effects, and can range from protective to detrimental depending upon the specific model and experimental conditions utilized. With lifetime exposure to daprodustat in a 2-year rat oral carcinogenicity study, an exacerbation of rat spontaneous, progressive cardiomyopathy (PCM)(focal myofiber degeneration/necrosis with inflammatory infiltrates) was observed at doses of 0.8 mg/kg/day and above, although total incidence and severity distribution within any daprodustat group were within historical control ranges. This is consistent with an equivocal threshold for exacerbation of spontaneous, PCM at 0.8 mg/kg/day which is also the threshold dose for observing increased Hct values in individual rats. Cardiomyopathy has not been associated with naturally occurring mutation in man which results in increased HIF stabilization. ECHO assessments performed in Phase IIb studies (24 weeks treatment duration) did not identify any clinically meaningful changes in left ventricular ejection fraction (LVEF). 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. Aside from congestion of retinal vessels and optic disc hyperaemia secondary to markedly increased red cell mass, no ocular abnormalities were observed in non-clinical studies. In clinical studies up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations was observed at doses ranging from 10 to 150 mg administered once daily and from 10 to 30 mg administered three times weekly.	• Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In 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 IIb studies (24 weeks treatment duration) did not identify any clinically meaningful changes in proliferative retinopathy, macular oedema, or choroidal neovascularization. Following review of clinical data 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 proinflammatory cytokines has been postulated to contribute to the neoangiogenesis, proliferation and infiltration of rheumatoid synovial fibroblasts [Westra, 2010; Muz, 2009]. No abnormalities were seen in non-clinical studies conducted to date. 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
Drug-drug interactions	Daprodustat is a substrate of cytochrome P450 (CYP)2C8: Co-administration of daprodustat with a strong CYP2C8 inhibitor (i.e., gemfibrozil) increased the Cmax and AUC of daprodustat, 4- and 19-fold, respectively, while co-administration of a weak CYP2C8 inhibitor (i.e., trimethoprim) increased the Cmax and AUC of daprodustat by 1.3- and 1.5-fold, respectively. Population PK analysis from completed Phase II studies suggests that co-administration of daprodustat with a moderate CYP2C8 inhibitor (i.e., clopidogrel) leads to a ~ 2-fold increase in AUC, with no clinically significant increase in the measured Hgb response. Although CYP2C8 induction studies were not performed, co-administration of daprodustat with an inducer of CYP2C8 (e.g. rifampin/rifampicin) may decrease the exposure of daprodustat. Even though co-administration of daprodustat with strong inhibitors and inducers of CYP2C8 is prohibited, inadvertent co-administration may occur. Due to the known time delay in enhancing erythropoiesis by daprodustat, co- administration with strong CYP2C8 inhibitors for up to 14 days is not anticipated to lead to immediate marked increases in Hgb 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 after	• Co-administration of daprodustat with all medicine is basically not permitted as outlined in Section 6.5. • Hgb will be closely monitored throughout the dosing period as outlined in the SoA (Section 1.2). • Specific guidance for discontinuation of daprodustat based on Hgb is provided in Section 7.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	approximately 10 - 14 days of dosing with rifampin [Brodie, 2013; Ohnhaus, 1989], daprodustat systemic exposure will decrease over time which will result in a lag period before an effect on Hgb is recognized and is of clinical concern. Daprodustat is an inhibitor of CYP2C8: A clinical drug interaction study between 25 mg and 100 mg daprodustat with a CYP2C8 substrate (i.e., pioglitazone) showed that there is no PK interaction at these doses of daprodustat. Daprodustat is a substrate of breast cancer resistance protein (BCRP): Population PK analysis from Phase II studies suggested that while BCRP inhibitors were a covariate for daprodustat CL/F (8.6% lower clearance) the predicted change in exposure was not considered to be of clinical relevance. Daprodustat is an inhibitor of organic anion transporter polypeptide (OATP)1B1/1B3: A clinical drug interaction study between 25 mg and 100 mg daprodustat with an OATP1B1/1B3 substrate (i.e., rosuvastatin) showed that no PK interaction at this these doses of daprodustat.	

2.3.2. Benefit Assessment

This study is being conducted in healthy male Japanese subjects with no significant medical history. Subjects will not receive benefit from this study.

2.3.3. 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, these can be addressed in clinical trials with proper subject selection, close safety monitoring, and specific risk characterization and mitigation.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Part 1 • To determine the bioequivalence of daprodustat 2 mg tablet vs. 4 mg tablet in healthy Japanese male subjects. Part 2 • To investigate the food effect on PK of daprodustat following a single dose of daprodustat in the fed and fasted state in healthy Japanese male subjects.	Parts 1 and 2 • Plasma PK parameters for daprodustat: AUC(0-t), Cmax, and the other parameters [AUC(0-inf), Tmax, t1/2, %AUCex, CL/F, Vz/F, kel and MRT].
Secondary Parts 1 and 2 • To assess the safety and tolerability of single dose of daprodustat following administration of daprodustat in healthy Japanese male subjects.	Parts 1 and 2 • Safety: AEs, clinical laboratory tests, vital signs (blood pressure, pulse and body temperature), and 12-lead ECG parameters.

4. STUDY DESIGN

4.1. Overall Design

This study consists of two parts; Part 1 is a single centre, single dose, open-label, randomised, 2-way crossover study in healthy Japanese male subjects. Part 2 is a

single centre, single dose in the fed and fasted state, open-label, randomised, 2-way crossover study in healthy Japanese male subjects.

In both parts (Part 1 and Part 2), healthy subjects will have a screening visit within 30 days prior to the first dose of study intervention, two intervention periods, and re-visit 7 (±1) days after the second dose for follow-up. All subjects will be administered daprodustat as a single oral dose, with assessments conducted for up to 24 hours post-dose. Subjects will be housed in the clinical research unit from Day -1 through Day 2 of each period. At least 5-day wash-out period will occur between each intervention period.

Subjects will participate in Parts 1 and 2, and receive the study intervention shown below;

Part 1 (Bioequivalence part)

- Daprodustat 2 mg tablet x 2, single dose, in the fasted state
- Daprodustat 4 mg tablet x 1, single dose, in the fasted state

Group	n	Period 1	Period 2
A	26	2 mg tablet x 2	4 mg tablet x 1
B	26	4 mg tablet x 1	2 mg tablet x 2

Part 2 (Food effect part)

- Daprodustat 4 mg tablet, single dose, in the fed state
- Daprodustat 4 mg tablet, single dose, in the fasted state

Group	n	Period 1	Period 2
C	6	4 mg tablet x 1 (fed)	4 mg tablet x 1 (fasted)
D	6	4 mg tablet x 1 (fasted)	4 mg tablet x 1 (fed)

Blood sampling for PK analysis will be performed prior to dosing and until 24 hours post-dose following each dose. The duration of each subject's participation will be approximately 6 weeks from screening to the follow-up.

Number of Participants

Sufficient participants will be randomised such that approximately 52 and 12 (a total of 64 subjects) evaluable participants complete the study of Part 1 and Part 2, respectively. The definition of the study complete is described in the section 4.4.

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence at the discretion of the sponsor in consultation with the investigator.

If PK parameters are not within the bioequivalence acceptance criterion because of an insufficient number of participants, one add-on participant study can be performed

using not less than half the number of participants with the same methodology as the initial study according to the Japanese BE guideline.

4.2. Scientific Rationale for Study Design

This is a 2-way crossover study design to compare the PK of daprodustat tablet (2 mg tablet vs. 4 mg tablet) and food effect on the PK of daprodustat following single oral doses in healthy Japanese male subjects. Part 1 is designed according to the Japanese BE guideline. To investigate the food effect in the closer clinical practice, a standard meal as recommended by the Japanese Society of Nephorology for chronic kidney disease [Jpn J Nephrol, 2014] will be used in Part 2.

A previous single-dose study in healthy male Japanese subjects (PHI115385) using an earlier tablet formulation confirmed that the mean t1/2 of daprodustat from 10 to100 mg was approximately 1.0 - 2.1 hours. Therefore, in this study, subjects will be hospitalised for 2 days in each period and undergo the examinations for safety assessments. The wash out between the 2 intervention periods is set to be ≥ 5 days, and the follow-up visit is set to be up to 7 (±1) days post the dose in Period 2.

4.3. Justification for Dose

A study is planned for the evaluation of the bioequivalence of daprodustat tablets (2 mg tablet vs. 4 mg tablet) (Part 1), because the dissolution tests of these tablets in water failed to demonstrate equivalence. To evaluate the bioequivalence of the daprodustat 2 mg and 4 mg tablet strengths, a single 4 mg dose has been selected for PK evaluation.

To investigate the effect of food on the PK of daprodustat (Part 2), a single 4 mg dose which is the starting dose in Phase III studies in Japan has been selected.

As of June 2017, more than 1700 patients and healthy subjects have received daprodustat. Overall, single oral doses of up to 500 mg (100 mg for Japanese) and repeated dose of up to 100 mg for 14 days administered to healthy subjects have been generally well tolerated.

4.4. End of Study Definition

A subject is considered to have completed the study if he has completed all phases of the study including the last scheduled procedure shown in the SoA.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 20 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Japanese participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

Weight

3. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5 - 24.9 kg/m^2 (inclusive).

Sex

4. Male

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of cardiovascular(CV), respiratory, hepatic, renal, gastrointestinal (GI), endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data
2. Abnormal blood pressure as determined by the investigator
3. Alanine aminotransferase (ALT) >1.5x upper limit of normal (ULN)
4. Bilirubin >1.5xULN (When direct bilirubin <35% is eligible.).
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
6. QTcF > 500 msec

   NOTES:

   - The QTcF is the QT interval corrected for heart rate according to Fridericia's formula, machine-read or manually over-read.

- The specific formula that will be used to determine eligibility and discontinuation 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 QT correction (QTc) for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

7. The values of haemoglobin (Hgb) at screening: ≥16.0 g/dL
8. History of deep vein thrombosis, pulmonary embolism or other thrombosis related condition
9. History of myocardial infarction (MI) or acute coronary syndrome, stroke or transient ischemic attack
10. Participants that have undergone cholecystectomy
11. History of malignancy within the prior 2 years or currently receiving treatment for cancer

    NOTES:

    - Only exception is localized squamous cell or basal cell carcinoma of the skin definitively treated 12 weeks prior to enrolment.
12. Any evidence of heart failure, as defined by the New York Heart Association (NYHA) functional classification system

Prior/Concomitant Therapy

13. Past or intended use of over-the-counter or prescription medication including vitamins, diet foods and herbal medications within 14 days prior to first dosing

Prior/Concurrent Clinical Study Experience

14. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day
15. Current enrolment or past participation (i.e. administration of last dose of investigational study intervention) within the last 30 days (or 5 half-lives, whichever is longer) before signing of consent in this clinical study involving an investigational study intervention or any other type of medical research

Diagnostic assessments

16. The participant with positive serological test for syphilis (RPR and TPHA), Human immunodeficiency virus (HIV) Antigen/Antibody, Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) antibody, or Human T-cell lymphotropic virus type 1 (HTLV-1) antibody at screening
17. Positive pre-study drug screen

Other Exclusions

18. Regular alcohol consumption within 6 months prior to the study defined as:

    - For an average weekly intake of >14 units for males. One unit is equivalent to 350 mL of beer, 150 mL of wine or 45 mL of 80 proof distilled spirits.
19. Smoking or history of regular use of tobacco- or nicotine-containing products (e.g. nicotine patch, electronic cigarette) within 6 months prior to screening

20. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study
21. History of donation of blood or blood products ≥ 400 mL within 3 months or ≥ 200 mL within 1 month prior to the first dosing day

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Subjects must fast from all food and drink (except water) at least 10 hours prior to any laboratory safety evaluations.
- Refrain from consumption of red wine, apples, star fruit, or citrus fruits/juices including blood oranges (with the exception of oranges, mandarins and lemons) from 7 days prior to the first dose of study medication until collection of the final PK sample, unless in the opinion of the Investigator and GSK Medical Monitor this will not interfere with the study procedures and compromise subject safety.
- Subjects must refrain from any food and drink except those provided during hospitalisation. Furthermore, subjects should avoid being crapulous and keep routine eating habits in mind when discharged.
- Lunch and dinner will be provided at approximately 4 and 10 hours post dose, respectively.

Part 1

- Subjects will refrain from any food and drink (except water) at least 10 hours before dosing and 4 hours after dosing on Day 1 of Period 1 and Period 2.
- No water is allowed within 2 hours before and after dosing, but it is allowed ad libitum at all other times.

Part 2

- Subjects should fast 10 hours before administration of a standard diet of CKD or dosing on Day 1 of Period 1 and Period 2.
- The standard CKD meal will consist of the following contents based on the dietary recommendations for CKD patients issued by the Japanese Society of Nephrology [Jpn J Nephrol, 2014].

Contents	Calorie (kcal)	Protein (g)	Salt (g)	Potassium (mg)
Criteria	500 - 700	12 - 16	1≤, <2	≤500

- Study subjects who are in fed state should consume a standard CKD meal in 20 minutes or less as breakfast and the drug product should be administered 30 minutes after the end of the meal.
- No water is allowed until 2 hours after dosing, but it is allowed ad libitum at all other times.
- The meal contents of Periods 1 and 2 on administration day are the same.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, all type of tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- During each dosing session, subjects will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from screening until the follow-up visit.

5.3.3. Activity

- Subjects will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g. watching television, reading, radio calisthenics).

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects 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.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

Study intervention name:	**Daprodustat 2 mg tablet**	**Daprodustat 4 mg tablet**
Dosage formulation:	White film coated tablet	White film coated tablet
Unit dose strength(s)/ Dosage level(s):	2 mg tablet strength / 4 mg dosage level	4 mg tablet strength / 4 mg dosage level
Route of administration	Oral	
Dosing instructions:	Administered in the fasted state in the morning with 150 mL of room temperature water	Administered in the fasted (and fed in part 2) state in the morning with 150 mL of room temperature water
Packaging and labelling	Study intervention will be provided in bottles. Each bottle will be labelled as required per country requirement.	
Manufacturer	GlaxoSmithKline	

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only subjects enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
6. 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open label study. Subjects will be divided into the study of Parts 1 and 2, and assigned to one of two groups (Part 1: A or B, Part 2: C or D) in accordance with the randomisation schedule generated by the Biomedical Data Sciences Department at GSK.

A description of each group is provided in the table below:

Part 1 (Bioequivalence part)

- Daprodustat 2 mg tablet x 2, single dose, in the fasted state
- Daprodustat 4 mg tablet x 1, single dose, in the fasted state

Group	n	Period 1	Period 2
A	26	2 mg tablet x 2	4 mg tablet x 1
B	26	4 mg tablet x 1	2 mg tablet x 2

Part 2 (Food effect part)

- Daprodustat 4 mg tablet, single dose, in the fed state
- Daprodustat 4 mg tablet, single dose, in the fasted state

Group	n	Period 1	Period 2
C	6	4 mg tablet x 1 (fed)	4 mg tablet x 1 (fasted)
D	6	4 mg tablet x 1 (fasted)	4 mg tablet x 1 (fed)

6.4. Study Intervention Compliance

Subjects will receive study intervention directly from the investigator or designee, under medical supervision in the clinic. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each subject's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Subjects must abstain from taking other prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

6.6. Dose Modification

This protocol allows no dose modification.

6.7. Intervention after the End of the Study

Subjects will not receive any additional intervention from GSK, after completion of the study because only healthy subjects are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A subject 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 subject must permanently discontinue study intervention for the pre-specified reasons below.

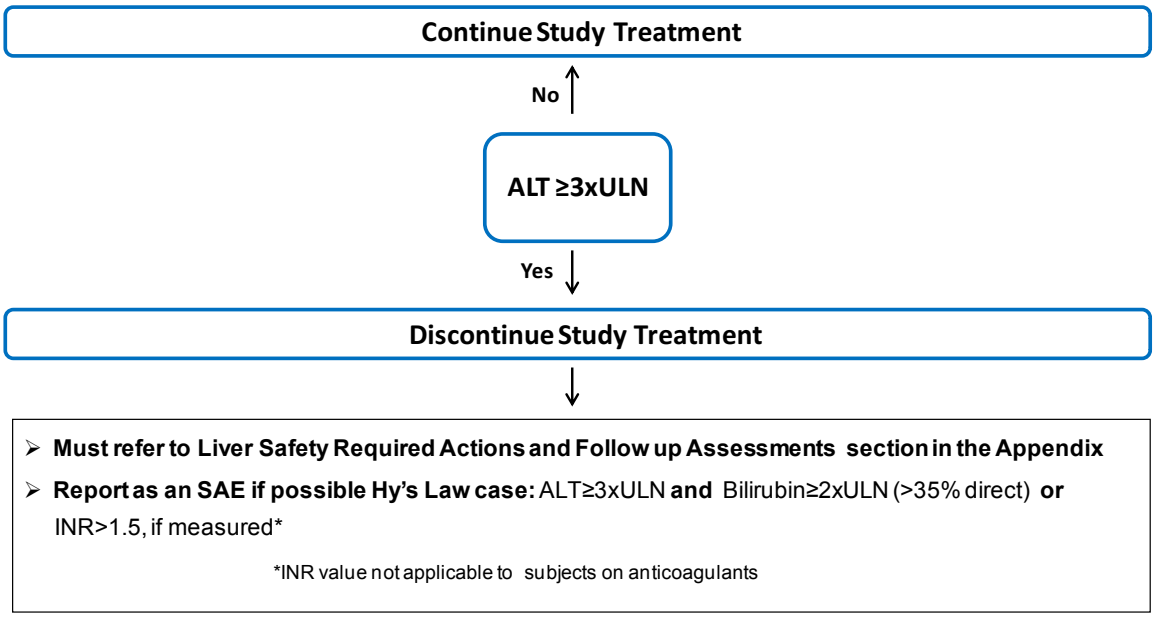
- Hgb value greater than the ULN.
- Diagnosis of cancer (new or recurrent), with the exception of localized squamous cell or basal cell carcinoma of the skin.
- Liver chemistry abnormalities exceeding the threshold criteria (Section 7.1.1).
- QTc abnormalities exceeding the threshold criteria (Section 7.1.2).

In all cases, the reason for study intervention discontinuation and the date of the last dose will be recorded in the subject's case report form (CRF) and the subject will be withdrawn from the study as described in Section 7.2.

7.1.1. Liver Chemistry Stopping Criteria

Study intervention will be discontinued **for a subject** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 4.

7.1.2. QTc Stopping Criteria

The same QTc formula must be used for each individual subject to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.

- For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
- Once the QTc formula has been chosen for a subject's eligibility, the same formula must continue to be used for that subject for all QTc data being collected for data analysis. Safety electrocardiograms (ECGs) and other non-protocol specified ECGs are an exception.

If the single QTc value meets either bulleted criterion, the additional double QTc values should be obtained over a brief (e.g. 5 - 10 minute) recording period.

A subject that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study intervention.

- QTcF > 500 msec
- Change from baseline: QTc >60 msec

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/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.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. 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). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timings are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 400 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Efficacy assessments are not evaluated in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A physical examination will include, at a minimum, assessments of the Skin, CV, Respiratory, GI and Neurological systems.
- Height and weight will be measured and recorded at screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Axillary temperature, pulse, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.2.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 adverse event (AE) section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 2 must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified 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 intervention or the study, or that caused the subject to discontinue the study intervention (see Section 7).

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

- All SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA. However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, or invasive tests) will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the 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 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.3.4) will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Adverse Events of Special Interest (AESI)

AESI have been identified based on non-clinical studies with daprodustat, clinical experience with recombinant human erythropoietins (rhEPOs), and current

information regarding HIF-regulated pathways in mediating hypoxia-associated pathophysiology. The currently identified AESI for daprodustat are as follows:

- Thrombosis and tissue ischemia secondary to excessive erythropoiesis
- Death, MI, stroke, venous thromboembolism, thrombosis of vascular access
- Cardiomyopathy
- Pulmonary artery hypertension (PAH)
- Increased cancer-related mortality and tumor progression and recurrence
- Esophageal and gastric erosions
- Proliferative retinopathy, macular edema, choroidal neovascularization
- Exacerbation of rheumatoid arthritis

8.3.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention 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 intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, 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, if appropriate according to local requirements.

8.4. Treatment of Overdose

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

There is no specific antidote for overdose with daprodustat. The expected manifestations of daprodustat overdose 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 subject's clinical status. Additionally, subjects should be monitored closely for CV events, increased heart rate and haematologic abnormalities.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the subject for AE/SAE and laboratory abnormalities until daprodustat can no longer be detected systemically (at least 14 days).
3. Obtain a plasma sample for PK analysis within 14 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

8.5. Pharmacokinetics

Blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of daprodustat as specified in the SoA. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

The primary objective of Part 1 is to assess the bioequivalence of different daprodustat tablets strength (2 mg vs 4 mg) in healthy Japanese male subjects.

The primary objective of Part 2 is to investigate food effect on PK of daprodustat in the fed state and fasted state in healthy Japanese male subjects.

9.1. Statistical Hypotheses

Part 1

The bioequivalence between daprodustat 2 mg tablet and 4 mg tablet will be demonstrated using a framework of statistical hypothesis testing. The ratio of the

geometric means (μ_{2mg}/μ_{4mg}) for AUC(0-t) and Cmax is the measure in the following statistical hypotheses:

H_0 (null hypothesis) : $\mu_{2mg}/\mu_{4mg} \leq 0.80$ or $\mu_{2mg}/\mu_{4mg} \geq 1.25$,

H_1 (alternative hypothesis) : $0.80 < \mu_{2mg}/\mu_{4mg} < 1.25$

A judgment by 90% CI will be conducted in this study. The null hypothesis is rejected if the 90% confidence interval (CI) of μ_{2mg}/μ_{4mg} falls within a range of 0.80 to 1.25, which results a conclusion of the bioequivalence. This is equivalent to carrying out two one-sided tests of hypothesis at the 5% level of significance.

If the 90% CI of μ_{2mg}/μ_{4mg} doesn't fall within a range of 0.80 to 1.25 (i.e., null hypothesis is not rejected), the bioequivalence is established if the point estimate (μ_{2mg}/μ_{4mg}) falls within a range of 0.90 to 1.11.

Part 2

No formal statistical hypotheses will be tested.

9.2. Sample Size Determination

Part 1

Refer to regulatory definition of bioequivalence criteria; 90% CI of the ratio for AUC(0-t) and Cmax between tablet strengths (2 mg x 2 vs. 4 mg x 1) should lie in the range of 0.80-1.25. Assuming the true ratio is 1.0 and the coefficient of variation within subject (%CVw) is 35%, in a 2-way crossover design 52 subjects in total (i.e. 26 subjects for each group) will be randomised to achieve at least 90% power for meeting the bioequivalence criteria.

The %CVw has been assumed conservatively from Japanese data in the previous Japanese study (PHI115385, Part 1) based on a power model using all dose groups. The power model used to estimate %CVw is as below.

$\log_e(\text{PK parameter}) = \mu + S_i + \beta * \log(D_j) + \varepsilon_{ij}$

where μ is the intercept, β is the slope, S_i is the random effect for subject i, D_j is the dose, ε_{ij} is the random error. The %CVw estimates based on the random error are 24.3% and 26.8% for AUC(0-inf) and Cmax, respectively. For a little more conservative looking at higher variation in lower strength doses, an estimate of %CVw has been set to be 35% for sample size considerations.

Part 2

The number of subjects is determined based on the feasibility rather than statistical considerations. A total of 12 subjects (i.e. 6 subjects for each group) will be randomised in a 2-way crossover design. Assuming a %CVw of 35% for AUC(0-t) and Cmax as described, it is estimated that the lower and upper bounds of the 90% CI for the ratio of AUC(0-t) and Cmax in the fed and fasted state will be within +/- 30%. If the estimated ratio is 1.0, its 90% CI would be approximately (0.78, 1.29).

9.2.1. Sample Size Sensitivity

Part 1

The powers for achieving the bioequivalence criterion based on the sample size of 52 are shown in the following table with various scenarios changing the %CVw.

	%CVw				
	25%	30%	35%	40%	45%
Power	99.6%	97.1%	**90.2%**	79.5%	66.7%

Part 2

The lower and upper bounds of the 90% CI for the ratio of AUC(0-t) or Cmax in the fed and fasted state are shown in the following table with various scenarios changing %CVw based on the sample size of 12, assuming the estimated ratio is 1.0.

	%CVw				
	25%	30%	35%	40%	45%
90% CI	(0.83, 1.20)	(0.80, 1.24)	**(0.78, 1.29)**	(0.75, 1.33)	(0.73, 1.37)

9.2.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment is planned.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who signed the ICF
Safety	This population will be defined for each Part. • All randomised subjects who received at least one dose of study intervention.
PK	This population will be defined for each Part. • All subjects in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).

9.4. Statistical Analyses

9.4.1. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Population for each Part.

For each tablet strength (Part 1) and the fed and fasted state (Part 2), the plasma concentrations of daprodustat will be summarized by nominal time and individual

plasma concentration-time profiles and median/mean profiles will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. a log-linear plot).

For both Part 1 and Part 2, from the plasma concentration-time data, the following PK parameters will be determined by non-compartmental methods with Phoenix WinNonlin (version 6.3 or higher), as data permit: AUC(0-t), AUC(0-inf), Cmax, Tmax, t1/2, %AUCex, CL/F, Vz/F, kel, MRT, and correlation coefficient between time and log concentration of daprodustat for the points used in estimation of kel. The bioequivalence between the tablets will be confirmed with comparisons of the values of the logarithmic parameters [AUC(0-t) and Cmax].

Calculations will be based on the actual sampling times recorded during the study. PK data, except for the correlation coefficient between time and log concentration for the points used in estimation of kel, will be presented in graphical and/or tabular form and will be summarized descriptively, using summary statistics (n, arithmetic mean with associated 95% CI, standard deviation (SD), minimum, median, and maximum). Except for Tmax, geometric mean with associated 95% CI, SD on $\log_e$ scale and coefficient of variation between subjects (%CVb) will also be provided. Listings will be generated for each derived plasma PK parameters.

The following statistical analysis methods will be used to assess the bioequivalence in Part 1 and the food effect in Part 2:

Part 1

Statistical Analysis Methods

The exposure (Cmax and AUC(0-t)) of daprodustat will be assessed by using a mixed effect model as described below:

$\log_e$ (PK parameter) = $\beta_0 + \gamma_i + \tau_j + \pi_k + \alpha_l + \varepsilon_{ijkl}$

where β_0 is the intercept, γ_i is the random subject effect for ith subject, τ_j is the tablet strength effect (j = 2 mg or 4 mg), π_k is the period effect (k = period 1 or period 2), α_l is the group effect (l= group A or group B), and ε_{ijkl} is the random error. The Kenward-Roger degree of freedom approach will be used.

Point estimates ($\log_e\mu$) for the model-based means of PK parameters on $\log_e$ scale will be provided for each tablet strength and a point estimate of the mean difference between tablet strengths ($\log_e\mu_{2mg}$ - $\log_e\mu_{4mg}$) will be constructed along with the associated 90% CIs using the residual variances. The point estimates, the point estimate of the mean difference, and the associated 90% CIs on $\log_e$ scale will be exponentially back-transformed to obtain the model-based geometric means (μ), and the ratio for AUC(0-t) and Cmax (μ_{2mg}/μ_{4mg}) and the associated 90% CIs, respectively.

The bioequivalence will be evaluated using the following criteria of Japan BE guideline. Evaluate using criterion 1 first, if criteria are not met, criterion 2 is used.

- Criterion 1

  The 90% CIs of the ratios of the geometric means for AUC(0-t) and Cmax (μ_{2mg}/μ_{4mg}) are within the range of 0.80 - 1.25.

- Criterion 2

  The ratio of the geometric means for AUC(0-t) and Cmax (μ_{2mg}/μ_{4mg}) is within the range of 0.90 - 1.11.

Part 2

Statistical Analysis Methods

To estimate the food effect on PK parameters (Cmax and AUC(0-t)) of daprodustat, the PK parameters will be analysed using a mixed effect model as described as below:

$\log_e$ (PK parameter) = $\beta_0 + \gamma_i + \tau_j + \pi_k + \alpha_l + \varepsilon_{ijkl}$

where β_0 is the intercept, γ_i is the random subject effect for ith subject, τ_j is the food effect (j = fed or fasted), π_k is the period effect (k = period 1 or period 2), α_l is the group effect (l= group C or group D), and ε_{ijkl} is the random error. The Kenward-Roger degree of freedom approach will be used.

Point estimates ($\log_e\mu$) for the model-based means of PK parameters on $\log_e$ scale will be provided for the fed and fasted state and a point estimate of the mean difference between fed and fasted state ($\log_e\mu_{fed} - \log_e\mu_{fasted}$) will be constructed along with the associated 90% CIs using the residual variances. The point estimates, the point estimate of the mean difference, and the associated 90% CIs on $\log_e$ scale will be exponentially back-transformed to obtain the model-based geometric means (μ), the ratio for AUC(0-t) and Cmax (μ_{fed}/μ_{fasted}) and the associated 90% CIs, respectively.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population for each Part.

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

AEs, changes from baseline in clinical laboratory tests, vital signs (blood pressure, pulse and body temperature), and 12-lead ECG parameters will be summarized for each tablet strength (Part 1) and the fed or fasted state (Part 2). No statistical comparison will be made for the safety summaries.

9.5. Interim Analyses

No interim analysis is planned in this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (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 by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
  - Notifying the IRB of SAE or other significant safety findings as required by IRB procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB 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 authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

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

10.1.5. 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 (CSR). The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps

ensure the data provided by trial subjects are used to maximum effect in the creation of knowledge and understanding.

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.6. Data Quality Assurance

- All subject 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 review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects 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 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.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the electronic case report form (eCRF) that are transcribed from source documents must be consistent with

the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the list of the source documents.

10.1.8. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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 or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

10.1.9. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 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 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count Red blood cell (RBC) count White blood cell (WBC) count Hgb Hct	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC) Reticulocyte count (‰)	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Uric acid	Triglyceride (TG)	Total Cholesterol	Low-density lipoprotein (LDL)-cholesterol
	High-density lipoprotein (HDL)-cholesterol	Lactate dehydrogenase (LDH)	γ-glutamyltranspeptidase (GGT)	Creatine phosphokinase (CPK)
	Amylase	Chloride	Phosphorus	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine drug screen* (at minimum): Phencyclidines (PCP), Benzodiazepines (BZO), Cocaine (COC), Amphetamines (AMP), Tetrahydrocannabinol (THC), Opiates (OPI), Barbiturates (BAR), Tricyclic			

	antidepressants (TCA) • Immunological*: Serological test for syphilis (RPR and TP), HIV antigen/antibody, HBs antigen, HCV antibody, HTLV-1 antibody *: Screening only

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 7.1 and Appendix 4. All events of ALT ≥3 ×ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN 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).

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject'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 subject's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s)

present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 subject 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 (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject 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.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the subject'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 subject identifiers, with the exception of the subject 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 subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the 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 subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g. check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality)

within 72 hours of SAE entry into the eCRF.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in Appendix 5.

10.4. Appendix 4: Liver Safety Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</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 colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Report the event to GSK within 24 hours
• 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 chemistry event follow up assessments
• Monitor the subject 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 INR) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT ≥ 3xULN AND bilirubin < 2xULN and INR ≤ 1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24-72 hrs
• Monitor subjects weekly until liver chemistries resolve, stabilize or return to</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis within 24 hrs after last dose.
• CPK and 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 CRF
• Record use of concomitant medications on the concomitant medications CRF page including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake CRF page
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.
• Liver imaging (ultrasound, magnetic</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
within baseline	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 intervention for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (> 35% direct bilirubin) or ALT ≥ 3xULN and INR > 1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and Hepatitis B core (HBc) antibody; Hepatitis C ribonucleic acid (RNA); Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody.

10.5. Appendix 5: Country-specific requirements

SPONSOR INFORMATION

Sponsor Legal Registered Address:

GlaxoSmithKline K.K. (GSK)
8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
Study Director: PPD Head, Medicines Development, Clinical Pharmacology Office

Sponsor Contact Address:

Lead Author:
PPD
Manager, GlaxoSmithKline K.K., Medicines Development, Clinical Pharmacology Office

Sponsor's Emergency Contact Information (10:00 - 18:00, Monday to Friday, except national holidays and year-end and new-year holidays);
Medicines Development (Clinical Pharmacology Office), GlaxoSmithKline K.K.
TEL: PPD (direct dialling)
FAX: PPD

Contact Information at Night and on Holidays (Monday to Friday: 18:00 - 10:00, Saturday, Sunday, national holidays, year-end and new-year holidays)
PPD (mobile: PPD
PPD (mobile: PPD

GSK's Medical Monitor:

PPD
GlaxoSmithKline K.K. (GSK)
8-1, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 Japan
TEL: PPD (mobile)／PPD (direct dialling)
FAX: PPD

Medical Institution and Investigator:

PPD
Medical Co. SOUSEIKAI Fukuoka Mirai Hospital
5-1 Kashiiteriha 3-chome, Higashi-ku, Fukuoka 813-0017 Japan
TEL: PPD
FAX: PPD

Laboratories:

Clinical Laboratory
Medical Co. SOUSEIKAI Fukuoka Mirai Hospital
Person in charge: PPD
5-1 Kashiiteriha 3-chome, Higashi-ku, Fukuoka 813-0017 Japan
TEL: PPD
FAX: PPD

Serology tests (except HTLV-1)
Person in charge: PPD
Medical Co. SOUSEIKAI Hakata Clinic
6-18 Tenyamachi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

HTLV-1
Person in charge: PPD
LSI Medience Inc.
30-1 Shimura 3-chome, Itabashi-ku, Tokyo 174-8555, Japan
TEL: PPD
FAX: PPD

Bioanalysis
Person in charge: PPD
PPD
3230 Deming Way, Middleton, Wisconsin 53562 USA
TEL: PPD
FAX: PPD

Contract research organization:

Role: Study Monitoring
Person in charge (Monitor Leader): PPD
Mediscience Planning Inc.
6-17 Tenyamachi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (Protocol & ICF)
Person in charge: PPD
Mediscience Planning Inc.
6-17 Tenyamachi, Hakata-ku, Fukuoka 812-0025 Japan
TEL: PPD
FAX: PPD

Role: Medical Writing (Clinical Study Report)
Person in charge: PPD
Mediscience Planning Inc.
8-10 Toranomon 2-chome, Minato-ku, Tokyo 105-0001 Japan
TEL: PPD
FAX: PPD

Role: Pharmacokineic Parameter Derivation
Person in charge: PPD
Mediscience Planning Inc.
HF Nihonbashi-hamacho Bldg.2-1, Nihonbashi-hamacho 1-chome, Chuo-ku,
Tokyo 103-0007 Japan
TEL: PPD
FAX: PPD

Role: Data Loading
Person in charge: PPD

Mediscience Planning Inc.
HF Nihonbashi-hamacho Bldg.2-1, Nihonbashi-hamacho 1-chome, Chuo-ku,
Tokyo 103-0007 Japan
TEL: PPD
FAX: PPD

10.6. Appendix 6: Abbreviations and Trademarks

Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMP	Amphetamines
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
AUC(0-t)	Area under the concentration-time curve from time 0 to the last measurable concentration
AUC(0-inf)	Area under the concentration-time curve from time 0 to infinite
%AUCex	Percentage of AUC for time t to infinity by extrapolation to AUC(0-inf)
BAR	Barbiturates
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BMI	Body mass index
BUN	Blood urea nitrogen
BZO	Benzodiazepines
CFR	Code of Federal Regulation
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic kidney disease
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed drug concentration
COC	Cocaine
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case report form
CSR	Clinical study report
CV	Cardiovascular
CVb	Coefficient of variation between subjects
CVw	Coefficient of variation within subject
CYP	Cytochrome P450
ECG	Electrocardiogram
ECHO	Echocardiograph
eCRF	Electronic case report form
EPO	Erythropoietin
GCP	Good Clinical Practice
GGT	γ -glutamyltranspeptidase
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
Hct	Haematocrit
HCV	Hepatitis C virus
HDL	High-density lipoprotein
Hgb	Haemoglobin
HIF	Hypoxia inducible factor

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HTLV-1	Human T-cell lymphotropic virus type 1
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
kel	Elimination rate constant
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
log	Logarithm
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular Hgb
MCHC	Mean corpuscular Hgb concentration
MCV	Mean corpuscular volume
MI	Myocardial infarction
MRT	Mean residence time
MSDS	Material Safety Data Sheet
msec	Millisecond
NQ	Non-quantifiable
NYHA	New York Heart Association
OATP	Organic anion transporter polypeptide
OPI	Opiates
PAH	Pulmonary artery hypertension
PASP	Pulmonary artery systolic pressure
PCI	Potential clinical importance
PCM	Progressive cardiomyopathy
PCP	Phencyclidines
pH	Hydrogen-ion exponent
PHD	prolyl-4-hydroxylase domain enzyme
PK	Pharmacokinetics
PRVP	Peak right ventricular pressure
QTc	QT correction
QTcF	QT duration corrected for heart rate by Friderician formula
RBC	Red blood cell
rhEPO	Recombinant human erythropoietin
RNA	Ribonucleic acid
RPR	Rapid Plasma Reagin
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions

t1/2	Terminal half-life
TCA	Tricyclic antidepressants
TG	Triglyceride
THC	Tetrahydrocannabinol
Tmax	Time to maximum observed drug concentration
TP	Treponema pallidum
TPHA	Treponema pallidum haemagglutination test
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
Vz/F	Apparent volume of distribution after oral administration
WBC	White blood cell

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