TITLE PAGE

Protocol Title: A two-part, randomized, double-blind, single-dose, crossover study to compare formulations produced by two methods of manufacture for bioequivalence and dissolution in healthy adult volunteers

Protocol Number: 213022

Compound Number or Name: GSK1278863

Study Phase: Phase 1

Short Title: BE and Dissolution PK Study

Sponsor Name and Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

IND: 101,291

Approval Date: 21-AUG-2020

PPD

From: PPD
Sent: Monday, August 24, 2020 7:35 PM
To: PPD
Subject: FW: Prot-213022-sponsign

From: Alex Cobitz PPD
Sent: Friday, August 21, 2020 1:59 PM
To: PPD
Cc:
Subject: RE: Prot-213022-sponsign

PPD ,

I approve.

Alex

From: PPD
Sent: Friday, August 21, 2020 12:36 PM
To: Alex Cobitz PPD
Subject: Prot-213022-sponsign

Dear Sponsor,

To approve the clinical protocol indicated below, reply to this email and state your approval.

PROTOCOL NUMBER: 213022

DOCUMENT IDENTIFIER: 2020N427368_00

PROTOCOL TITLE: A two-part, randomized, double-blind, single-dose, crossover study to compare formulations produced by two methods of manufacture for bioequivalence and dissolution in healthy adult volunteers

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Alexander R. Cobitz, M.D., Ph.D
Title of Sponsor Signatory:	Executive Director, Clinical Development

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A two-part, randomized, double-blind, single-dose, crossover study to compare formulations produced by two methods of manufacture for bioequivalence and dissolution in healthy adult volunteers

Short Title: BE and Dissolution PK study

Rationale: Daprodustat tablets manufactured via Process 1 (twin screw granulation) have been administered in the daprodustat Phase III program and with the intent to be commercialized. Daprodustat tablets produced by a second process (Process 2, using high shear wet granulation) are being developed to enable manufacturing flexibility and add supply capacity.

To support the development of daprodustat tablets via process 2, the proposed study, Study 213022, will be conducted and will consist of two parts, Part A and Part B. Part A and Part B will be conducted independently. Results from Part A will not be required prior to the start of Part B.

Part A will be a three-treatment period, period balanced crossover design to characterize the pharmacokinetic (PK) profile of 4 mg reference tablet made by Process 1 compared to two sets of 4 mg tablets made by Process 2 each with successively differentiated dissolution profiles. PK results from Part A will be used to justify how much variation in dissolution profiles may be acceptable and to establish the clinical relevance of dissolution profiles in order to obtain regulatory flexibility in the dissolution specification.

Part B will be a two-treatment period, period balanced crossover design to assess the PK bioequivalence (BE) of tablets produced by Process 1 and Process 2 following administration of a single dose of 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg of daprodustat in 5 groups of healthy participants. The purpose of Part B is to demonstrate BE for each of the dose strengths. The results from Part B will be used to support the global file and supplying Japan with daprodustat manufactured by the new process for commercial use.

Objectives and Endpoints:

Part A

Objectives	**Endpoints**
Primary	
• To characterize single dose PK profile of 4 mg daprodustat tablets with two different dissolution profiles made by Process 2 relative to the reference 4 mg daprodustat tablet made by Process 1	Area under the concentration-time curve [AUC (0-t)] and Maximum observed concentration (C_{max}) of daprodustat
Secondary	
• To assess remaining daprodustat pharmacokinetic parameters	AUC (0-inf), Time of occurrence of Cmax (T_{max}), half life ($t_{1/2}$), clearance/fraction (CL/F) and volume/fraction (V/F) of daprodustat
Safety	
• To evaluate the safety and tolerability of single doses of daprodustat made by Process 2 relative to daprodustat made by process 1	Safety and tolerability will be assessed by clinical data from adverse event (AE) reporting, vital signs, and clinical laboratory tests

Part B

Objectives	**Endpoints**
Primary	
• To establish BE between daprodustat tablets made by two different manufacturing processes, Process 1 and Process 2, for the following dose strengths administered as a single dose: • 1 mg	AUC (0-t) and C_{max} of daprodustat

Objectives	**Endpoints**
• 2 mg • 4 mg • 6 mg • 8 mg	
Secondary	
• To assess remaining daprodustat PK parameters	AUC (0-inf), T_{max}, $t_{1/2}$, CL/F and V/F of daprodustat
Safety	
• To evaluate the safety and tolerability of single doses of daprodustat made by Process 2 relative to daprodustat made by Process 1	Safety and tolerability will be assessed by clinical data from adverse event (AE) reporting, vital signs, and clinical laboratory tests

Overall Design: Part A of this randomized, double-blind, single-dose, 3-period crossover study in healthy volunteers will compare the PK parameters and safety of 4 mg of daprodustat tablets with two different dissolution profiles made by Process 2 relative to the reference 4 mg daprodustat tablet made by Process 1.

Part B of this randomized, double-blind, single-dose, 2-period crossover study in healthy volunteers will establish the BE and compare the safety of daprodustat tablets produced by two different manufacturing processes (Process 1 and Process 2) for each of the following dose strengths: 1 mg, 2 mg, 4 mg, 6 mg, and 8mg. Participants will be randomized to only one dose strength.

Disclosure Statement: This is comprised of two discrete Parts. Part A is a 3-period cross over evaluating relative bioavailability. Part B is a 2-period cross over evaluating bioequivalence. Participants will participate in Part A or Part B, but not both.

Number of Participants:

The expected number of participants who will complete Part A is 30.

The expected number of participants who will complete Part B is 190.

The expected number of participants who will complete the study is 220.

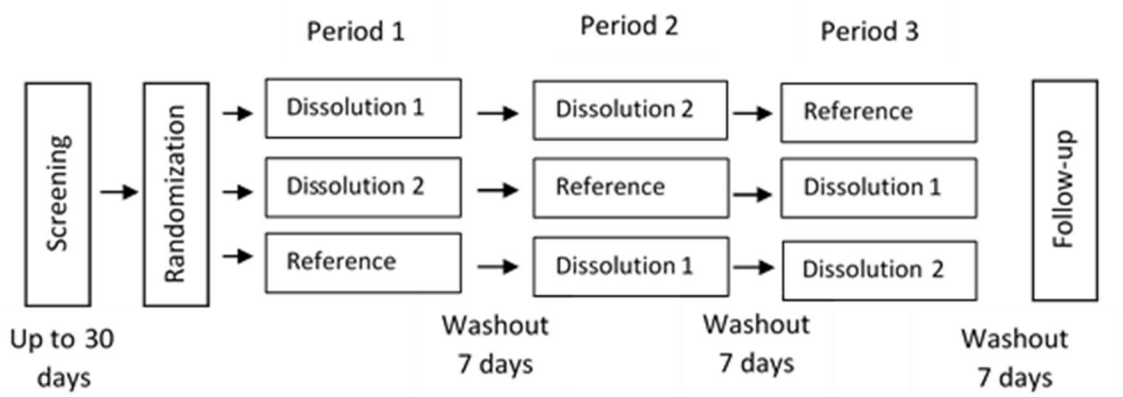
Intervention Groups and Duration: Part A participants can expect a study duration of approximately 56 days from screening through the follow up visit; Part B participants can expect a study duration of approximately 49 days from screening through the follow up visit.

For both Part A and Part B, the screening period is up to 30 days, each single-dose treatment period is up to 48h, each washout period between treatments (and between the last dose and follow up) is at least 7 days.

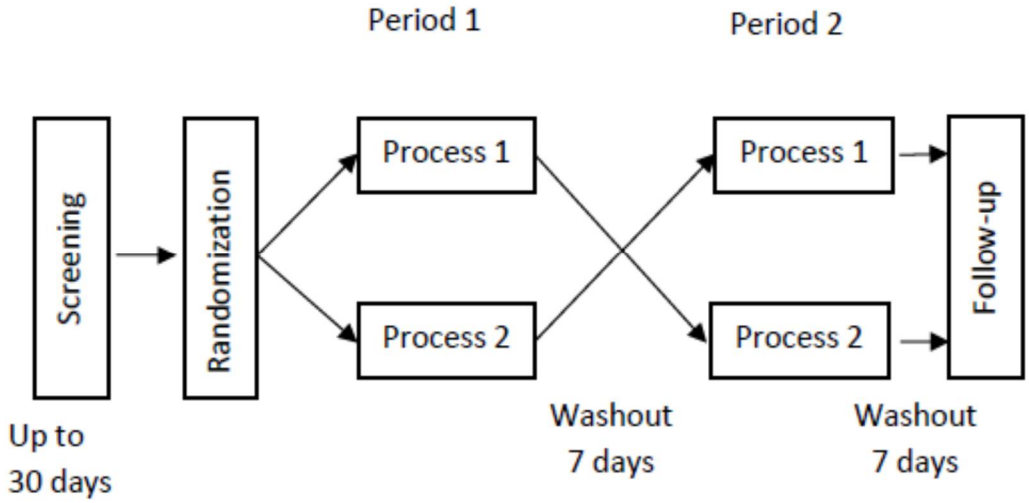
Data Monitoring or Other Committee: No

1.2. Schema

Part A study schematic



Part B study schematic:



1.3. Schedule of Activities (SoA)

Part A -OR- Part B

Procedure	Screen[1]	Intervention (Part A Periods 1, 2, & 3 OR Part B Periods 1 & 2)[10]												Follow-up[9]
		Day -1	Day 1										Day 2	
			Pre-dose	0h	0.5h	1h	2h	2.5h	3h	4h	6h	8h	12h	24h	
Informed Consent	X														
Inclusion / Exclusion[2]	X	X													
Demography	X														
Physical Examination[3]	X	X													
12-Lead electrocardiogram (ECG)	X														
Vital Signs[4]	X	X	X												X
Clinical Laboratory Test[5]	X	X													X
Pregnancy Test[6]	X	X													X
Urine Drug Screen and Alcohol Screen[7]	X														
Randomization		X													
Study Intervention Dose[8]				X											
PK Blood Sampling			X		X	X	X	X	X	X	X	X	X	X	
AE/Serious AE	←----------														----------→
Concomitant Medication Review	←----------														----------→
Admission to Unit		X													
Discharge from Unit														X	
Outpatient Visit	X														X
COVID-19 testing (PCR or antigen)	X	X[12]	<----------Ad hoc based on continuous review----------												>

[1] Within 30 days of Day 1, Period 1
[2] Re-check eligibility at Day -1 (admission to Unit)
[3] Brief Physical Examination on Day -1
[4] Body temperature, pulse, systolic & diastolic blood pressure (semi-supine)

[5] Hematology, clinical chemistry (including liver), and urinalysis
[6] Urine or serum per site standard; females only
[7] Alcohol screening can be performed via urine or breathalyser per site standard
[8] Time 0 is the time of study interventional drug dosing, and all subsequent timed assessments are calculated from Time 0.
[9] 7 (±1) days from dose day Period 3, Part A -**OR-** 7 (± 1) days from dose day Period 2, Part B. Same assessments will be performed for early withdraw visit.
[10] A minimum of 7 days is required between each treatment-period's dosing, i.e., at least 7 days between Period 1 and Period 2, and between Period 2 and Period 3 dosing in Part A, and 7 days between Period 1 and Period 2 dosing in Part B
12 COVID-19 PCR or antigen testing may be done prior to Day -1 (admission to the study unit) such that the results are timed to arrive just prior to admission, ideally within 72h of admission to the study unit.

2. INTRODUCTION

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

Daprodustat (GSK1278863) is a small molecule, oral inhibiter of the HIF-PHD enzymes which may present several important advantages over other erythropoietin stimulating agents (ESAs). It is an oral medication and does not require cold-chain storage as do some ESAs, thus increasing ease of use for patients. Moreover, data indicate that daprodustat can effectively raise hemoglobin (Hgb) concentrations with lower EPO levels than those observed after administration of ESAs [Provenzano, 2011]. CCI [redacted]

2.1. Study Rationale

Daprodustat tablets manufactured via Process 1 have been administered in the daprodustat Phase III program and with the intent to be commercialized. Daprodustat tablets produced by a second process (Process 2) are being developed to enable manufacturing flexibility and add supply capacity.

To support the development of daprodustat tablets via Process 2, the proposed study, Study 213022, will be conducted and will consist of two parts, Part A and Part B. Part A and Part B will be conducted independently. Results from Part A will not be required prior to the start of Part B.

Part A will be a three-treatment period, period balanced crossover design to characterize the pharmacokinetic (PK) profile of 4 mg reference tablet made by Process 1 compared to two sets of 4 mg tablets made by Process 2 each with successively differentiated dissolution profiles. PK results from Part A will be used to justify how much variation in dissolution profiles may be acceptable and to establish the clinical relevance of dissolution profiles in order to obtain regulatory flexibility in the dissolution specification.

Part B will be a two-treatment period, period balanced crossover design to assess the PK bioequivalence (BE) of tablets produced by Process 1 and Process 2 following

administration of a single dose of 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg of daprodustat in 5 groups of healthy participants. The purpose of Part B is to demonstrate BE for each of the dose strengths. The results from Part B will be used to support global file and supplying Japan with daprodustat manufactured by the new process.

2.2. Background

Daprodustat is a HIF-PHI currently being investigated as a treatment for anemia associated with CKD in both dialysis dependent (DD) and non-dialysis dependent (ND) participants, with adequate safety and efficacy demonstrated in clinical trials of up to 24 weeks' duration. Both pre-clinical and clinical data show that daprodustat stimulates EPO production resulting in increased erythropoiesis and elevation in Hgb concentrations. These increases in Hgb are achieved with peak EPO levels substantially lower than those observed with ESAs [Hofherr, 2018] [Holdstock, 2016]. Daprodustat is approved in Japan.

Data from completed clinical and pre-clinical studies are provided in the Daprodustat Investigator Brochure (IB) [GlaxoSmithKline Document Number RM2008/00267/11, 2020].

Considering the global COVID-19 pandemic, all participants will be screened for COVID-19 prior to, during and at the end of the study period. Please see further details for risk assessment and mitigation strategy below.

2.3. Benefit/Risk Assessment

Pre-clinical and clinical data to date have not identified prohibitive risks associated with daprodustat at the exposures planned for this study in healthy subjects. Overall, the compound has been generally well tolerated with no clinically significant safety-related findings observed to date following administration in completed studies of up to 500 mg single dose and up to 100 mg once daily for 2 weeks in healthy subjects and up to 24 mg once daily for 12 months in CKD patients.

Based on the non-clinical studies, the primary areas of interest for daprodustat are related to gastrointestinal (GI) tolerability (e.g., stomach erosions with bleeding) and potential for thrombosis with ischemia secondary to erythrocytosis (excessive erythropoiesis).

In addition, several events of special interest have been identified based on clinical experience with ESAs including increased risk of cancer related morbidity and mortality; increased risk of major cardiovascular events (e.g., stroke, myocardial infarction, congestive heart failure); and worsening hypertension.

Lastly based on what is currently known of the possible roles for HIF-regulated pathways in mediating hypoxia-associated pathophysiology, pulmonary artery hypertension and tissue neo-vascularization (e.g., retinal, joint synovium) have also been identified as areas of special interest.

Where appropriate, specific eligibility criteria or monitoring instructions relevant to these theoretical concerns are included in the study protocol.

More detailed information about the known and expected benefits and risks and reasonably expected adverse drug reactions of daprodustat may be found in the Investigator's Brochure [GlaxoSmithKline Document Number RM2008/00267/11, 2020].

2.3.1. Benefit Assessment

Study participants will not derive any benefit from taking the investigational product during the study.

Study participants will receive study evaluations and assessments and be made aware of any findings that may affect decisions about their individual health.

By participating, study participants will be contributing to the process of developing this clinically-valuable oral alternative to rhEPO for the treatment of anemia in CKD.

Study participants may receive a stipend for the inconveniences of study participation, participant to local policies and ethical (institutional review board) approval.

2.3.2. Overall Benefit: Risk Conclusion

Overall, the available data from non-clinical and clinical studies has not identified prohibitive risks associated with daprodustat at the exposures planned for this study. While there are a number of important potential risks identified for daprodustat, these can be addressed with proper participant selection, close safety monitoring, and specific risk characterization and mitigation.

3. OBJECTIVES AND ENDPOINTS

Part A

Objectives	**Endpoints**
Primary	
• To characterize single dose PK profile of 4 mg daprodustat tablets with two different dissolution profiles made by Process 2 relative to the reference 4 mg daprodustat tablet made by Process 1	Area under the concentration-time curve [AUC (0-t)] and Maximum observed concentration (C_{max}) of daprodustat
Secondary	
• To assess remaining daprodustat pharmacokinetic parameters	AUC (0-inf), Time of occurrence of Cmax (T_{max}), half life ($t_{1/2}$), clearance/fraction (CL/F) and volume/fraction (V/F) of daprodustat
Safety	
• To evaluate the safety and tolerability of single doses of daprodustat made by Process 2 relative to daprodustat made by process 1	Safety and tolerability will be assessed by clinical data from adverse event (AE) reporting, vital signs, and clinical laboratory tests

Part B

Objectives	**Endpoints**
Primary	
• To establish BE between daprodustat tablets made by two different manufacturing processes, Process 1 and Process 2, for the following dose strengths administered as a single dose: • 1 mg	AUC (0-t) and C_{max} of daprodustat

Objectives	Endpoints
• 2 mg • 4 mg • 6 mg • 8 mg	
Secondary	
• To assess remaining daprodustat PK parameters	AUC (0-inf), T_{max}, $t_{1/2}$, CL/F and V/F of daprodustat
Safety	
• To evaluate the safety and tolerability of single doses of daprodustat made by Process 2 relative to daprodustat made by Process 1	Safety and tolerability will be assessed by clinical data from adverse event (AE) reporting, vital signs, and clinical laboratory tests

4. STUDY DESIGN

Part A of this clinical trial is a bioavailability study.

Part B of this clinical trial is a bioequivalence study. As such, reserve samples from this study must be retained (Appendix 7).

4.1. Overall Design

Part A of this randomized, double-blind, single-dose, 3-period crossover study in healthy volunteers will compare the PK parameters and safety of 4 mg of daprodustat tablets with two different dissolution profiles made by Process 2 (high shear wet granulation) relative to the reference 4 mg daprodustat tablet made by Process 1 (twin screw granulation).

Part B of this randomized, double-blind, single-dose, 2-period crossover study in healthy volunteers will establish the BE and compare the safety of daprodustat tablets produced by two different manufacturing processes (Process 1 and Process 2) for each of the following dose strengths: 1 mg, 2 mg, 4 mg, 6 mg, and 8mg.

Part A and B will be conducted independently, i.e., Part B starting will not await Part A finishing.

4.2. Scientific Rationale for Study Design

Part A will be utilizing a randomized, three-period, single dose crossover design which is well-recognized for assessing PK properties of tablets with two different dissolution profiles.

Part B will be utilizing a randomized, two-period, single dose crossover design which is well established for the demonstration of BE between two drug products according to BE guidance from Japan (MHLW, 2012) and the United States (FDA, 2014).

The double-blind design will allow for the appropriate assessments of the safety/tolerability of the two products with as little bias as possible.

4.2.1. Participant Input into Design

Direct participant input into the study design has not been solicited. Measures to reduce participant inconvenience have been incorporated, balanced with study output requirements, such as flexible scheduling at the research unit, provision of in-dwelling catheter for blood sampling, and stipend for participant time / inconvenience.

4.3. Justification for Dose

The doses 1 mg, 2 mg, 4 mg 6 mg, and 8 mg are selected for the study based on the dosing of daprodustat in the clinical program and specifically to support the bridging strategy for Process 1 and Process 2 globally.

4.4. End of Study Definition

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

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial.

This applies to both part A and B separately.

5. STUDY POPULATION

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

Approximately 48 healthy volunteer participants may be screened to obtain 36 participants eligible for randomization for Part A. The expected number of participants who will complete Part A is 30.

Approximately 275 healthy volunteer participants may be screened to obtain 210 participants eligible for randomization for Part B. The expected number of participants who will complete Part B is 190 (38 per dose cohort).

Approximately 323 healthy volunteer participants may be screened to obtain 246 participants eligible for randomization. The expected number of participants who will complete the study is 220.

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

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

Weight

3. Body weight ≥ 45 kg and body mass index (BMI) within the range 19-31 kg/m^2 (inclusive).

Sex

4. Male or female

   Female participants: A female participant is eligible to participate if she is not breastfeeding, and at least one of the following applies (see Appendix 4):

   (i) Not pregnant as confirmed by pregnancy testing

   (ii) Not a woman of childbearing potential (WOCBP)

   (iii) For WOCBP that are currently utilizing a highly-effective contraceptive method prior to enrolment, agrees to follow the contraceptive guidance during the treatment period to the follow-up visit.

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 informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions Any medical condition in a prospective study participant not meeting the definition above, Type of Participant and Disease Characteristics.

a. History of malignancy within the prior 2 years OR currently receiving treatment for cancer. Note: the ONLY exception is localized squamous- or basal-cell carcinoma of the skin definitively treated 12 weeks or more prior to enrolment.

b. **Prior/Concomitant Therapy** Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and Medical Monitor the medication will not interfere with the study procedures or compromise participant safety

Prior/Concurrent Clinical Study Experience

c. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 30 days prior to Day 1 in this study
    - Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day

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

e. Part A participants may not participate in Part B, and Part B participants may not participate in Part A if enrolment is concurrent or overlaps.

Diagnostic assessments

f. Positive pre-study drug/alcohol screen

g. Regular use of known drugs of abuse

h. A positive laboratory confirmation of COVID-19 infection, or high clinical index of suspicion for COVID-19

Other Exclusions

i. Regular alcohol consumption within 6 months prior to the study defined as:
    - average weekly intake of >[14] units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.

j. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening

k. 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

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Both Part A and Part B will be conducted under fasting conditions (after an overnight fast)
- Participants will refrain from any food and drink (except water) at least 10 h before dosing and 4 h after dosing of the investigational product. Water is allowed ad libitum at all times.
- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 24 hours before the start of study intervention until after the final dose.

5.3.2. Caffeine, Alcohol, and Tobacco

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

5.3.3. Activity

- Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests, for 24 hours prior to admission to the clinical research unit, and while in the clinical research unit. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened participant to consultation with the GSK Medical Monitor. In the case of a re-screen, the participant should be assigned a new participant number.

5.5. Self-isolation

Where it is site policy to do so, participants will be asked to attend the Unit a few days prior to admittance to receive a COVID-19 test (Polymerase chain reaction [PCR] or antigen). Once tested, participants will be asked to self-isolate at home until their admittance to the Unit for their next dosing period.

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 participant according to the study protocol.

6.1. Study Intervention(s) Administered

Part A

Part A will include a screening visit and 3 treatment periods. These treatment periods, Periods 1, 2 and 3, will be conducted in the same manner; and there will be a minimum of a 7-day washout period between treatment periods. A single dose of investigational product will be administered for each treatment. The screening visit will be conducted within 30 days prior to the first dose in Period 1.

A follow up visit will occur 7 days after administration of the last dose of study medication in Period 3.

- Eligible participants will be enrolled and randomized in a 1:1 ratio to a treatment sequence of either Regimen A, B, or C:

Regimen	Period 1	Period 2	Period 3
A	Daprodustat 4 mg Dissolution profile #1 from Process 2	Daprodustat 4 mg Dissolution profile #2 from Process 2	Daprodustat 4 mg Reference Process 1
B	Daprodustat 4 mg Dissolution profile #2 from Process 2	Daprodustat 4 mg Reference Process 1	Daprodustat 4 mg dissolution profile #1 from Process 2
C	Daprodustat 4 mg Reference Process 1	Daprodustat 4 mg Dissolution profile #1 from Process 2	Daprodustat 4 mg Dissolution profile #2 from Process 2

The total study duration for each participant will be approximately 8 weeks (minimum) for Part A. All participants will receive study treatment according to the randomization schedule.

Part B

For each of the dose strengths being evaluated, the study will be setup and conducted in the same manner, but a different set of healthy volunteers will be recruited. A total of 5 groups of healthy volunteers will be recruited for the respective dose strengths being evaluated. A single dose will be administered for all dose strengths.

Evaluation of each dose strength will include a screening visit and 2 treatment periods; there will be a minimum of a 7-day washout period between study treatment administration in Period 1 and Period 2. The screening visit will be conducted within 30 days prior to the first dose in Period 1 for each dose strength.

There will be a post-treatment follow-up visit 7 days after participants receive last dose of study medication in the second treatment period.

- For the 1 mg dose strength, eligible participants will be enrolled in the study and randomized in a 1:1 ratio to a treatment sequence of either Regimen D or E:

Regimen	Period 1	Period 2
D	Daprodustat 1 mg Process 2	Daprodustat 1 mg Process 1
E	Daprodustat 1 mg Process 1	Daprodustat 1 mg Process 2

- For the 2 mg dose strength, eligible participants will be enrolled in the study and randomized in a 1:1 ratio to a treatment sequence of either Regimen F or G:

Regimen	Period 1	Period 2
F	Daprodustat 2 mg Process 2	Daprodustat 2 mg Process 1
G	Daprodustat 2 mg Process 1	Daprodustat 2 mg Process 2

- For the 4 mg dose strength, eligible participants will be enrolled in the study and randomized in a 1:1 ratio to a treatment sequence of either Regimen H or I:

Regimen	Period 1	Period 2
H	Daprodustat 4 mg Process 2	Daprodustat 4 mg Process 1
I	Daprodustat 4 mg Process 1	Daprodustat 4 mg Process 2

- For the 6 mg dose strength, eligible participants will be enrolled in the study and randomized in a 1:1 ratio to a treatment sequence of either Regimen J or K:

Regimen	Period 1	Period 2
J	Daprodustat 6 mg Process 2	Daprodustat 6 mg Process 1
K	Daprodustat 6 mg Process 1	Daprodustat 6 mg Process 2

- For the 8 mg dose strength, eligible participants will be enrolled in the study and randomized in a 1:1 ratio to a treatment sequence of either Regimen L or M:

Regimen	Period 1	Period 2
L	Daprodustat 8 mg Process 2	Daprodustat 8 mg Process 1
M	Daprodustat 8 mg Process 1	Daprodustat 8 mg Process 2

The total study duration for each participant will be approximately 7 weeks (minimum) for Part B. All participants will receive study treatment according to the randomization schedule.

Daprodustat will be supplied as film coated tablets for oral administration containing 1, 2, 4, 6, or 8 mg of daprodustat. The doses, tablet size, and description are provided in Table 1. Participants are to take the daprodustat tablet(s) daily with water, and these tablets can be taken without regard to food.

Table 1 Description of Daprodustat and Placebo Tablets

Tablet size	Dose	Description
7 mm	Daprodustat 1 mg, 2 mg, 4 mg	7.0 mm round, compound radius, white film coated tablets
9 mm	Daprodustat 6 mg and 8 mg	9.0 mm round, compound radius, white film coated tablets

6.2. Preparation/Handling/Storage/Accountability

The Investigator will be supplied with investigational products in amounts that exceed the quantity needed to perform the clinical trial. Please see the Study Reference Manual for further information.

i. The investigator or designee must confirm 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.

- Only participants enrolled in the study may receive study intervention and only authorized 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 labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

  - Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study using Pre-Coded Randomization provided to site	On Day (-1), participants will be assigned a unique number (randomization number) in ascending numerical order at each study site(s). The randomization number encodes the participant's assignment to one of the 3 regimen sequences of Part A, or one of the 2 regimen sequences for a given dose strength of Part B in the study, according to the randomization schedule generated prior to the study by the Statistics Department at GSK, or designee. Participants randomized to Part B will only be randomized to one dose strength. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study. A central randomization approach will be used.

Blinded study with unblinded site pharmacist who is dispensing drug	Participants will be randomized in a [1:1] ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the dispensation of the study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

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GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

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

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer, i.e., rifampin/rifampicin, a strong inducer of CYP2C8) 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.

Because daprodustat is a CYP2C8 substrate, examples of prescription drugs listed below will be prohibited as indicated above (also refer to exclusion criteria Section 5.2):

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

Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

6.6. Dose Modification

No dose modifications will be made during this bioequivalence study.

6.7. Intervention after the End of the Study

Since the study is a pharmacokinetic study in healthy participants, there are no arrangements for post-study treatment of a medical condition.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will not remain in the study after his or her discontinuation/early withdrawal assessments. See the SOA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

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

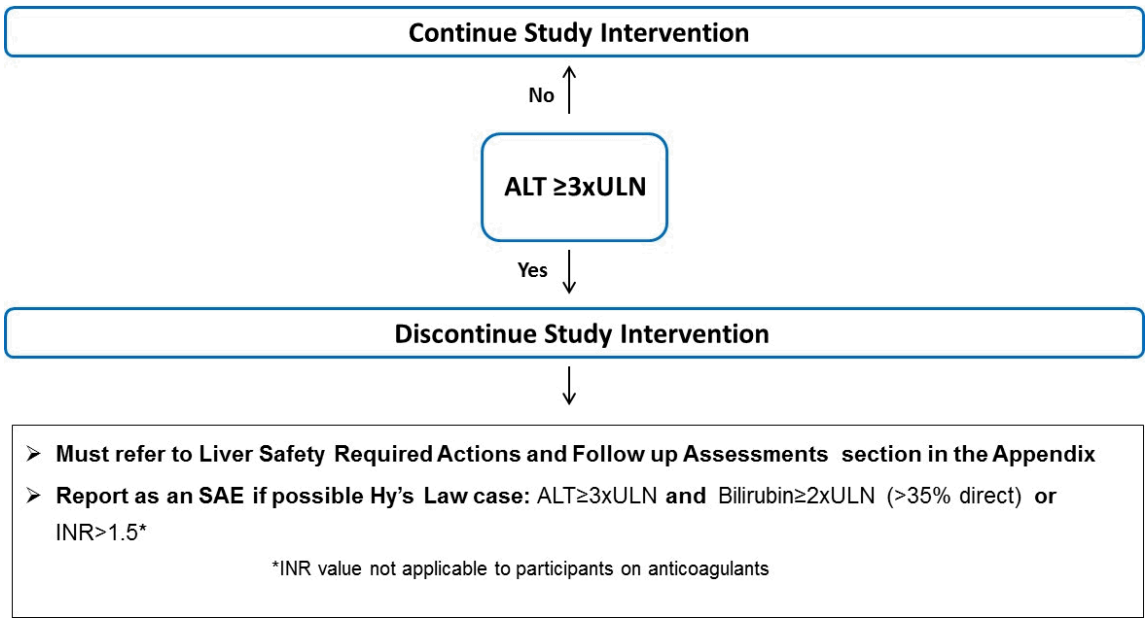
Discontinuation of study intervention for abnormal liver tests is required when:

1. a participant meets one of the conditions outlined in the algorithm

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

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

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Appendix 5 for required Liver Safety Actions and Follow up Assessments

7.1.2. Other Stopping Criteria

A participant must permanently stop dosing for the pre-specified reasons below.

- Hemoglobin actual value >1 g/dL over 2 weeks following dosing
- Becomes pregnant
- Diagnosis of cancer (new or recurrent), with the exception of localized squamous cell or basal cell carcinoma of the skin
- Need for more than 14 days use of prohibited medication (Section 6.5.)

7.1.3. Temporary Discontinuation

There is no provision in this relative and bioequivalence study for a temporary discontinuation per se. Withdrawal from study intervention (i.e., the decision of either the participant or the Principal Investigator to stop dosing or not complete all dosing occasions) will require the participant's withdrawal from the study (see Section 7.2).

7.2. Participant Discontinuation/Withdrawal from the Study

- If a participant develops COVID-19 like symptoms during the course of the study the following actions should be taken:
    - Participants who develop a high clinical index of suspicion for COVID-19 disease should be isolated and tested for COVID-19 in accordance with site procedures.
    - Assessments should be continued per the protocol during this period; withdrawal of participants from the study will be at the discretion of the Principal Investigator but should first be discussed and agreed with the GSK Medical Monitor.
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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 or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study are handled as stated in Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing 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 participant 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 participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Safety Assessments

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

8.1.1. Physical Examinations

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

8.1.2. Vital Signs

- Oral temperature, pulse, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Vital signs measurements taken from the device can be repeated once if clinically significant changes or a machine error occurs. If the measurements continue to be out of range, these will be repeated at the investigator's discretion.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and taken prior to blood collection for laboratory tests.
- For all vital signs (to be taken before blood collection for laboratory tests), a single measurement of systolic and diastolic blood pressure and pulse will be performed as outlined in the SoA (see Section 1.3).

8.1.3. Electrocardiograms

- A single 12-lead ECG (to be taken before vital signs and blood collection for laboratory tests) will be obtained, in the semi-supine position after 5 minutes rest, as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals.

8.1.4. 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 AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention 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 time period judged reasonable by the investigator, the etiology 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.

8.2. Adverse Events and Serious Adverse Events

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

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

The investigator and any 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 participant to discontinue the study (see Section 7).

8.2.1. 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 (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- 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 unless they are assessed as related to study participation.

- 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 the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.2.2. 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 participant is the preferred method to inquire about AE occurrence.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.2.6.), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices 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 SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 7 days after the last dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.2.6. Adverse Events of Special Interest

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

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

8.3. Treatment of Overdose

For this study, any dose of daprodustat greater than the dose indicated within the treatment arm within a 24-hour time period ± 1 hour will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.

1. Closely monitor the participant for AE/SAE and laboratory abnormalities until daprodustat can no longer be detected systemically (at least 2 days).
2. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
3. 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 participant.

8.4. Pharmacokinetics

Blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of daprodustat as specified in the SoA.

- A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling 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.
- 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.
- Samples will be used to evaluate the PK of daprodustat. Each plasma sample will be divided into 2 aliquots (1 each for PK, and a back-up). Samples collected for analyses of daprodustat plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Part A:

There will be no formal statistical hypotheses for part A.

The comparison of two 4 mg daprodustat tablets with different dissolution profiles relative to the reference 4 mg daprodustat tablet made by Process 1 will be performed using descriptive statistics. The ratio of the geometric means (μ dissolution 1, 2/μ Process 1) for AUC(0-t) and Cmax will be calculated and 90% confidence interval (CI) will be generated as part of the descriptive statistics.

Part B:

For each tablet strength of daprodustat (1 mg, 2 mg, 4 mg, 6 mg, and 8mg), the following statistical hypotheses will be used:

The bioequivalence between daprodustat manufacturing process 1 and process 2 will be assessed using a framework of statistical hypothesis testing. The ratio of the geometric means (μ Process 2 /μ Process 1) for AUC(0-t) and Cmax is the measure in the following statistical hypotheses:

H0 (null hypothesis) : μ Process 2 /μ Process 1 $\leq$ 0.80 or μ Process 2 /μ Process 1 $\geq$ 1.25,

H1 (alternative hypothesis) : 0.80 < μ Process 2 /μ Process 1 < 1.25

Bioequivalence will be determined if the 90% confidence interval (CI) of μ Process 2 /μ Process 1 falls within a range of 0.80 to 1.25. This is equivalent to carrying out two one-sided tests of hypothesis at the 5% level of significance.

A demonstration of bioequivalence requires the null hypothesis for both AUC and Cmax to be rejected. All doses must meet the criteria for bioequivalence to be concluded.

9.2. Sample Size Determination

Part A:

A total sample size of 30 participants (10 participants per regimen) is recommended for the 3-way crossover design of Part A.

With a coefficient of variation within participant (%CVw) of 25% (based on Cmax having the highest CV), N=30 in a 3x3 crossover design, and assuming an observed ratio of 1.0, the estimated half-width of the 90% CI for the comparison of the ratio of the PK parameter will be 11% of the point estimate. On the normal scale, this would result in a 90% CI of (0.90, 1.11)

Additional participants may be recruited as replacement for withdrawn participants including those impacted by COVID-19.

Part B:

A total sample size of 190 participants is required for Part B. A sample size of 38 participants (19 participants per regimen) is required to complete each of the five bioequivalence 2-way crossover design comparison of doses 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg of daprodustat.

Sample size calculation assumes a true ratio is 1.0, the coefficient of variation within participant (%CVw) of 25% (based on Cmax having the highest CV), power of 97%, and a regulatory definition of BE criteria; the 90% confidence interval (CI) of the ratio for Cmax between manufacturing processes should lie within the range of 0.80-1.25.

Additional participants may be recruited as replacement for withdrawn participants including those impacted by COVID-19.

Total:

A total sample size of 220 participants are required to complete for both part A and part B combined. If a 15% dropout rate is assumed for the for the 3-way crossover design of part A, and a 10% dropout rate is assumed for the five 2-way crossover design of Part B, a total sample size of around 246 participants randomized is required.

For AUC, assuming a true ratio of 1.0, the coefficient of variation within participant (%CVw) of 19%, a sample size of 38, and a regulatory definition of BE criteria; the 90% confidence interval (CI) of the ratio for AUC(0-t) between manufacturing processes should lie within the range of 0.80-1.25, results in >99% individual power per dose.

The %CVw has been assumed from the GSK daprodustat study 207727 and PHI115385. The largest %CVw seen in Part 1 of study 207727 (bioequivalence of 2x2mg and 4mg tablets of daprodustat) was 22.6%, from Cmax. The highest %CVw for AUC was 14.6%. The %CVw from study PHI115385, Part 1 was based on a power model using all dose groups. The power model used to estimate %CVw is as below.

$\log_e(\text{PK parameter}) = \mu + Si + \beta * \log(Dj) + \varepsilon ij$

where μ is the intercept, β is the slope, Si is the random effect for participant i, Dj is the dose, εij 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. An average of the highest Cmax %CVw from these studies (22.6% and 26.8%) gives an estimated Cmax %CVw of 25%. An average of the highest AUC %CVw from these studies (14.6% and 24.3%) gives an estimated AUC %CVw of 19%.

The global power for part B is 87%. This accounts for the 10 CIs needed to be generated to assess bioequivalence across the 5 doses, each with one CI for AUC and Cmax. The individual power per dose for Cmax is 97% and for AUC is >99% as noted above.

9.3. Populations for Analyses

The following populations are defined for both Part A and B separately:

Population	Description
Enrolled	All participants who signed the ICF
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
PK	All participants 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

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Part A and Part B will be conducted independently. Upon completion of Part A, Part A will be unblinded and the results of Part A will be analysed, and headline results will be generated. The results of Part A will not determine if Part B begins. Part B can begin regardless of the completion or outcome of the analysis of Part A.

9.4.1. General Considerations

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

For both Part A and Part B, 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 A and Part B, 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, CL/F, Vz/F. 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, 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 loge scale and coefficient of variation between participants (%CVb) will also be provided. Listings will be generated for each derived plasma PK parameters.

9.4.2. Primary Endpoint(s)

The primary objective of Part A is to characterize the PK profile of two 4 mg daprodustat tablets with different dissolution profiles relative to the reference 4 mg daprodustat tablet made by Process 1.

The primary objective of Part B is to assess the bioequivalence between manufacturing Process 1 and Process 2 for the following tablet strengths: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg.

Part A:

For Part A the following statistical analysis method will be used:

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

loge (PK parameter) = $\beta 0 + \gamma i + \tau j + \pi k + \varepsilon ijkl$

where $\beta 0$ is the intercept, γi is the random participant effect for ith participant, τj is the tablet manufacturing effect (j = dissolution 1, dissolution 2, Process 1), πk is the period effect (k = period 1, period 2, period 3), and $\varepsilon ijkl$ is the random error. The Kenward-Roger degree of freedom approach will be used.

Point estimates ($\log_e \mu$, model-based means of PK parameters on $\log_e$ scale) for the model-based means of PK parameters on loge scale will be provided for dissolution 1, dissolution 2, and Process 1 and a point estimate of the mean difference between comparisons ($\log_e \mu$ dissolution 1, 2 - $\log_e \mu$ Process 1) 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 loge scale will be exponentially back-transformed to obtain the model-based geometric means (μ), and the ratio for AUC(0-t) and Cmax (μ dissolution 1, 2 /μ Process 1) and the associated 90% CIs, respectively.

Part B:

For each tablet strength of daprodustat (1 mg, 2 mg, 4 mg, 6 mg, and 8 mg), the following statistical analysis method will be used:

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

loge (PK parameter) = $\beta 0 + \gamma i + \tau j + \pi k + \varepsilon ijkl$

where $\beta 0$ is the intercept, γi is the random participant effect for ith participant, τj is the tablet manufacturing effect (j = Process 1 or Process 2), πk is the period effect (k = period 1 or period 2), and $\varepsilon ijkl$ is the random error. The Kenward-Roger degree of freedom approach will be used.

Point estimates ($\log_e \mu$, model-based means of PK parameters on $\log_e$ scale) for the model-based means of PK parameters on loge scale will be provided for each tablet strength and a point estimate of the mean difference between processes ($\log_e \mu$ Process 2 - $\log_e \mu$ Process 1) 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 loge scale will be exponentially back-transformed to obtain the model-based geometric means (μ), and the ratio for AUC(0-t) and Cmax (μ Process 2 /μ Process 1) and the associated 90% CIs, respectively.

Bioequivalence will be evaluated using the FDA BE guidelines, Criterion 1. It is noted that if Criterion 1 fails, the next step per Japan BE guidance is Criterion 2. However, the study design is based on Criterion 1 given its more stringent criteria

• Criterion 1:

The 90% CIs of the ratios of the geometric means for AUC(0-t) and Cmax (μ Process 2 /μ Process 1) are within the range of 0.80 - 1.25.

• Criterion 2

The ratio of the geometric means for AUC(0-t) and Cmax (μ Process 2 / μ Process 1) is within the range of 0.90 - 1.11.

A sensitivity analysis to jointly assess BE across all doses may be performed on Part B using a statistical model incorporating all doses used in Part B. See report and analysis plan (RAP) for further details.

9.4.3. Secondary Endpoint(s)

Summary statistics will be provided for AUC(0-inf), Tmax, t1/2, CL/F and V/F separately for both Part A and Part B.

9.4.4. Safety Analyse(s)

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, and vital signs will be summarized for each Part A and Part B. No statistical comparison will be made for the safety summaries.

9.5. Interim Analyses

There is no interim analysis planned for the study. Part A is not considered an interim for Part B as it is analyzed separately, and Part B will be conducted regardless of the outcome of Part A.

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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, 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 enough, 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 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 and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about daprodustat or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the daprodustat approved for medical use or approved for payment coverage.

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/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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. The investigator

will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the 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 participants are used to maximum effect in the creation of knowledge and understanding

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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 participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the 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.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

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 enough notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

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 multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants 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.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at screening, Day (-1), and at the follow up visit during study.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cells (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular Hgb (MCH) %Reticulocytes	White blood cells (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	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein

Laboratory Assessments	**Parameters**			
	Glucose fasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • • COVID-19 testing (PCR or antigen performed at additional time noted in the SoA tables and as required) The results of each test must be entered in the CRF.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study 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 NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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:
○ Results in death
○ Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes enough 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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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 (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the study reference manual (SRM).

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

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

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

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

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

10.4.2. Contraception Guidance:

Female participants of childbearing potential that are not currently utilizing a highly-effective contraceptive method (non-hormonal) are eligible to participate if a pregnancy test conducted during screening and again pre-dose (Day -1) is negative. It is not

necessary to require participants to start a new contraceptive method if they are not already established on one.

Female participants of childbearing potential that are currently utilizing a highly-effective contraceptive method are eligible to participate if they agree to continue to use this method consistently and correctly as described below. In this instance a negative pregnancy test during screening and again pre-dose (Day -1) would not be required.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Intrauterine device (IUD)
Bilateral tubal occlusion
Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
ACCEPTABLE METHODS[c]
Male or female condom with or without spermicide[d]
Cervical cap, diaphragm, or sponge with spermicide
A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. d. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will be withdrawn from the study

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or <u>international normalized ratio (INR)</u> >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 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 event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained 48h of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
</table>

Liver Chemistry Stopping Criteria	
INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; Hepatitis B antigen (HBsAg) and HBcAb; Hepatitis C ribonucleic acid (RNA); Cytomegalovirus Immunoglobulin M (IgM) antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

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

10.6. Appendix 6: Abbreviations and Trademarks

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
BE	Bioequivalence
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
CKD	Chronic kidney disease
CL	Clearance
Cmax	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical study report
CV	Cardiovascular
CVb	Between participant coefficient of variability
CVw	Coefficient of variation within participant
CYP	Cytochrome P450 enzyme
DD	Dialysis dependent
dL	deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EPO	Erythropoietin
ESA	Erythropoietin stimulating agents
F	Fraction
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
Hgb	Hemoglobin
HIF	Hypoxia-inducible factor
HIPAA	Health Insurance Portability and Accountability Act

HPLC	High performance liquid chromatography
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IDSL	Integrated Data Standards Library
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalization ratio
IP	Investigational product
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
kg	Kilogram
LDH	Lactate dehydrogenase
MCH	Mean corpuscular Hgb
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
MSDS	Material Safety Data Sheet
ND	Nondialysis dependent
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
%CV	Coefficient of variation of the mean
PHD	prolyl-4-hydroxylases
PHI	Prolyl-hydoxylase inhibitor
PK	Pharmacokinetic
QTc	Corrected QT interval
RAP	Report and Analysis Plan
RBC	Red blood cells
rh	Recombinant human
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
t½	Half life
Tmax	Time of occurrence of Cmax

ULN	Upper limit of normal
UK	United Kingdom
V	Volume
μ	Mean
μM	Micromolar
WBC	White blood cells
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

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10.7. Appendix 7: Handling of Clinical Testing Samples for Pivotal Bioequivalence Studies

The follow are responsibilities of the Investigator of the Study Site:

- Ensure that a quantity of the clinical testing samples (e.g., study drug product and study drugs to be retained as reserve samples), enough to conduct the study, is randomly (non-systematically) selected from the drug shipment. The remaining testing study drugs must be retained as reserve samples.

- Ensure that an adequate record is maintained of the receipt and distribution of all testing samples on the Drug Accountability forms. Storage of the study drugs to be retained as reserve samples is the responsibility of the Investigator and under no conditions can the reserve samples be returned to the Sponsor for storage.

- Ensure that the study drugs to be retained as reserve samples are stored in the original primary packaging and outer cartons. The carton must be closed using tamper evident tape, and an additional label affixed to the outer carton indicating "Reserve Sample for GlaxoSmithKline Study 213022." The label should have an area for the Investigator or pharmacist to sign and date it and the label must not be placed over any existing label(s).

- Store all study drugs to be retained as reserve samples under the appropriate environmental conditions. For products requiring refrigeration or freezing, and for sites located in areas with extreme climate, the temperature must be controlled and a weekly temperature log must be maintained. The storage area must be segregated from the area where the clinical study was conducted and should be limited to access by authorized personnel only.

- Ensure that the reserve samples are retained for a period of at least 5 years following the date on which the application or supplemental application is approved. In the case of non-approval, the retention period is at least 5 years following the date of completion of the corresponding study.

- Consult with the Sponsor if the storage of the study drugs to be retained as reserve samples presents problems.

- Contract with an independent third party to provide storage for study drugs to be retained as reserve samples if storage at the study site is not possible. Before the transfer of the study drugs to be retained as reserve samples, the Sponsor must assess and approve the facilities of the third party.

- The independent third party must store the study drugs to be retained as reserve samples under the appropriate environmental conditions. For products requiring refrigeration or freezing, and for sites located in areas with extreme climate, the temperature must be controlled and a weekly temperature log must be maintained.

- Transfer the study drugs to be retained as reserve samples to an independent third party for storage if the Investigator or study site ceases business.

- When an independent third-party stores reserve samples, provide the Sponsor with the name and address of the facility and a contact name and telephone number. Provide the independent third party with a contact name and number for the Sponsor.

- Upon request from the United States Food and Drug Administration (FDA), release the study drugs retained as reserve samples to the FDA and provide the FDA with a written assurance that the reserve samples came from the same supplies used to conduct the specific bioavailability or bioequivalence study.

10.8. Appendix 8: COVID-19 Considerations

OVERALL RATIONALE FOR THIS APPENDIX

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until study completion.

STUDY PROCEDURES DURING COVID-19 PANDEMIC

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

As outlined in Section 8, Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

Protocol Defined Procedures/Visits:

- The protocol defined interval for the collection of samples during the follow-up visit (see Section 1.3 Schedule of Activities), may be extended up to a maximum length of 14 days.

Data Management/Monitoring:

- If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.

- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK

11. REFERENCES

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