Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for a single centre, single dose, open-label, randomised, 2-way crossover study in healthy Japanese male subjects to evaluate bioequivalence of daprodustat tablets (2 mg tablet vs. 4 mg tablet) (Part 1) and the food effect on the pharmacokinetics of daprodustat (Part 2)
Compound Number	:	GSK1278863
Effective Date	:	10-JUL-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 207727.
- This RAP is intended to describe the final analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver	Date	Approval Method
PPD Biostatistics Group 2, Biomedical Data Sciences Japan	NA	NA

RAP Team Approvals:

Approver	Date	Approval Method
PPD Lead Programmer; Statistical Programming & Reporting Group, Biomedical Data Sciences Japan	09-JUL-2018	Pharma TMF
PPD Clinical Lead; Clinical Pharmacology Office	09-JUL-2018	Pharma TMF
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol GlaxoSmithKline Document Number 2017N354137_00.

REVISION HISTORY

Note that minor wording changes are not included in below.

Reporting and Analysis Plan_207727_Amendment_Final_V1.1 [10-JUL-2018]			
Section # and Name	**Description of Change**		**Brief Rationale**
6.1 - Overview of Planned Study Population Analyses	Listing of reasons for treatment discontinuation was added.		eCRF screen was changed to capture treatment discontinuation.
6.1.1- Details of Planned Study Population Summaries	Removed the detail of summary display for race and racial combinations		Corrections
10.9 - Appendix 9: List of Data Displays	Table 1.5, Table 1.6 Listing 4, Listing 5 Listing 8, Listing 9 Table 3.7, Table 3.8 modified Figure 3.9, Figure 3.10 modified	Programming notes corrected. Listing for treatment discontinuation added IDSL/Example shell corrected Order of PK parameters in a title Order of PK parameters in a title	Corrections

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol (Dated: 12/Mar/2018) are outlined below. The change was intended to create some displays required by EudraCT with the "Enrolled" population.

Protocol

Section 9.3 Population for Analyses

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

Reporting & Analysis Plan

Section 4. Analysis Populations

Population	Description
Screened	All subjects who signed the ICF
Enrolled	· All subjects who passed screening and entered the study. · Note screening failures (who never passed screening even if rescreened) and subjects screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.
Safety	This population will be defined for each Part. · All randomised subjects who received at least one dose of study intervention.
PK	This population will be defined for each Part. · All subjects in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).

2.2. Study Objective(s) and Endpoint(s)

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

2.3. Study Design

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Design Features</td><td>
This study consists of two parts; Part 1 is a single centre, single dose, open-label, randomised, 2-way crossover study in healthy Japanese male subjects. Part 2 is a single centre, single dose in the fed and fasted state, open-label, randomised, 2-way crossover study in healthy Japanese male subjects.
In both part (Part 1 and Part 2), healthy subjects will have a screening visit within 30 days prior to the first dose of study treatment, two treatment periods, and re-visit 7 (±1) days after the second dose for follow-up. All subjects will be administered daprodustat as a single oral dose, with assessments conducted for up to 24 hours post-dose. Subjects will be housed in the Clinical Research Unit from Day -1 through Day 2 of each period. At least 5-day wash-out period will occur between each treatment period.
</td></tr>
<tr><td>Dosing</td><td>
Subjects will be divided into the study of Part 1 and 2, and will be randomized to one of two groups (Part 1: A or B, Part 2: C or D) in the following table;
Part 1 (Bioequivalence part)
Daprodustat 2 mg tablet x 2, single dose, in the fasted state
Daprodustat 4 mg tablet x 1, single dose, in the fasted state
<table>
<tr><th>Group</th><th>n</th><th>Period 1</th><th>Period 2</th></tr>
<tr><td>A</td><td>26</td><td>2 mg tablet x 2</td><td>4 mg tablet x 1</td></tr>
<tr><td>B</td><td>26</td><td>4 mg tablet x 1</td><td>2 mg tablet x 2</td></tr>
</table>
Part 2 (Food effect part)
Daprodustat 4 mg tablet, single dose, in the fed state
Daprodustat 4 mg tablet, single dose, in the fasted state
<table>
<tr><th>Group</th><th>n</th><th>Period 1</th><th>Period 2</th></tr>
<tr><td>C</td><td>6</td><td>4 mg tablet x 1 (fed)</td><td>4 mg tablet x 1 (fasted)</td></tr>
<tr><td>D</td><td>6</td><td>4 mg tablet x 1 (fasted)</td><td>4 mg tablet x 1 (fed)</td></tr>
</table>
Blood sampling for PK analysis will be performed prior to dosing and until 24 hours post-dose following each dose. The duration of each subject's participation will be approximately 6 weeks from screening to the follow-up.
</td></tr>
<tr><td>Time & Events</td><td>
Refer to Appendix 2: Schedule of Activities
</td></tr>
<tr><td>Treatment Assignment</td><td>
Subjects will be assigned to one of two groups in accordance with the randomisation schedule generated by the Biomedical Data Sciences Department at GSK, prior to the start of the study, using validated internal software.
</td></tr>
<tr><td>Interim Analysis</td><td>
No interim analysis is planned.
</td></tr>
</table>

2.4. Statistical Hypotheses / Statistical Analyses

Part 1:

The bioequivalence between daprodustat 2 mg tablet and 4 mg tablet will be demonstrated using a framework of statistical hypothesis testing. The ratio of the geometric means (μ_{2mg}/μ_{4mg}) for AUC(0-t) and Cmax is the measure in the following statistical hypotheses:

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

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

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

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

Part 2:

No formal statistical hypothesis will be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	All participants who signed the ICF.	Study Population
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	Study Population
Safety	This population will be defined for each Part. • All randomised participants who received at least one dose of study treatment.	Study Population, Safety
Pharmacokinetic (PK)	This population will be defined for each Part. • 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

Refer to Section 10.9: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
Part 1 (Schedule 1)			
D1	2 mg x 2	2 mg x 2	1
D2	4 mg x 1	4 mg x 1	2
Part 2 (Schedule 2)			
D3	4 mg fed	4 mg fed	1
D4	4 mg fasted	4 mg fasted	2

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. 2mg x 2 / 4mg x 1
2. fed / fasted

5.2. Baseline Definitions

Baseline definitions defined in the table are applicable to each period.

For all endpoints (except as noted in baseline definitions) 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 Signs	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.

5.3. Examination of Covariates, Other Strata and Subgroups

5.3.1. Covariates and Other Strata

The list of covariates may be used in descriptive summaries and statistical analyses. Additional covariates of clinical interest may also be considered.

Category	Details
Covariates	See Section 8.1.5.1, describing pharmacokinetic analyses using statistical model

5.4. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Schedule of Activities
10.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Reporting Standards for Missing Data
10.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on Safety population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition for the Subject Conclusion Record	Y		Y
Treatment Status and Reasons for Discontinuation of Study Treatment			Y
Screening Status and Reasons for Screen Failure	Y		Y
Number of Subjects Enrolled by Country and Site ID	Y		
Planned and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y
Inclusion/Exclusion Criteria Deviations			Y
Population Analysed			
Subjects Excluded from PK Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Race and Racial Combinations			Y
Age Ranges	Y		
Medical Conditions and Concomitant Medications			
Medical Conditions			Y
Concomitant Medications			Y
Exposure			
Exposure to Study Treatment			Y
Meal			
Meal start and end days/times on fed treatment			Y

NOTES:

- Y = Yes display generated.

6.1.1. Details of Planned Study Population Summaries

Summaries will be provided by Part (2 mg x 2 and 4 mg x 1 in Part 1, fed and fasted in Part 2), unless otherwise specified.

Subject Disposition

Subject Disposition for the Subject Conclusion Record

The number and percentage of subjects who completed the study as well as subjects who withdrew from the study will be summarized. Reason for withdrawal will also be summarized for subjects who withdrew from the study. Only the total column will appear.

Screening Status and Reasons for Screen Failure

This will be based on Screened population. The number and percentage of subjects who passed screening and who failed screening and therefore were not entered into the study will be summarized along with the reasons for failure will be summarized for those subjects who failed screening. Only the total column will appear.

Number of Subjects Enrolled by Country and Site ID

This will be based on Enrolled population. The number of subjects summarized by Country, Site ID and Investigator name will be presented. Only the total column will appear.

Protocol Deviations

Important Protocol Deviations

The number and percentage of subjects who had important protocol deviations defined as part of the protocol deviation management plan for the study, will be summarized. Only the total column will appear.

Demographic and Baseline Characteristics

Demographic Characteristics

The number and percentage of subjects or summary statistics will be provided for each demographic characteristic and only the total column will appear: Sex, Age (years), Age Group (years), Ethnicity, Race detail, Height, Weight, and Body Mass Index. Age Group (years) will be categorized into three ('≤18', '19-64', '≥65'). Each demographic characteristic will be summarized using the minimum set of summary statistics.

Age Ranges

This will be based on Enrolled population. The number and percentage of subjects within each age range category will be provided. Only the total column will appear. Only age ranges that are applicable to the study will be included (i.e., only ‘18-64 years’). This is based on the standard of EMA clinical trial results disclosure requirements.

7. SAFETY ANALYSES

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

7.1. Adverse Events Analyses

Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC and PT	Y		Y
All AEs by Maximum Intensity	Y		
Drug-Related AEs by SOC and PT	Y		
Drug-Related AEs by Maximum Intensity	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT and Verbatim Text			Y
Serious and Other Significant AEs			
Serious AEs			Y
AEs Leading to Withdrawal from Study			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.1.1. Details of Planned Adverse Events Summaries

Summaries will be provided by Part (2 mg x 2 and 4 mg x 1 in Part 1, fed and fasted in Part 2), unless otherwise specified.

Adverse Events (AEs)

All AEs by SOC and PT

The number and percentage of subjects with all relevant adverse events will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

All AEs by Maximum Intensity by SOC and PT

The number and percentage of subjects with adverse events by intensity (e.g., mild, moderate, severe) will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

Drug-related AEs by SOC and PT

The number and percentage of subjects with all drug-related adverse events will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

Drug-related AEs by Maximum Intensity by SOC and PT

The number and percentage of subjects with drug-related adverse events by intensity (e.g., mild, moderate, severe) will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 9: List of Data Displays.

Display Type	Absolute		
	Summary		Individual
	T	F	L
Chemistry			
Chemistry Changes from Baseline	Y		
Chemistry Values	Y		Y
Chemistry Data Shifts from Baseline Relative to Normal Range	Y		
All Chemistry Data for Subjects with any Value of PCI			Y
Chemistry Values of PCI			Y
Haematology			
Haematology Changes from Baseline	Y		
Haematology Values	Y		Y
Haematology Data Shifts from Baseline Relative to Normal Range	Y		
All Haematology Data for Subjects with any Value of PCI			Y
Haematology Values of PCI			Y
Urinalysis			
Urinalysis Concentration Changes from Baseline (Gravity and pH)	Y		
Urinalysis Data (Gravity and pH)	Y		Y
Urinalysis Data (Glucose, Protein, Blood, Ketones, Bilirubin, and Urobilinogen)	Y		Y
Hepatobiliary (Liver)			
Liver Monitoring/Stopping Event Reporting			Y
Medical Conditions for Subjects with Liver Stopping Events			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.2.1. Details of Planned Clinical Laboratory Displays

Summaries will be provided by Part (2 mg x 2 and 4 mg x 1 in Part 1, fed and fasted in Part 2), unless otherwise specified.

Chemistry/Haematology Laboratory Tests

Laboratory Changes from Baseline and Values

Each quantitative laboratory test and the changes in value from baseline will be summarized at every assessed time point using n, mean, standard deviation, median, minimum, and maximum by treatment group.

Laboratory Data Shifts from Baseline Relative to Normal Range

The number and percentage of subjects with laboratory results within each normal range (Low, Normal, High) during each period will be summarized relative to their baseline category by laboratory test. The percentages are based on the number of subjects in the treatment group with data for the laboratory test at the specified planned time (n). Subjects are only counted once in the total column.

Urinalysis Laboratory Tests

Urinalysis Concentration Changes from Baseline (Gravity and pH)

Gravity and pH test and the changes in value from baseline will be summarized at every assessed time point using n, mean, standard deviation, median, minimum, and maximum by treatment group.

Urinalysis Data (Glucose, Protein, Blood, Ketones, Bilirubin, and Urobilinogen)

The number and percentage of subjects with the above urinalysis results (character results) will be summarized by treatment group.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 9: List of Data Displays.

Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y		Y			
ECG Values	Y		Y	Y		
All ECG Values for Subjects with any Value of PCI			Y			
Vital Signs						
Vitals Values	Y		Y	Y		
All Vital Signs for Subjects with any Value of PCI			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.3.1. Details of Planned Other Safety Displays

Summaries will be provided by Part (2mg tablet x 2 and 4mg tablet x 1 in Part 1, fed state and fasted state in Part 2), unless otherwise specified.

ECG

ECG Findings

The number and percentage of subjects with ECG findings (ECG interpretation) will be summarized by treatment group.

ECG Values

Each ECG parameter value and the change from baseline will be summarized by treatment group at every assessed time point using n, mean, standard deviation, median, minimum, and maximum.

Vital Signs

Vital Signs

Each vital sign parameter and the changes in value from baseline will be summarized by treatment group at every assessed time point using n, mean, standard deviation, median, minimum, and maximum.

8. PHARMACOKINETIC ANALYSES

8.1. Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

8.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.4.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters of daprodustat will be calculated by standard non-compartmental 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.

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 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).
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
Cmax (ng/mL)	Maximum observed plasma concentration following each dose will be obtained directly from the concentration-time data.
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
%AUCex (%)	The percentage of AUC(0-inf) obtained by extrapolation (%AUCex) will be calculated as follows: %AUCex = (AUC(0-inf) – AUC(0-t)) / AUC(0-inf) x 100
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))
MRT (h)	Mean residence time will be calculated as follows: MRT = AUMC(0-inf) / AUC(0-inf)
Tlast (h)	The time of the last measurable (positive) concentration.
kel	The first order rate constant associated with the terminal (log-linear) portion of the curve.

Parameter	Parameter Description
(lambda_z) (/h)	
lambda_z_lower	The lower limit on time for values to be included in the calculation of kel.
lambda_z_upper	The upper limit on time for values to be included in the calculation of kel.
#pts	The number of time points used in computing kel.
R-square	The goodness of fit statistic for the terminal elimination phase.

NOTES:

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

8.1.2. Summary Measure

In Part 1, the ratio of geometric mean for AUC(0-t) and Cmax between daprodustat 2 mg tablet x 2 and 4 mg tablet x 1 will be used for the comparison between daprodustat 2mg tablet x 2 vs. daprodustat 4mg tablet x 1.

In Part 2, the ratio of geometric mean for AUC(0-t) and Cmax between fed and fasted state will be used for the comparison between the fed state vs. the fasted state.

8.1.3. Population of Interest

The pharmacokinetic analyses will be based on the PK population, unless otherwise specified.

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent events which may affect the evaluation of bioequivalence and food effect will not be anticipated.

8.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Section 8.1.6: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

8.1.5.1. Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma profiles).

Endpoint / Variables

- Derived plasma PK parameters (AUC(0-t), Cmax) of daprodustat

Model Specification (Part 1)

Part 1

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

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

  β_0: intercept
  γ_i: random subject effect for ith subject, following $N(0, \sigma_b^2)$
  τ_j: tablet strength effect (j = 2 mg or 4 mg)
  π_k: period effect (k = period 1 or period 2)
  α_l: group effect (l= group A or group B)
  ε_{ijkl}: random error for subject i, tablet strength j, period k, group l, following $N(0, \sigma_w^2)$
- 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.
- The least square means for each tablet strength will be estimated based on the fitted model. The mean difference between tablet strengths (2mg - 4mg) and its 90% CIs will be also estimated using the within-subject variance.
- The estimates of least square means for each tablet strength, the treatment difference between tablet strength and the 90% CIs will be exponentially back-transformed to obtain the estimates of geometric means of AUC(0-t) and Cmax for each tablet strength, the ratio of geometric means (2mg/4mg) and its 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 2

- To estimate the food effect on PK parameters (AUC(0-t) and Cmax) of daprodustat, the PK parameters will be analysed using a mixed effect model as described as below (almost the same as Part 1):

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

  β_0: intercept
  γ_i: random subject effect for ith subject
  τ_j: food effect (j = fed or fasted)

π_k: period effect (k = period 1 or period 2)
α_l: group effect (l= group C or group D)
ε_{ijkl}: random error for subject i, food effect j, period k, group l.

- The model restrictions will be the same as Part 1.
- The way of construction for the estimates of summary statistics will be the same as Part 1
  - Note that the ratio of geometric means (fed/fasted) and its 90% CIs for AUC(0-t) and Cmax will be estimated.
  - AUC(0-inf) 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 (2mg - 4mg in Part 1, fed - fasted in Part 2) within each subject will be calculated using only data from the subjects who have completed both 2mg and 4mg in Part 1, or both fed and fasted in Part 2. 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

Part 1 and Part 2

- Results of Part 1 and Part 2 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 tablet strength (Part 1) or for each food state (Part 2), respectively. The estimates of the geometric means ratio between tablet strengths (Part 1) or between fed and fasted state (Part 2) will be presented along with the associated 90% CIs and %CVw.
- For Part 1, the bioequivalence between daprodustat 2 mg tablet and 4 mg tablet will be evaluated as follows:
  - The bioequivalence is established when the 90% CI of the ratio for AUC(0-t) and Cmax between tablet strength (2 mg x 2 vs. 4 mg x 1) are within the range of 0.80 to 1.25.
  - Even if the 90% CI doesn't meet the above criteria, the bioequivalence is established when the point estimate of the ratio for AUC(0-t) and Cmax between tablet strength (2 mg x 2 vs. 4 mg x 1) are within the range of 0.90 to 1.11.
- AUC(0-inf) will also be provided in the model results presentation, but the evaluation of the bioequivalence will not be done based on AUC(0-inf).

8.1.6. Details of Planned Pharmacokinetic Displays

Summaries will be provided by Part (2mg tablet x 2 and 4mg tablet x 1 in Part 1, fed state and fasted state in Part 2), unless otherwise specified.

Daprodustat Plasma Concentration-Time Data

Daprodustat plasma concentrations at every scheduled time point will be summarized using n, mean, standard deviation, median, minimum, and maximum.

Derived Daprodustat Plasma Pharmacokinetic Parameters (non-transformed)

Daprodustat plasma pharmacokinetic parameters (AUC(0-t), AUC(0-inf), Cmax, Tmax, t1/2, %AUCex, CL/F, Vz/F, kel, and MRT) will be summarized using n, mean, 95% CI, standard deviation, median, minimum, and maximum.

Derived Daprodustat Plasma Pharmacokinetic Parameters (log-transformed)

For each pharmacokinetic parameters with a log-normal distribution (AUC(0-t), AUC(0-inf), Cmax, t1/2, %AUCex, CL/F, Vz/F, kel, and MRT), the log-transformed parameters will be summarized using n, geometric mean, 95% CI of geometric mean, standard deviation of log-transformed data and between subject coefficient of variation (%CVb).

Analysis of Tablet Strength/Food Effect for AUC(0-t) and Cmax

The analysis results will be presented as described in Section 8.1.5.1 - *Model Results Presentation*. AUC(0-inf) will also be analysed and provided in a display.

9. REFERENCES

GlaxoSmithKline Document Number 2017N354137_00 Study ID 207727. 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). Report Date 12-Mar-2018.

Japanese Society of Nephrology. Dietary recommendations for chronic kidney disease, 2014. Jpn J Nephrol. 2014;56(5):533-59.

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the PDMP and the data handling will be determined prior to DBR.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

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

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

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

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

4: Haematology, clinical chemistry and urinalysis.

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

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

7: 7(±1) days post-dose of Period 2.

10.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

10.3.1. Study Phases

Assessments and events (e.g., study withdrawal) will be classified according to the time of occurrence relative to dosing start Date and Time by Period. The following definitions will be applicable to both Part 1 and Part 2.

Study Phase	Definition
Pre-Treatment	Reference Day < Previous Day of Dosing Start Date in Period 1
Period 1	Previous Day of Dosing Start Date in Period 1 ≤ Reference Day < Previous Day of Dosing Start Date in Period 2
Period 2	Previous Day of Dosing Start Date in Period 2 ≤ Reference Day

10.3.1.1. Study Phases for Adverse Events

The study phases for AEs will be categorized into pre-treatment, period 1, and period 2 based on AE onset date and time.

Study Phase	Definition
Pre-Treatment	AE Onset Date and Time < Study First Dosing Start Date and Time
Period 1	Study First Dosing Start Date and Time ≤ AE Onset Date and Time < Dosing Start Date and Time in Period 2
Period 2	Dosing Start Date and Time in Period 2 ≤ AE Onset Date and Time
Time since Study First Dose (min)	If study phase of the event is pre-treatment, AE Onset Date and Time - Study First Dosing Start Date and Time otherwise AE Onset Date and Time – Study First Dosing Start Date and Time + 1 min
Time since Period First Dose (min)	If study phase of the AE is pre-treatment, set to missing If study phase of the AE is period 1, AE Onset Date and Time – Dosing Start Date and Time in Period 1 + 1 min If study phase of the AE is period 2, AE Onset Date and Time – Dosing Start Date and Time in Period 2 + 1 min
Time since Last Dose (min)	If study phase of the AE is pre-treatment, set to missing If AE Onset Date and Time ≥ Study Last Dosing Start Date and Time, AE Onset Date and Time – Study Last Dosing Start Date and Time+ 1 min
Duration (min)	AE Resolution Date and Time – AE Onset Date and Time + 1 min
Drug-related	If relationship is marked 'YES' on eCRF or value is missing.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be treatment emergent.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

10.3.1.2. Study Phases for Concomitant Medication

The study phases for concomitant medications represent the period of medication star. The study phases will be categorized into pre-treatment, period 1, and period 2 based on medication start date and time.

Study Phase	Definition
Pre-Treatment	Start Date and Time < Study First Dosing Start Date and Time
Period 1	Study First Dosing Start Date and Time ≤ Start Date and Time < Dosing Start Date and Time in Period 2
Period 2	Dosing Start Date and Time in Period 2 ≤ Start Date and Time

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: N/A
HARP Compound	: N/A
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0).	
Generation of RTF Files	
• RTF files will be generated.	

10.4.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visit
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Office will be created according to GUI_51487. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	No PK parameters derived by programmer are planned. :
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters in GUI_51487.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards: Standards for the Transfer and Reporting of PK Data using HARP

10.5. Appendix 5: Derived and Transformed Data

10.5.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dosing Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dosing Date → Study Day = Ref Date – First Dosing Date
  • Ref Date ≥ First Dosing Date → Study Day = Ref Date – (First Dosing Date) + 1

Period Day

• Calculated as the number of days from Dosing Date in Period 1 or Period 2.
  • If Study Phase of Ref Assessment or Event = Pre-Treatment or Missing
  → Period Day = Missing
  • If Study Phase of Ref Assessment or Event = Period 1
  → If Ref Date is on or after Dosing Date in Period 1, Period Day = Ref Date – Dosing Date in Period 1 + 1 day
  → If Ref Date is before Dosing Date in Period 1, Period Day = Ref Date – Dosing Date in Period 1
  • If Study Phase of Ref Assessment or Event = Period 2
  → If Ref Date is on or after Dosing Date in Period 2, Period Day = Ref Date – Dosing Date in Period 2 + 1 day
  → If Ref Date is before Dosing Date in Period 2, Period Day = Ref Date – Dosing Date in Period 1

10.5.2. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ A date and month will be imputed as '30th June' as it will not be captured. • Date of Informed Consent will be used as reference date of calculation.

10.5.3. Safety

Laboratory Parameters
Imputation
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1 • The default convention for reporting of clinical laboratory units will be the international system of units (SI units).
PCI
• For PCI listings of the absolute neutrophils and lymphocytes count, PCI cutoffs will be calculated by multiplying the percentages given for each subject by the absolute white blood count.

10.6. Appendix 6: Reporting Standards for Missing Data

10.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completion of all phases of the study including the follow up visit. • If subjects prematurely withdraw from the study, additional replacement participants may be recruited and assigned to the same treatment sequence. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.6.2.1. Handling of Missing and Partial Dates and Times

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF does not allow for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month will not be missing. • The eCRF allows for the possibility of missing times to be recorded for AE start and end dates. Missing times will be imputed using the following convention: o If the missing time is a start time, a '00:00' will be used for the time. o If the missing time is a stop time, a '23:59' will be used for the time. • The recorded missing time will be displayed in listings without imputed values.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The eCRF allows for the possibility of missing times to be recorded for concomitant medications start and end dates. Missing times will be imputed using the following convention:

Element	Reporting Detail
	○ If the missing time is a start time, a '00:00' will be used for the time. ○ If the missing time is a stop time, a '23:59' will be used for the time. • The recorded partial date and missing time will be displayed in listings without imputed values.

10.7. Appendix 7: Values of Potential Clinical Importance

10.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haematocrit	Ratio of 1			0.54
		Δ from BL	↓0.075	
Haemoglobin	g/L			180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	G/L		30	
Calcium	mmol/L		2	2.75
Creatinine	μmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	μmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	μmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

10.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

10.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
BL	Baseline
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CSR	Clinical Study Report
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DP	Decimal Places
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
MRT	Mean Residence Time
NQ	Non-quantifiable
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PT	Preferred Term
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RTF	Rich Text File
SAC	Statistical Analysis Complete
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class

Abbreviation	Description
SOP	Standard Operation Procedure
t1/2	Terminal half-life
Tmax	Time to maximum observed blood drug concentration
TFL	Tables, Figures & Listings
ULN	Upper Limit of Normal
WNL	WinNonlin

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.9	Not Applicable
Safety	2.1 to 2.36	Not Applicable
Pharmacokinetic	3.1 to 3.8	3.1 to 3.10
Section	**Listings**	
ICH Listings	1 to 75	

10.9.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 10: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.9.3. Deliverables

Delivery Priority	Description
SAC	Final Statistical Analysis Complete

10.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1A	Summary of Subject Disposition (Part 1)	ICH E3, FDAAA, EudraCT Only total column will appear	SAC
1.2.	Safety	ES1A	Summary of Subject Disposition (Part 2)	ICH E3, FDAAA, EudraCT Only total column will appear	SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements Only total column will appear. Not provided separately by Part	SAC
1.4.	Enrolled	NS1	Summary of Number of Subject by Country and Site ID	EudraCT/Clinical Operations Only total column will appear. Not provided separately by Part	SAC
Protocol Deviation					
1.5.	Safety	DV1	Summary of Important Protocol Deviations (Part 1)	ICH E3 Only total column will appear	SAC
1.6.	Safety	DV1	Summary of Important Protocol Deviations (Part 2)	ICH E3 Only total column will appear	SAC
Demographic and Baseline Characteristics					
1.7.	Safety	DM3	Summary of Demographic Characteristics (Part 1)	ICH E3, FDAAA, EudraCT Only total column will appear	SAC
1.8.	Safety	DM3	Summary of Demographic Characteristics (Part 2)	ICH E3, FDAAA, EudraCT Only total column will appear	SAC
1.9.	Enrolled	DM11	Summary of Age Ranges	EudraCT/Clinical Operations Only total column will appear. Not provided separately by Part	SAC

10.9.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	Safety	AE1CP	Summary of All AE by SOC and PT (Part 1)	ICH E3 Include total column	SAC
2.2.	Safety	AE1CP	Summary of All AE by SOC and PT (Part 2)	ICH E3 Include total column	SAC
2.3.	Safety	AE5A	Summary of All AEs by Maximum Intensity by SOC and PT (Part 1)	ICH E3 Include total column	SAC
2.4.	Safety	AE5A	Summary of All AEs by Maximum Intensity by SOC and PT (Part 2)	ICH E3 Include total column	SAC
2.5.	Safety	AE1CP	Summary All Drug-Related AE by SOC and PT (Part 1)	ICH E3 Include total column	SAC
2.6.	Safety	AE1CP	Summary All Drug-Related AE by SOC and PT (Part 2)	ICH E3 Include total column	SAC
2.7.	Safety	AE5A	Summary of All Drug-Related AEs by Maximum Intensity by SOC and PT (Part 1)	ICH E3 Include total column	SAC
2.8.	Safety	AE5A	Summary of All Drug-Related AEs by Maximum Intensity by SOC and PT (Part 2)	ICH E3 Include total column	SAC
Laboratory: Chemistry					
2.9.	Safety	LB1	Summary of Chemistry Data (Part 1)		SAC
2.10.	Safety	LB1	Summary of Chemistry Data (Part 2)		SAC
2.11.	Safety	LB1	Summary of Chemistry Change from Baseline (Part 1)	ICH E3 Include baseline value	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	Safety	LB1	Summary of Chemistry Change from Baseline (Part 2)	ICH E3 Include baseline value	SAC
2.13.	Safety	LB4	Summary of Chemistry Data Shifts from Baseline Relative to Normal Range (Part 1)	ICH E3	SAC
2.14.	Safety	LB4	Summary of Chemistry Data Shifts from Baseline Relative to Normal Range (Part 2)	ICH E3	SAC
Laboratory: Haematology					
2.15.	Safety	LB1	Summary of Haematology Data (Part 1)		SAC
2.16.	Safety	LB1	Summary of Haematology Data (Part 2)		SAC
2.17.	Safety	LB1	Summary of Haematology Change from Baseline (Part 1)	ICH E3 Include baseline value	SAC
2.18.	Safety	LB1	Summary of Haematology Change from Baseline (Part 2)	ICH E3 Include baseline value	SAC
2.19.	Safety	LB4	Summary of Haematology Data Shifts from Baseline Relative to Normal Range (Part 1)	ICH E3	SAC
2.20.	Safety	LB4	Summary of Haematology Data Shifts from Baseline Relative to Normal Range (Part 2)	ICH E3	SAC
Laboratory: Urinalysis					
2.21.	Safety	LB1	Summary of Urinalysis Data (Gravity and pH) (Part 1)		SAC
2.22.	Safety	LB1	Summary of Urinalysis Data (Gravity and pH) (Part 2)		SAC
2.23.	Safety	LB1	Summary of Urinalysis Change from Baseline (Gravity and pH) (Part 1)	ICH E3 Include baseline value	SAC
2.24.	Safety	LB1	Summary of Urinalysis Change from Baseline (Gravity and pH) (Part 2)	ICH E3 Include baseline value	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.25.	Safety	UR3b	Summary of Urinalysis Data (Glucose, Protein, Blood, Ketones, Bilirubin, and Urobilinogen) (Part 1)		SAC
2.26.	Safety	UR3b	Summary of Urinalysis Data (Glucose, Protein, Blood, Ketones, Bilirubin, and Urobilinogen) (Part 2)		SAC
ECG					
2.27.	Safety	EG1	Summary of ECG Findings (Part 1)	IDSL	SAC
2.28.	Safety	EG1	Summary of ECG Findings (Part 2)	IDSL	SAC
2.29.	Safety	EG2	Summary of ECG Values (Part 1)	IDSL	SAC
2.30.	Safety	EG2	Summary of ECG Values (Part 2)	IDSL	SAC
2.31.	Safety	EG2	Summary of Change from Baseline in ECG Values (Part 1)	IDSL Include baseline value	SAC
2.32.	Safety	EG2	Summary of Change from Baseline in ECG Values (Part 2)	IDSL Include baseline value	SAC
Vital Signs					
2.33.	Safety	VS1	Summary of Vital Signs (Part 1)	IDSL	SAC
2.34.	Safety	VS1	Summary of Vital Signs (Part 2)	IDSL	SAC
2.35.	Safety	VS1	Summary of Change from Baseline in Vital Signs (Part 1)	ICH E3 Include baseline value	SAC
2.36.	Safety	VS1	Summary of Change from Baseline in Vital Signs (Part 2)	ICH E3 Include baseline value	SAC

10.9.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable Priority**
3.1.	PK	PK01	Summary of Daprodustat Plasma Concentration-Time Data (Part 1)		SAC
3.2.	PK	PK01	Summary of Daprodustat Plasma Concentration-Time Data (Part 2)		SAC
3.3.	PK	PK03	Summary of Derived Daprodustat Plasma Pharmacokinetic Parameters (non-transformed) (Part 1)		SAC
3.4.	PK	PK03	Summary of Derived Daprodustat Plasma Pharmacokinetic Parameters (non-transformed) (Part 2)		SAC
3.5.	PK	PK05	Summary of Derived Daprodustat Plasma Pharmacokinetic Parameters (log-transformed) (Part 1)		SAC
3.6.	PK	PK05	Summary of Derived Daprodustat Plasma Pharmacokinetic Parameters (log-transformed) (Part 2)		SAC
3.7.	PK	PK_T1	Analysis of Tablet Strength Effect for Cmax, AUC(0-t), and AUC(0-inf) (Part 1)	Example Shell in Appendix 10	SAC
3.8.	PK	PK_T1	Analysis of Food Effect for Cmax, AUC(0-t), and AUC(0-inf) (Part 2)	Example Shell in Appendix 10	SAC

10.9.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.1.	PK	PK16b	Individual Daprodustat Plasma Concentration-Time Plots by Subject (Part 1)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.2.	PK	PK16b	Individual Daprodustat Plasma Concentration-Time Plots by Subject (Part 2)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.3.	PK	PK16b	Individual Daprodustat Plasma Concentration-Time Plots by Tablet Strength (Part 1)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.4.	PK	PK16b	Individual Daprodustat Plasma Concentration-Time Plots by Food State (Part 2)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.5.	PK	PK17	Mean (+SD) Daprodustat Plasma Concentration-Time Plots (Part 1)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.6.	PK	PK17	Mean (+SD) Daprodustat Plasma Concentration-Time Plots (Part 2)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.7.	PK	PK18	Median Daprodustat Plasma Concentration-Time Plots (Part 1)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.8.	PK	PK18	Median Daprodustat Plasma Concentration-Time Plots (Part 2)	A graph on linear and semi-logarithmic scales will be produced.	SAC
3.9.	PK	PK_F1	Plot of Individual Daprodustat Plasma Cmax, AUC(0-t), and AUC(0-inf) by Tablet Strength (Part 1)	Example Shell in Appendix 10	SAC
3.10.	PK	PK_F1	Plot of Individual Daprodustat Plasma Cmax, AUC(0-t), and AUC(0-inf) by Food State (Part 2)	Example Shell in Appendix 10	SAC

10.9.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines Not provided separately	SAC
2.	Safety	ES3	Listing of Reasons for Study Withdrawal (Part 1)	ICH E3	SAC
3.	Safety	ES3	Listing of Reasons for Study Withdrawal (Part 2)	ICH E3	SAC
4.	Safety	SD3	Listing of Reasons for Treatment Discontinuation (Part 1)	ICH E3	SAC
5.	Safety	SD3	Listing of Reasons for Treatment Discontinuation (Part 2)	ICH E3	SAC
6.	Safety	TA2	Listing of Planned and Actual Treatments (Part 1)	IDSL	SAC
7.	Safety	TA2	Listing of Planned and Actual Treatments (Part 2)	IDSL	SAC
Protocol Deviations					
8.	Safety	DV2A	Listing of Important Protocol Deviations (Part 1)	ICH E3	SAC
9.	Safety	DV2A	Listing of Important Protocol Deviations (Part 2)	ICH E3	SAC
10.	Safety	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations (Part 1)	ICH E3	SAC
11.	Safety	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations (Part 2)	ICH E3	SAC
Populations Analysed					
12.	Safety	SP3A	Listing of Subjects Excluded from PK Population (Part 1)	ICH E3	SAC
13.	Safety	SP3A	Listing of Subjects Excluded from PK Population (Part 2)	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
14.	Safety	DM4	Listing of Demographic Characteristics (Part 1)	ICH E3	SAC
15.	Safety	DM4	Listing of Demographic Characteristics (Part 2)	ICH E3	SAC
16.	Safety	DM10	Listing of Race (Part 1)	ICH E3	SAC
17.	Safety	DM10	Listing of Race (Part 2)	ICH E3	SAC
Prior and Concomitant Medications					
18.	Safety	MH3	Listing of Medical Conditions (Part 1)	IDSL	SAC
19.	Safety	MH3	Listing of Medical Conditions (Part 2)	IDSL	SAC
20.	Safety	CM5	Listing of Concomitant Medications (Part 1)	IDSL	SAC
21.	Safety	CM5	Listing of Concomitant Medications (Part 2)	IDSL	SAC
Exposure					
22.	Safety	EX4	Listing of Exposure Data (Part 1)	ICH E3	SAC
23.	Safety	EX4	Listing of Exposure Data (Part 2)	ICH E3	SAC
Meal					
24.	Safety	CP_ML1x	Listing of Dosing Times, Meal Start and End Times on Fed Treatment Days (Part 2)		SAC
Safety					
Adverse Events					
25.	Safety	AE9CP	Listing of All Adverse Events (Part 1)	ICH E3	SAC
26.	Safety	AE9CP	Listing of All Adverse Events (Part 2)	ICH E3	SAC
27.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events (Part 1)	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
28.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events (Part 2)	ICH E3	SAC
29.	Safety	AE2	Listing of Relationship between System Organ Class and Verbatim Text	IDSL Not provided separately	SAC
Serious and Other Significant Adverse Events					
30.	Safety	AE9CPa	Listing of Serious Adverse Events (Part 1)	ICH E3	SAC
31.	Safety	AE9CPa	Listing of Serious Adverse Events (Part 2)	ICH E3	SAC
32.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event (Part 1)	ICH E3	SAC
33.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event (Part 2)	ICH E3	SAC
34.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study (Part 1)	ICH E3	SAC
35.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study (Part 2)	ICH E3	SAC
Hepatobiliary (Liver)					
36.	Safety	MH3	Listing of Medical Conditions for Participants with Liver Stopping Events (Part 1)	IDSL	SAC
37.	Safety	MH3	Listing of Medical Conditions for Participants with Liver Stopping Events (Part 2)	IDSL	SAC
38.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events (Part 1)	IDSL	SAC
39.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events (Part 2)	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
All Laboratory					
40.	Safety	LB6	Listing of All Chemistry Data (Part 1)		SAC
41.	Safety	LB6	Listing of All Chemistry Data (Part 2)		SAC
42.	Safety	LB6	Listing of All Chemistry Data for Subjects with Any Value of Potential Clinical Importance (Part 1)	ICH E3	SAC
43.	Safety	LB6	Listing of All Chemistry Data for Subjects with Any Value of Potential Clinical Importance (Part 2)	ICH E3	SAC
44.	Safety	LB6	Listing of All Haematology Data (Part 1)		SAC
45.	Safety	LB6	Listing of All Haematology Data (Part 2)		SAC
46.	Safety	LB6	Listing of All Haematology Data for Subjects with Any Value of Potential Clinical Importance (Part 1)	ICH E3	SAC
47.	Safety	LB6	Listing of All Haematology Data for Subjects with Any Value of Potential Clinical Importance (Part 2)	ICH E3	SAC
48.	Safety	LB6	Listing of Chemistry Values of Potential Clinical Importance (Part 1)		SAC
49.	Safety	LB6	Listing of Chemistry Values of Potential Clinical Importance (Part 2)		SAC
50.	Safety	LB6	Listing of Haematology Values of Potential Clinical Importance (Part 1)		SAC
51.	Safety	LB6	Listing of Haematology Values of Potential Clinical Importance (Part 2)		SAC
52.	Safety	LB6	Listing of Urinalysis Data (gravity and pH) (Part 1)		SAC
53.	Safety	LB6	Listing of Urinalysis Data (gravity and pH) (Part 2)		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
54.	Safety	LB14	Listing of Urinalysis Data (Glucose, Protein, Blood, Ketones, Bilirubin, and Urobilinogen) (Part 1)	ICH E3	SAC
55.	Safety	LB14	Listing of Urinalysis Data (Glucose, Protein, Blood, Ketones, Bilirubin, and Urobilinogen) (Part 2)	ICH E3	SAC
ECG					
56.	Safety	EG4	Listing of All ECG Values (Part 1)		SAC
57.	Safety	EG4	Listing of All ECG Values (Part 2)		SAC
58.	Safety	EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance (Part 1)	IDSL	SAC
59.	Safety	EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance (Part 2)	IDSL	SAC
60.	Safety	EG4	Listing of ECG Values of Potential Clinical Importance (Part 1)	IDSL	SAC
61.	Safety	EG4	Listing of ECG Values of Potential Clinical Importance (Part 2)	IDSL	SAC
62.	Safety	EG6	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding (Part 1)	IDSL	SAC
63.	Safety	EG6	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding (Part 2)	IDSL	SAC
64.	Safety	EG6	Listing of Abnormal ECG Findings (Part 1)	IDSL	SAC
65.	Safety	EG6	Listing of Abnormal ECG Findings (Part 2)	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
66.	Safety	VS5	Listing of All Vital Signs Data (Part 1)	IDSL	SAC
67.	Safety	VS5	Listing of All Vital Signs Data (Part 2)	IDSL	SAC
68.	Safety	VS5	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance (Part 1)	IDSL	SAC
69.	Safety	VS5	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance (Part 2)	IDSL	SAC
70.	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance (Part 1)	IDSL	SAC
71.	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance (Part 2)	IDSL	SAC
PK					
72.	PK	PK08	Listing of Daprodustat Plasma Pharmacokinetic Concentration-Time Data (Part 1)	IDSL	SAC
73.	PK	PK08	Listing of Daprodustat Plasma Pharmacokinetic Concentration-Time Data (Part 2)	IDSL	SAC
74.	PK	PK14	Listing of Derived Daprodustat Plasma Pharmacokinetic Parameters (Part 1)	IDSL All PK parameters in Section 8.1.1.2 will be provided in a listing	SAC
75.	PK	PK14	Listing of Derived Daprodustat Plasma Pharmacokinetic Parameters (Part 2)	IDSL All PK parameters in Section 8.1.1.2 will be provided in a listing	SAC

10.10. Appendix 10: Example Mock Shells for Data Displays

Example: PK_T1 Page 1 of n
Protocol: 207727
Population: PK

Table X
Analysis of [Tablet Strength Effect/Food Effect] for Cmax, AUC(0-t), and AUC(0-inf) (Part [1 or 2])

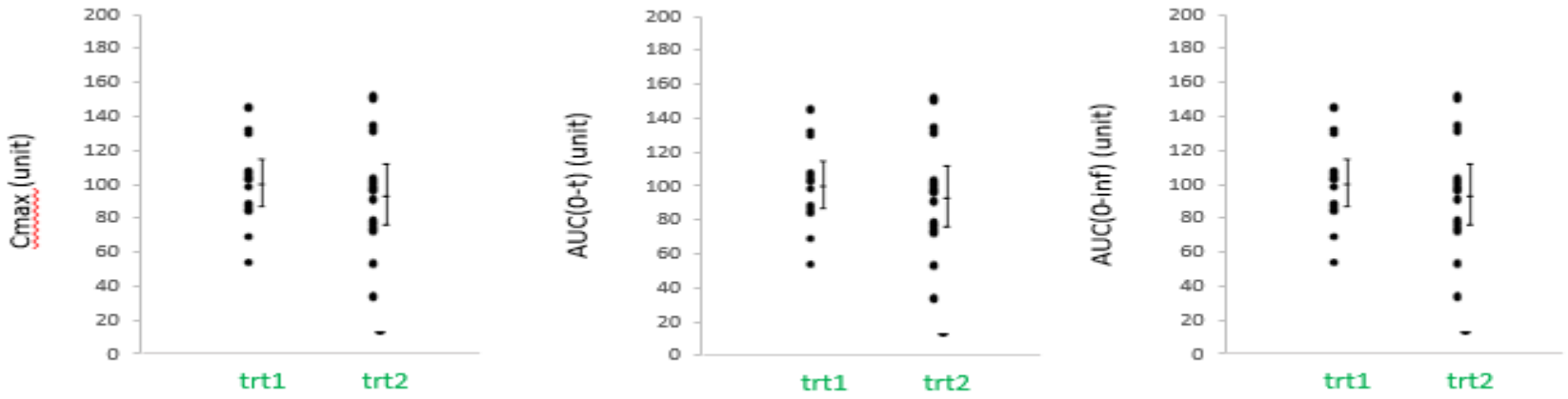
Parameter	Treatment	N	n	Adjusted Geom Mean	Ratio (trt2/trt1)	90% CI	%CVw[1]
Cmax (unit)	trt1	xx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
	trt2	xx	xx	xx.xxx			
AUC(0-t)(unit)	trt1	xx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
	trt2	xx	xx	xx.xxx			
AUC(0-inf) (unit)	trt1	xx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
	trt2	xx	xx	xx.xxx			

[1] Within-subject variability of each PK parameter

Programming notes: For Part1, trt1 = “4mg x 1” and trt2 = “2mg x 2”. For Part2, trt1 = “fasted” and trt2 = “fed”.

Example: PK_F1
Protocol: 207727
Population: PK

Table X
Plot of Individual Daprodustat Plasma Cmax, AUC(0-t), AUC(0-inf) by [Tablet Strength Effect/Food Effect] (Part [1 or 2])



Note: Geometric mean and 95% CI

Programming notes: For Part1, trt1 = "4mg x 1" and trt2 = "2mg x 2". For Part2, trt1 = "fasted" and trt2 = "fed".
Programming notes: AUC(0-inf) will also be presented.
Programming notes: Figures will be presented in left (Cmax), center (AUC(0-t), and right (AUC(0-inf).