Statistical Analysis Plan

Study ID: 213022

Official Title of Study: 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

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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:** GSK1278863 **Short Title:** BE and Dissolution PK Study

Sponsor Name: GlaxoSmithKline Research & Development Limited

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Version history

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	22-OCT-2020	21-AUG-2020	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 213022.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. 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

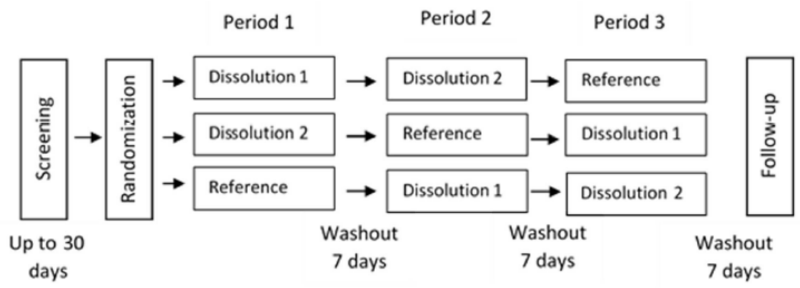
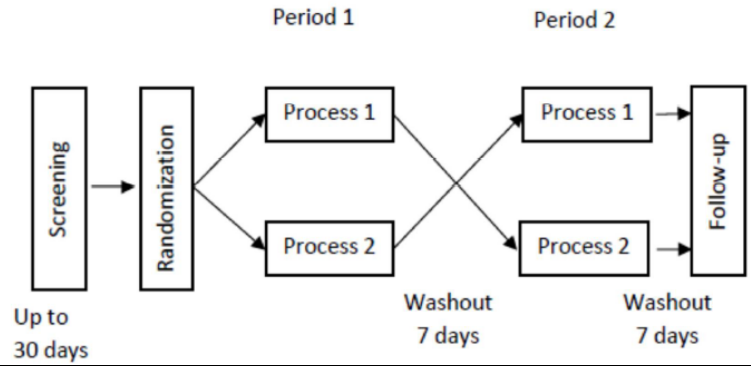
Objectives	Endpoints
Primary	
• To establish BE between daprodustat tablets made by two different manufacturing processes, Process 1 and Process 2, for the following dose strengths administered as a single dose: • 1 mg • 2 mg • 4 mg • 6 mg • 8 mg	AUC (0-t) and C_{max} of daprodustat
Secondary	
• To assess 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

1.1.2. Estimands

Objective	Estimand Category	Estimand Variable/End point	Intercurrent Event Strategy	Population Level Summary Measure
Part A Primary Objective: 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	Primary, Part A	AUC (0-t) and Cmax of daprodustat	Intercurrent events: Treatment discontinuationWhile-on-treatment strategy - all available data up until the treatment discontinuation will be analysed. (Interest is in the treatment effect prior to the withdrawal). Subjects' data available up to the treatment discontinuation will be included in the descriptive PK summaries. If a subject discontinues treatment during a period, the missing data post withdrawal will not be imputed.The derived PK parameters for e.g., AUC, Cmax etc. of that partially completed period will be calculated, if data permits.	1) Descriptive statistics (Section REF _Ref54661353 \n \h 4.3.2)(2) Treatment Ratios (Section REF _Ref518462394 \n \h 4.2.2)
Part B Primary Objective: To establish BE between daprodustat tablets made by two different manufacturing processes, Process 1 and Process 2, for the following dose	Primary, Part B	AUC (0-t) and Cmax of daprodustat	Intercurrent events: Treatment discontinuationWhile-on-treatment strategy - all available data up until the treatment discontinuation will be analysed. (Interest is in the treatment effect prior to the withdrawal). Subjects' data available up to the treatment discontinuation will be included in the descriptive PK summaries. If a subject discontinues treatment during a period, the missing data post withdrawal will not be imputed.The derived PK parameters for e.g., AUC,	(1) Descriptive statistics (Section REF _Ref54661353 \n \h 4.3.2)(2) Treatment Ratios (Section REF _Ref518462394 \n \h 4.2.2)

Objective	Estimand Category	Estimand Variable/End point	Intercurrent Event Strategy	Population Level Summary Measure
strengths administered as a single dose: • 1 mg • 2 mg • 4 mg • 6 mg • 8 mg			Cmax etc. of that partially completed period will be calculated, if data permits.	

1.2. Study Design

Overview of Study Design and Key Features	
Part A study schematic  **Part B study schematic:** 	
Design Features	Study Phase: Phase 1 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. 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.

	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.
Study intervention	**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. **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.
Study intervention Assignment	**Part A** • 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

Part B

- 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
Interim Analysis	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.		

2. 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/μ Process 1 and μ dissolution 1/μ Process 2) 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 8 mg), 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

2.1. Multiplicity Adjustment

No multiplicity adjustments will be made for the final analysis of the primary endpoint. Although the primary endpoint for Part B will include statistical testing, doses of Part B will be enrolled and analysed independent of each other, therefore no Type I error adjustments will be made. There will be no formal statistical hypotheses for part A.

3. ANALYSIS SETS

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

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who signed the ICF	• Study Population
Safety	• All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.	• Study Population, Safety
Pharmacokinetic (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).	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

Pharmacokinetic parameters of daprodustat will be calculated by standard noncompartmental
analysis according to current working practices and using the currently supported version of WinNonlin 6.3 or higher. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

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: 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]. The comparison of the difference will be assessed on

the log scale with point estimates exponentiated back to provide geometric mean ratio and associated 90% CI.

Calculations will be based on the actual sampling times recorded during the study. PK data, will be presented in graphical and 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.

4.1.1. General Methodology

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

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.**Baseline Definition**

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Haematology	X	X		Day -1
Chemistry	X	X		Day -1
12-lead ECG & Vital	X			Screening
Vital Signs	X	X	X	Day 1 (Pre-dose)

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.**Multicenter Studies**

It is anticipated that patient accrual will be spread across centers based on Part A, Part B, and dose and summaries of data by center would unlikely be informative and will not, therefore, be provided.**Primary [Endpoint(s)/Estimand(s)] Analyses**

Part A

Objectives	Endpoints
Primary	
• To characterize single dose PK profile of 4 mg daprodustat tablets with two different	Area under the concentration-time curve [AUC (0-t)] and Maximum observed

Objectives	Endpoints
dissolution profiles made by Process 2 relative to the reference 4 mg daprodustat tablet made by Process 1	concentration (C_{max}) of daprodustat

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 • 2 mg • 4 mg • 6 mg • 8 mg	AUC (0-t) and C_{max} of daprodustat

4.2.1. Definition of 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.

Part B will have one primary objective and two endpoints, AUC (0-t) and Cmax.

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.

Parameter	Parameter Description
AUC(0-t) (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) to the time of last quantifiable concentration (AUC(0-t)) will be calculated by a

Parameter	Parameter Description
	combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations (i.e., Linear Up/Log Down calculation method in Phoenix WinNonlin Professional).
Cmax (ng/mL)	Maximum observed plasma concentration following each dose will be obtained directly from the concentration-time data.

4.2.2. Main analytical approach

Endpoint / Variables
Part A: AUC (0-t) and C_{max} of daprodustat **Part B:** AUC (0-t) and C_{max} of daprodustat
Model Specification
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 model parameters will be estimated using Restricted Maximum Likelihood with the Newton-Raphson algorithm. The Kenward-Roger degree of freedom approach will be used. Given the random effect for subject i, the random error is assumed to be independently distributed within the subject. Point estimates, $\log_e \mu$, 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/μ Process 1 and μ dissolution 1/μ Process 2)) and the associated 90% CIs, respectively.

Within-subject variability (%CVw) for the PK parameters will be estimated using within-subject variance from the analysis model as follows:

$$\%CVw\ (\%) = [\exp(\sigma_w^2) - 1]^{1/2} \times 100$$

AUC(0-inf) will be analyzed in the same manner.

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 (separate model for each dose strength):

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

$$\log_e(\text{PK parameter}) = \beta 0 + \gamma i + \tau j + \pi k + \varepsilon ijkl$$

where β0 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 εijkl is the random error.

The model parameters will be estimated using Restricted Maximum Likelihood with the Newton-Raphson algorithm.

The Kenward-Roger degree of freedom approach will be used.

Given the random effect for subject i, the random error is assumed to be independently distributed within the subject.

Point estimates $\log_e\mu$, 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.

Within-subject variability (%CVw) for the PK parameters will be estimated using within-subject variance from the analysis model as follows:

$$\%CVw\ (\%) = [\exp(\sigma_w^2) - 1]^{1/2} \times 100$$

AUC(0-t) will be analyzed in the same manner.

Model Checking & Diagnostics

- In case there is a problem with model convergence, the arithmetic means for loge-transformed AUC(0-t) and Cmax and the treatment differences within each subject will be calculated using only data from the subjects who have completed all periods. The mean treatment difference and paired-t test based 90% CIs for treatment difference in loge scale will be estimated. The results will be provided in an exponentially back-transformed scale.
- This will be done for both Part A and Part B.

Model Results Presentation

- Results of Part A and Part B will be presented in the same manner, separately.
- The estimates of geometric means of PK parameters (AUC(0-t) and Cmax) will be presented for each dissolution profile and Process 1 (Part A) or for Process 1 and 2 for each tablet strength (Part B), respectively. The estimates of the geometric means ratio between each dissolution profile and Process 1 (Part A) or between Process 1 and 2 (Part B) will be presented along with the associated 90% CIs and %CVw.
- AUC(0-t) will also be provided in the model results presentation, but the evaluation of the bioequivalence for Part B will not be done based on AUC(0-t).

Model Results Interpretation

Part A:

- There will be no formal statistical hypotheses for part A.

Part B:

- 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.

4.2.3. Sensitivity analyses

A sensitivity analysis to jointly assess BE across all doses will be performed on Part B using a statistical model incorporating all doses used in Part B if at least one dose fails to achieve BE in Part B.

Model Specification
• loge (PK parameter) = β_0 + Si + β_1*log(dose) + β_2*F + β_3*F*log(dose) + εj o β_0 is the Intercept of reference; β_1 is the main effect for dose for reference (slope); β_2 is the difference of intercept between the two formulations; β_3 is the difference of slope between the two formulations o Dose: 1, 2, 4, 6, or 8 mg; F: manufacturing process (process 1 or process 2) o Si is the random effect for subject I; Ej is the random error • Model based comparison for each dose o For each dose, a contrast statement will provide the estimate and 90% CI, these will be used to evaluate BE: ▪ 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. o This model will incorporate all 5 doses within one model
Model Checking & Diagnostics
• In case there is a problem with model convergence, the arithmetic means for loge-transformed AUC(0-t) and Cmax and the treatment differences within each subject will be calculated using only data from the subjects who have completed all periods. The mean treatment difference and paired-t test based 90% CIs for treatment difference in loge scale will be estimated. The results will be provided in an exponentially back-transformed scale.
Model Results Presentation
• The estimates of the geometric means ratio between Process 1 and 2 (Part B) will be presented along with the associated 90% CIs and %CVw.

4.3. Secondary [Endpoint(s)/Estimand(s)] Analyses

Part A

Objectives	Endpoints
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

Part B

Objectives	Endpoints
Secondary	
• To assess remaining daprodustat PK parameters	AUC (0-inf), T_{max}, $t_{1/2}$, CL/F and V/F of daprodustat

4.3.1. Definition of endpoint(s)

Parameter	Parameter Description
AUC(0-inf) (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) extrapolated to infinite time (AUC(0-inf)) will be calculated as follows: AUC(0-inf) = AUC(0-t) + Ct / kel
Tmax (h)	The time to maximum observed plasma drug concentration following each dose will be obtained directly from the concentration-time data.
t1/2 (h)	Terminal half-life will be calculated as follows: t1/2 = ln2 / kel
CL/F (mL/h)	Apparent clearance following oral dosing will be calculated as follows: CL/F = Dose / AUC(0-inf)
Vz/F (mL)	Apparent volume of distribution after oral administration will be calculated as follows: Vz/F = Dose / (kel x AUC(0-inf))

NOTES:

- Additional parameters may be included as required.
- Kel is the terminal phase rate constant.
- Ct is the last observed quantifiable concentration.

4.3.2. Main analytical approach

The secondary endpoints of both Part A and Part B will be summary statistics of those PK parameters not summarized in the primary endpoint (AUC (0-inf), T_{max}, $t_{1/2}$, CL/F and V/F).

All pharmacokinetic endpoints will be summarized in tabular form. Descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum) will be calculated for all pharmacokinetic endpoints by regimen.

A participant listing of individual PK parameters for each treatment group will be provided. Pharmacokinetic parameters will be summarized by treatment group using descriptive statistics.

4.4. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

Summaries will be provided separately for Part A and Part B.

4.4.1. Extent of Exposure

A listing of exposure will be created for both Part A and Part B. Summary tables of exposure will also be created.

4.4.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards. An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, AEs leading to permanent discontinuation of study intervention, study intervention related AEs leading to permanent discontinuation of study intervention, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced.Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).A summary of number and percentage of participants with any adverse events by maximum severity will be produced. A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing. The summary table will be displayed by PT only.All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary tables will be displayed by PT and SOC. A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the

relationship to study intervention as 'Yes' or missing.**Adverse Events of Special Interest**

The following will be considered adverse events of special interest (AESI) for the purpose of analyses:• 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 hypertensionThe summary of event characteristics will be provided for each AESI respectively, including number of participants with any event, number of events, number of participants with any event that is serious. The percentage will be calculated in two ways, one with number of participants with event as the denominator and the other with total number of participants as the denominator. The worst-case approach will be applied at participant level for the maximum grade, i.e. a participant will only be counted once as the worst case from all the events experienced by the participant. For action taken to an event, a participant will be counted once under each action.**Additional Safety Assessments**

4.4.3.1. Laboratory Data

Laboratory data will be summarized based on observed values by visit, as well as change from baseline by visit. A listing of all laboratory data and a listing of PCI laboratory data will be produced.

Laboratory data includes the following variables:

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	Total Protein

Laboratory Assessments	Parameters			
			(ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	
	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.			

4.4.3.2. Vital Signs

Vital signs data will be summarized based on observed values by visit, as well as change from baseline by visit. A listing of all Vital signs data and a listing of PCI Vital signs data will be produced.

Vital signs data includes the following variables:

- Oral temperature
- Pulse
- Blood pressure (SBP, DBP)

4.4.3.3. ECG

ECG data will be summarized based on observed values by visit, as well as change from baseline by visit. A listing of all ECG data and a listing of PCI ECG data will be produced.

4.5. 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.

4.6. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol [(Dated: 21-AUG-2020)].

5. 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.

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

where μ is the intercept, β is the slope, S_i is the random effect for participant i, D_j is the dose, ε_{ij} is the random error. The %CVw estimates based on the random error are 24.3% and 26.8% for AUC(0-inf) and Cmax, respectively. 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.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
BE	Bioequivalence
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline

Abbreviation	Description
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
OPS	Output and Programming Specification
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
SAP	Statistical Analysis Plan
SD	Standard deviation

6.1.2. Trademarks

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7. REFERENCES

GlaxoSmithKline Document Number 2017N354137_00, GSK1278863, A single centre, single dose, open-label, randomised, 2-way crossover study in healthy Japanese male subjects to evaluate the bioequivalence of daprodustat tablets (2 mg tablet vs. 4 mg tablet) (Part 1) and the food effect on the pharmacokinetics of daprodustat (Part 2). 12-Mar-2018

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