Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function
Compound Number	:	GSK1278863
Effective Date	:	22-NOV-2017

Description:

- The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in Clinical Pharmacology Study Report for Protocol 200231.

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the Reporting and Analysis Plan
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe: • The planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol 200231. This RAP is intended to describe the safety and pharmacokinetic (PK) analyses required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC).
Protocol	• This RAP is based on original protocol (Dated: [23-May-2017]) for study 200231 [GlaxoSmithKline Document Number: 2016N305941_00].
Primary Objectives	• To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), and GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI). • To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat in plasma.
Primary Endpoints	• Daprodustat and its metabolites in plasma area under the concentration-time curve from time zero (predose) extrapolated to infinite time [AUC (0-∞)], percentage of AUC (0-∞) obtained by extrapolation (%AUCex), time zero (predose) to time of last quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life ($t_{½}$), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat. • Unbound concentration and unbound fraction in plasma of daprodustat at 3, 12, and 24 hours (h) post dose (as data permit).
Secondary Objectives	• To characterize the effect of hepatic impairment on the pharmacodynamics (PD) effect of daprodustat. • To assess the safety and tolerability of a single 6 mg dose of daprodustat.

Overview	Key Elements of the Reporting and Analysis Plan
Secondary Endpoints	• Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and erythropoietin area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable erythropoietin concentration [AUC (0-t, EPO)]. • Safety and tolerability parameters, including adverse events and clinical laboratory tests.
Study Design	• A phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with moderate (Part 1) and either mild or severe (Part 2) hepatic impairment and matched, healthy control participants with normal hepatic function. **Part 1:** • Part 1 will include 2 cohorts. Cohort 1 includes participants with moderate hepatic impairment, and Cohort 2 includes matched healthy control participants. • Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (n=8; Child-Pugh score of 7-9). • All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. • Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 1 of the study. **Part 2:** • Part 2 will include 2 cohorts. Cohort 3 includes participants with either mild or severe hepatic impairment, and Cohort 4 includes matched healthy control participants. • Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with either mild impairment (Child-Pugh score of 5-6) or participants with severe impairment (Child-Pugh score of 10-13) (n=8). • All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. • Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 2 of the study. • All participants' total involvement with the study will be up to 7 weeks.
Planned Analyses	• An informal interim analysis of the primary PK endpoints of AUC (0-∞), AUC(0-t) and Cmax will be conducted for completion of Part 1 of the study. • The final planned analyses will be performed, as defined in this RAP document, after database freeze has been declared. • Safety and PK/PD data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data

Overview	Key Elements of the Reporting and Analysis Plan
	Standards Library (IDSL) standards.
Analysis Population	• Screened Population: All participants who were screened will be considered for this population. This population will be used for summarizing screening status. • Enrolled Population: All participants who were successfully screened and enrolled for the trial and for whom a record exists on the study database. This population will be used for summarize number of subjects by Country and Site ID and age ranges. • Safety Population: All participants who received at least 1 dose of study medication. This will be the primary population for the safety analyses. • PK Population: All participants in the 'Safety Population' for whom a PK sample has been obtained and analyzed will be included in the PK population. This population will be used in the evaluation of PK data. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PK data. • PD Population: All participants in the 'Safety Population' who had at least 1 PD assessment. PD samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PD data.
Hypothesis	No formal hypotheses will be tested.
Interim Analyses	An informal interim analysis of the primary PK endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria: ➢ If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to the healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group. ➢ If a $\geqslant$ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to the healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The parameters “Emax” and “AUC (E, last)” in the list of secondary endpoints in the protocol have been replaced/added with “Cmax, EPO”, “Tmax, EPO” and “AUC (0-t, EPO)”, respectively. These new parameters provide a more accurate reflection of the scope for the PD analysis. There were no other changes or deviations to the originally planned statistical analysis specified in the protocol [Dated: 23-May-2017].

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), and GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI).	• Daprodustat and its metabolites plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC (0-∞)], percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time zero (pre-dose) to last time of quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life ($t_{½}$), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat.
• To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat in plasma.	• Unbound concentration and unbound fraction in plasma of daprodustat at 3, 12 and 24 h post dose (as data permit).
Secondary Objectives	**Secondary Endpoints**
• To characterize the effect of hepatic impairment on the PD effect of daprodustat.	• Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and erythropoietin area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable concentration [AUC (0-t, EPO)].
• To assess the safety and tolerability of a single 6 mg dose of daprodustat.	• Safety and tolerability parameters, including adverse events and clinical laboratory tests.

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	A phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with moderate (Part 1) and either mild or severe (Part 2) hepatic impairment and matched, healthy control participants with normal hepatic function.

Overview of Study Design and Key Features	
	Part 1: Part 1 will include 2 cohorts. Cohort 1 includes participants with moderate hepatic impairment, and Cohort 2 includes matched healthy control participants. Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (n=8; Child-Pugh score of 7-9). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 1 of the study. **Part 2**: Part 2 will include 2 cohorts. Cohort 3 includes participants with either mild or severe hepatic impairment, and Cohort 4 includes matched healthy control participants. Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with either mild impairment (Child-Pugh score of 5-6) or participants with severe impairment (Child-Pugh score of 10-13) (n=8). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 2 of the study. All participant's total involvement with the study will be up to 7 weeks.
Dosing	**Part 1** All participants will be administered 6 mg of daprodustat as a single oral dose, with assessments conducted for up to 48 h post dosing (Please refer to Appendix 2) **Part 2** If conducted, all participants will be administered 6 mg of daprodustat as a single oral dose, with assessments conducted for up to 48 h post dosing.
Treatment Assignment	• Part 1 consists of up to 16 participants (8 in each cohort, excluding possible replacements).

Overview of Study Design and Key Features	
	• Part 2 consists of up to 16 participants (8 in each cohort, excluding possible replacements). • All participants will receive the same treatment of a single oral 6 mg dose of daprodustat.
Interim Analyses	• An informal interim analysis of the primary PK endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria: ➢ If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group. ➢ If a ≥ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

2.4. Statistical Hypotheses

No formal hypotheses will be tested for this study. An estimation approach will be used to evaluate the effect of hepatic impairment (i.e., moderate and potentially either mild or severe) on the PK of daprodustat. The primary comparisons of interest are the single dose PK parameters, including Cmax and AUC of daprodustat in each hepatic impaired cohort compared to the normal hepatic function cohort.

The point estimates of the geometric least squares (GLS) mean ratio for the PK parameters and associated 90% confidence intervals (CIs) will be provided for cohort comparisons (hepatically impaired : healthy participants). The PK parameters will be log-transformed prior to analysis and cohort comparisons will be expressed as ratios on the original scale. %AUCex and Tmax and will be summarized descriptively.

3. PLANNED ANALYSES

3.1. Interim Analyses

An informal interim analysis of the primary endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

- If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group.

- If a ≥ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

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 and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Endpoint(s) Evaluated
Screened Population	• All participants who were screened will be considered for this population. This population will be used for summarizing screening status.	• Screen Failure
Enrolled Population	• All participants who were successfully screened and enrolled for the trial and for whom a record exists on the study database. This population will be used for summarize number of subjects by Country and Site ID and age ranges.	• Study Population
Safety Population	• All participants who received at least one dose of study medication. This will be the primary population for the safety analyses.	• Study Population • Safety
PK Population	• All participants in the 'Safety Population' for whom a PK sample has been obtained and analyzed will be included in the PK population. This population will be used in the evaluation of PK data. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PK data.	• PK
PD Population	• All participants in the 'Safety Population' who had at least 1 PD assessment. PD samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PD data.	• PD

NOTES:

- Please refer to Appendix 10 which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant 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 and deviations which may lead to exclusion from the analysis are captured and categorized on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Treatment States and Phases
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
10.7	Appendix 7: Values of Potential Clinical Importance
10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population displays will be based on the "Safety" population, unless otherwise specified.

Table 2 provides an overview of the planned study population displays, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated	
	Table	Listing
Subject Disposition		
Subject Disposition	Y	
Reasons for Screening Failures [1]	Y	Y
Reasons for Withdrawals		Y
Important Protocol Deviations	Y	Y
Inclusion and Exclusion Criteria Deviations		Y
Demography		
Demographic Characteristics	Y	Y
Race & Racial Combinations	Y	Y
Study Populations	Y	Y
Summary of Number of Subjects by Country and Site ID	Y	
Summary of Age Ranges	Y	
Summary of Child-Pugh score	Y	Y
Medical/Surgical History & Concomitant Medications		
Medical/Surgical History		Y
Concomitant Medication	Y	Y
Exposure and Treatment Compliance		
Exposure to Study Treatment		Y

NOTES:

- Y = Yes display generated.

[1] Conditional displays, if data is available table and listing will be generated.

7. PRIMARY STATISTICAL ANALYSES

7.1. Interim Analyses

An informal interim analysis of the primary PK endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

- If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group.

- If a ≥ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

7.2. Pharmacokinetic Analyses

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of Clinical Pharmacology Sciences and Study Operations (CPSSO), GlaxoSmithKline.

The merge of PK concentration data and CRF data will be performed by PPD Programming under the direct auspices of Clinical Programming, GlaxoSmithKline.

Derivation of PK parameters will be performed by PPD PK group under the direct auspices of Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline.

Statistical analysis of PK data and parameters will be performed by PPD Statistics and Programming under the direct auspices of Clinical Statistics, GlaxoSmithKline.

7.2.1. Overview of Planned Pharmacokinetic Analyses

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

Table 3 provides an overview of the planned non-compartmental PK analyses of daprodustat and its six metabolites, (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6) and GSK2531401 (M13)) with full details being presented in Appendix 10: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK Concentrations				Y[3]	Y[1] [2]	Y[1]	Y[3]							
Plasma PK Parameters	Y[4]			Y			Y	Y[4]		Y	Y			

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- 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.

[1] Linear and Semi-Logarithmic plots will be created on the same display.
[2] Separate mean and median plots will be generated.
[3] Unbound PK Concentrations for Daprodustat only will be summarized on a separate display.
[4] Supportive SAS Output from Statistical Analysis.

7.2.1.1. Drug Concentration Measures

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

7.2.1.2. Pharmacokinetic Parameters

7.2.1.2.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.4.3. Reporting Process & Standards).
- Plasma concentration-time data for daprodustat and its six predominant metabolites will be analysed by non-compartmental methods according to current working practices with WinNonlin 6.4 or higher.
- Non-compartmental analysis will be performed in accordance with GSK PK Guidance document GUI_51487.
- All calculations of non-compartmental parameters will be based on actual sampling times recorded during the study.
- PK parameters described in Table 4 will be determined from plasma concentration-time data as data permits.

Table 4 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (daprodustat and its six metabolites).
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity calculated as: **AUC(0-∞) = AUC(0-t) + C(t) / lambda_z** (daprodustat and its six metabolites) where C(t) is the last measurable concentration.
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: **[AUC (0-∞) – AUC(0-t)] / AUC (0-∞) x 100** (daprodustat and its six metabolites)
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data. (daprodustat and its six metabolites)
Lambda_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve. (daprodustat and its six metabolites)
Tmax	Time to reach Cmax, determined directly from the concentration-time data. (daprodustat and its six metabolites)
t½	Apparent terminal phase half-life will be calculated as: **t½ = ln2 / Lambda_z** (daprodustat and its six metabolites)
fu	Unbound fraction (fu) of daprodustat will be calculated using the total and unbound plasma concentration of daprodustat generated at 3, 12 and 24 h post dose for both normal and hepatic impaired participants using the following formula: **Fu=Cunbound/Ctotal**
free AUC(0-t)	AUC(0-t) * fu (daprodustat)

Parameter	Parameter Description
free AUC(0-∞)	AUC(0-∞) * fu (daprodustat)
free Cmax	Cmax * fu (daprodustat)

7.2.1.2.2. Statistical Analysis of Pharmacokinetic Parameters

For each of the parameters AUC (AUC(0-∞), AUC (0-t) and %AUCex)-total and free, t½, Tmax and Cmax-total and free the following summary statistics will be calculated and tabulated by each cohort:

- **Untransformed Data:** N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum and maximum.
- **Log_e-transformed Data:** Geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and between subject geometric coefficient of variation (%CVb).

The following PK statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined plasma profiles). Pharmacokinetic analysis and Statistical analyses of the PK parameter data will be the responsibility of PPD.

Planned Pharmacokinetic Statistical Analyses
Endpoint(s)
• Plasma primary PK endpoints include AUC (0-t), AUC (0-∞), Cmax and t½, as data permit
Model Specification
• The log-transformed AUC(0-t), AUC (0-∞), Cmax and t½ values for daprodustat and metabolites will be analyzed separately using analysis of variance (ANOVA) as appropriate to the study design, fitting a fixed effect term for cohort. Point estimates and 90% CIs for the differences of interest (hepatically impaired versus healthy participants) will be constructed using the residual variance.
Model Checking & Diagnostics
• Refer to Appendix 8 : Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Statistical analysis by ANOVA will be presented in tabular format with geometric mean ratios for the hepatically impaired versus healthy participants and 90% CI for the ratios of AUC (0-t), AUC (0-∞), Cmax and t½ for daprodustat and metabolites.
Endpoint(s)
• Tmax

Planned Pharmacokinetic Statistical Analyses
Model Specification
• If data permit, Tmax will be analyzed nonparametrically using the Mann Whitney U test (Wilcoxon rank sum test). The point estimates and 90% CI for the median differences will be derived for hepatic impairment and healthy participants based on Hodges-Lehmann estimation.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The point estimates and 90% confidence intervals for the median differences will be calculated for the cohort difference (hepatically impaired – healthy participants).

Sensitivity Pharmacokinetic Statistical Analyses
Endpoint(s)
• AUC(0-t), AUC(0-∞), Cmax and t1/2
Model Specification
• The log-transformed AUC(0-t), AUC(0-∞), Cmax and t½ values for daprodustat and metabolites will be analyzed separately using analysis of covariance (ANCOVA) as appropriate to the study design, fitting fixed effect terms for cohort, gender, age and BMI. Point estimates and 90% CIs for the differences of interest (hepatically impaired versus healthy participants) will be constructed using the residual variance.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Statistical analysis by ANCOVA will be presented in tabular format with geometric mean ratios for the difference between participants with hepatically impairment and healthy participants, and 90% CI for the ratios of AUC(0-t), AUC(0-∞), Cmax and t½ for daprodustat and metabolites.

7.3. Pharmacodynamic Analyses

7.3.1. Overview of Planned Pharmacodynamic Analyses

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

Table 5 provides an overview of the planned PD analyses, with full details being presented in Appendix 10: List of Data Displays.

Table 5 Overview of Planned Pharmacodynamic Analyses

Display Type	Untransformed													
	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PD Concentrations				Y	Y[1][2]	Y[1]	Y							
PD Parameters				Y	Y		Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Linear and Semi-Logarithmic plots will be created on the same display.

[2] Separate mean and median plots will be generated.

7.3.1.1. Pharmacodynamic Parameters

7.3.1.1.1. Deriving Pharmacodynamic Parameters

- Although erythropoietin (EPO) is an endogenous substance, the plasma concentrations of erythropoietin will not be corrected for baseline endogenous levels Pharmacodynamic analysis will be performed on uncorrected (absolute erythropoietin concentrations) data only.

- Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable erythropoietin concentration [AUC (0-t, EPO)] will be listed and summarised if data is available.

- Pharmacodynamic parameters described in Table 6 will be determined from plasma absolute erythropoietin concentration-time data as data permits.

Table 6 Derived Pharmacodynamic Parameters

Parameter	Parameter Description
Cmax, EPO	Maximum observed EPO concentration
Tmax, EPO	Time of the maximum observed EPO concentration
AUC (0-t, EPO)	Area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable erythropoietin concentration

8. SAFETY ANALYSES

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

8.1. Overview of Planned Adverse Events Analyses

Adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary and summarized by cohort.

Counting of AEs will be based on the number of subjects – not the number of AEs. For example, if a subject experiences the same AE (i.e. same preferred term) more than once, they are counted only once under the count for the preferred term. If a subject experiences more than one AE in a particular system organ class (SOC), they will only be included once in the count for the SOC, but will appear in the count for each appropriate preferred term within the SOC. Therefore, the sum of the numbers of subjects with each preferred term event within a SOC may exceed the total number of subjects with at least one event.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 7 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs	Y		Y
Serious AEs	Y		Y
Drug Related AEs	Y		Y
AEs leading to withdrawal	Y		Y
Summary of Common (>=25%) Non-serious Adverse Events by System Organ Class and Preferred Term	Y		
Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Y		
Relationship Between System Organ Class and Verbatim Text			Y
Subject Numbers for Individual Adverse Events			Y
AEs of special interest [1]			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- 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.

[1] Conditional displays, if data is available listing will be generated.

8.2. Overview of Planned Clinical Laboratory Analyses

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 8 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Clinical Chemistry	Y		Y	Y		
Clinical Chemistry (Values Outside the PCI Range)			Y			
Haematology						
Haematology	Y		Y	Y		
Haematology (Values Outside the PCI Range)			Y			
Urinalysis						
Urinalysis			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- 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.

8.3. Overview of Planned Other Safety Analyses

Table 9 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays

Table 9 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ 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		
ECG Values Outside the PCI Range			Y			
Maximum QTc Values Post-Baseline Relative to Baseline by Category				Y		
Maximum Increase in QTc Values Post-Baseline Relative to Baseline by				Y		

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Category						
Vital Signs						
Vitals Values	Y		Y	Y		
Vital Signs Measurements Outside the PCI Range			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.

9. REFERENCES

GlaxoSmithKline Document Number 2016N305941_00 (Original – 23-MAY-2017): A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function.

GUI_137354, Information for Authors: Reporting and Analysis Plan (RAP), Global

GUI_51487, Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global

SOP_54838, Development, Review & Approval of Reporting & Analysis Plan (RAP), Global

10. APPENDICES

Section	Appendix
RAP Section 4: Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
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Section 10.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.5	Appendix 5: Derived and Transformed Data • General • Study Population • Safety • Pharmacokinetic • Pharmacodynamic

Section 10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
	• Premature Withdrawals
	• Handling of Missing Data
	  ○ Handling of Missing Dates
	  ○ Handling of Partial Dates

Section 10.7	Appendix 7: Values of Potential Clinical Importance • Laboratory Values • ECG • Vital Signs
Section 10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.9	Appendix 9: Abbreviations & Trade Marks
Section 10.10	Appendix 10: List of Data Displays

10.1 Appendix 1: Protocol Deviation Management

There are no pre-defined categories leading to exclusion from the PK population but all protocol deviations will be reviewed on a case-by-case basis.

No subjects will be excluded from the safety population.

10.2 Appendix 2: Time & Events

10.2.1 Protocol Defined Time & Events

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Informed Consent	X																	
Inclusion & Exclusion Criteria	X	X																
Demography	X																	
Full physical exam	X																	
Medical history	X																	
Past/current medications	X																	
Laboratory assessments [3]	X																X	X
Drug/Alcohol Screen	X	X																
12-lead ECG	X	X															X	X
Vital Signs and Weight	X	X															X	X
Pregnancy Test	X[4]	X[4]																

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Females only: Estrogen and FSH[5]	X																	
Admission to Unit		X																
Brief Physical Exam		X															X	X
Administration of daprodustat				X														
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Protein binding sample			X						X					X	X			
EPO blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X												X		X	X
Discharge from Unit																	X	

[1] All participants will undergo screening assessments within 28 days of enrolment.
[2] A follow-up visit will occur 10-14 days after the dose of study treatment.
[3] Laboratory assessment guidance can be found in Protocol Appendix 3.
[4] For women of childbearing potential that are not using an approved method of contraception (see Protocol Appendix 6), one negative pregnancy test between Day -7 and Day -4 AND another negative pregnancy test on Day -1 is required. Additional guidance can be found in Protocol Section.9.5.5.
[5] All females are to have estrogen and FSH measured at screening.

10.3 Appendix 3: Treatment States

10.3.1 Treatment States for AE Data

Assessments and events will be classified according to date of occurrence relative to the start and/or stop date of the study treatment.

Treatment State	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before the treatment stop date 2 days Study Treatment Start Date $\leqslant$ AE Start Date $\leqslant$ Study Treatment Stop Date + 2 days
Post-Treatment	If AE onset date is after the treatment stop date + 2 days AE Start Date > Study Treatment Stop Date + 2 days
AE Onset Time Since First Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date $\leqslant$ AE Onset Date = AE Onset Date - Treatment Start Date +1 day Missing otherwise
AE Duration (Days)	AE Resolution Date – AE Onset Date + 1 day
AE 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 On-Treatment.

10.4 Appendix 4: Data Display Standards & Handling Conventions

10.4.1 Study Treatment & Display Descriptors

Treatment Group Descriptions			
Study Part	Cohort		Data display for reporting
	Code	Description	Description[2]
1	1	Moderate Hepatic Impairment	Cohort 1
1	2	Matched Healthy Controls for Moderate Hepatic Impairment	Cohort 2
2	3	Mild Hepatic Impairment / Severe Hepatic Impairment[1]	Cohort 3
2	4	Matched Healthy Controls for Mild Hepatic Impairment / Matched Healthy Controls for Severe Hepatic Impairment[1]	Cohort 4

[1] Either Mild or Severe Hepatic Impairment participants will be selected based on part 1 results.

[2] The word "Cohort" may be omitted from displays in order to limit wrapping

10.4.2 Baseline Definition & Derivations

10.4.2.1 Baseline Definitions

For all endpoints (except as noted in Table 9) the baseline value will be the latest non-missing pre-dose assessment. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used, unless otherwise stated.

Table 10 Baseline Definitions

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
12 Lead ECG & Vital Signs	X	X		Day -1
Haematology	X			Screening
Clinical Chemistry	X			Screening
Pharmacodynamic				
EPO blood sampling			X	Pre-Dose

10.4.2.2 Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.4.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries. Unless otherwise stated, if baseline data is missing or post-dose data is missing no derivation will be performed.
- The baseline definition will be footnoted on all change from baseline displays.

10.4.3 Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS 9.3 or latest software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: arenv/arprod/GSK1278863/mid200231/final
QC Spreadsheet	: arenv/arwork/GSK1278863/mid200231/final/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & AdaM IG Version 1.0). • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated only for SAC.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • 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. • 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: o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. o 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 (see Section 4.1).

Reporting Standards	
• 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. ○ Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables, unless otherwise stated. • Unscheduled visits will not be included in 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, %
Reporting of Pharmacokinetic and Pharmacodynamic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 and Standards for the Transfer and Reporting of PK and PD Data using HARP. For NQ values, refer to GUI_51487.
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics. (Log_e Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log transformed data and %CVb will be reported. CVb (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 [NOTE: SD = SD of log_e transformed data]
Parameters Not Being Log_e Transformed	%AUCex and Tmax
Summary Tables	Cmax, Tmax, AUC(0-t), AUC (0-∞), t1/2, and %AUCex as data permit. The following PK parameters will not be summarised: first point, last point, and number of points used in the determination of λz.
Summary of Statistical analysis	Geometric mean ratio of hepatic impaired : healthy, point estimate and an associated 90% CI.
Listings	Include PK Parameters Cmax, Tmax, AUC(0-t), AUC (0-∞), and t1/2 as data permit. Include the first point, last point and number of points used in the determination of λz.
Reporting of Pharmacodynamic Parameters	
Descriptive Summary Statistics	N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum and maximum
Parameters	Cmax, EPO, Tmax, EPO and AUC (0-t, EPO)
Summary Tables	Cmax, EPO, Tmax, EPO and AUC (0-t, EPO) as data permit
Listings	Include PD Parameters Cmax, EPO, Tmax, EPO and AUC (0-t, EPO) as data permit

Reporting Standards
Graphical Displays
• Refer to IDSL Statistical Principles 7.01 to 7.13 and Standards for the Transfer and Reporting of PK and PD Data using HARP.

10.5 Appendix 5: Derived and Transformed Data

10.5.1 General

Multiple Measurements at One 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.
- The worst finding/interpretation associated with multiple measurements as the finding/interpretation for that time point.
- Subjects having both High and Low values for Normal Ranges at any post-baseline visits 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 Treatment start date:
  - Ref Date = Missing → Day = Missing
  - Ref Date < Treatment start Date → Study Day = Ref Date – Treatment start Date
  - Ref Data ≥ Treatment start Date → Study Day = (Ref Date – Treatment start Date) + 1

10.5.2 Study Population

Demographics

Age

- GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  - Any subject with a missing day will have this imputed as day '15'.
  - Any subject with a missing date and month will have this imputed as '30th June'.
- Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)

- Calculated as **Weight (kg) / [Height (m)]^2**

10.5.3 Safety

Laboratory Parameters

- 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 decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Decimal Places = '< x' becomes x – 0.01

Laboratory Parameters

- Example 2: 1 Decimal Places = '> x' becomes x + 0.1
- Example 3: 0 Decimal Places = '< x' becomes x – 1

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as :
  [1] If QTcB is machine read & QTcF is not provided, then :

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
- Machine read values of RR should not be replaced with derived values.

Corrected QT Intervals

- When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements.
- IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as :

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

AEs

AEs OF Special Interest

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

10.6 Appendix 6: Premature Withdrawals & Handling of Missing Data

10.6.1 Premature Withdrawals

Element	Reporting Detail
General	• A completed subject is one who has completed all phases of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study. • All subjects who withdraw prematurely from the study will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). • All available data collected up until the point of withdrawal, and the follow-up visits will be used in the analyses and will be listed and all available planned data will be included in the summaries according to the populations defined in Section 4 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: • 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. • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects 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 Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows 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 may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: • Missing Start Day: First of the month will be used unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered On-treatment as per

Element	Reporting Detail
	Appendix 3: Treatment States and Phases). • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • AEs with entirely missing or unknown start dates will be assumed to be on-treatment for reporting. • AEs with missing end dates are not anticipated to affect reporting.

10.6.2.2 Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month • 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 recorded partial date will be displayed in listings.
Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made for calculating the time to onset and the duration of the event: • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month, unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered on-treatment as per Appendix 3: Treatment States). • 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, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • The recorded partial date will be displayed in listings.

10.6.2.3 Handling of PK Concentration Data

Element	Reporting Detail
General	• The PK population will be used for the concentration listing, summaries and plotting of the individual concentration-time profiles. • PK assay results from samples collected from a subject with vomiting occurring within 2 times the median Tmax will not be considered as evaluable. • For missing and NQ values, refer to GUI_51487.

10.6.2.4 Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Imputation	• No imputation will be performed for missing data

10.7 Appendix 7: Values of Potential Clinical Importance

10.7.1 Laboratory Values

Laboratory Values of Potential Clinical Importance **(Healthy subjects)**

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	>0.075	
Hemoglobin	g/L	Male		180
		Female		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
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		> 44.2
Glucose	mmol/L		3	9
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 Values of Potential Clinical Importance **(Healthy subjects)**

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

ECG Values of Potential Clinical Importance **(Hepatic Impaired Subjects)**

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 480
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 Values of Potential Clinical Importance **(Healthy Subjects)**

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

Vital Sign Values of Potential Clinical Importance **(Hepatic Impaired Subjects)**

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 90	> 160
Diastolic Blood Pressure	mmHg	< 45	> 95
Heart Rate	bpm	< 50(females) and <45(males)	> 100

10.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

Endpoint(s)	• PK End points AUC(0-t), AUC (0-∞), Cmax, and t½
Analysis	• ANOVA (primary) and ANCOVA (sensitivity)

Assumptions:

- For the Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored.
- Non-parametric analyses will be conducted if the normality assumption does not hold.

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1 Abbreviations

λz	Terminal phase rate constant
ADaM	Analysis Data Model
AE	Adverse Event
Ae	Excretion of unchanged drug
AIC	Akaike's Information Criteria
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC (0-∞)	Area under the concentration-time curve 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
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CKD	Chronic kidney disease
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling and Simulation
CPSR	Clinical Pharmacology Study Report
CPSSO	Clinical Pharmacology Sciences and Study Operations
CRF	Case Report Form
CV_b	Coefficient of Variation (Between)
DBR	Database Release
DP's	Decimal places
ECG	Electrocardiogram
Emax	Maximum observed effect
EPO	Erythropoietin
FSH	Follicle stimulating hormone
fu	Fraction unbound in plasma
GSK	GlaxoSmithKline
h	Hour
HARP	Harmonized Analysis and Reporting Process
Hg	Mercury
HI	Hepatic Impairment
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
kg	Kilogram
L	Litres
mg	Milligram
mL	Millilitre

mm	Millimetre
MM	Mixed Model
nm	Nanometer
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamic
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development
QSI	Quantitative Sciences India
QTc	Electrocardiogram QT interval corrected for heart rate
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables, Figures & Listings
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPDS	Statistics, Programming and Data Sciences
t½	Terminal phase half-life
Tmax	Time of occurrence of Cmax
ULN	Upper Limit of Normal

10.9.2 Trademarks

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
WinNonlin

10.10 Appendix 10: List of Data Displays

10.10.1 Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.11	N/A
Safety	2.1 to 2.19	N/A
Pharmacokinetic	3.1 to 3.9	3.1 to 3.3
Pharmacodynamic	4.1 to 4.2	4.1 to 4.3
Section	**Listings**	
ICH Listings	1 to 47	

10.10.2 Deliverable

Delivery	Description
IA	Interim Analysis Complete
SAC	Final Statistical Analysis Complete

10.10.3 Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.2	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
1.3	Enrolled	DV1	Summary of Important Protocol Deviations		SAC
Demography					
1.4	Safety	SAFE_T1	Summary of Child-Pugh Score		SAC
1.5	Safety	DM1	Summary of Demographic Characteristics		SAC
1.6	Enrolled	DM11	Summary of Age Ranges		SAC
1.7	Safety	DM5	Summary of Race and Racial Combinations		SAC
1.8	Safety	DM6	Summary of Race and Racial Combination Details		SAC
1.9	Enrolled	SP1A	Summary of Study Population		SAC
1.10	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC
Medical/Surgical History & Concomitant Medications					
1.11	Safety	CM1	Summary of Concomitant Medications		SAC

10.10.4 Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term		SAC
2.2	Safety	AE1CP	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
2.3	Safety	AE1CP	Summary of Adverse Events Leading to Withdrawal from Study		SAC
2.4	Safety	AE1CP	Summary of Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.5	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.6	Safety	AE15	Summary of Common (>=25%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
Laboratory Measurements					
2.7	Safety	LB1	Summary of Chemistry Values		SAC
2.8	Safety	LB1	Summary of Chemistry Changes from Baseline		SAC
2.9	Safety	LB17	Summary of Worst Case Chemistry Results Relative to Potential Clinical Importance Criteria Post-Baseline Relative to Baseline		SAC
2.10	Safety	LB1	Summary of Haematology Values		SAC
2.11	Safety	LB1	Summary of Haematology Changes from Baseline		SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12	Safety	LB17	Summary of Worst Case Haematology Results Relative to Potential Clinical Importance Criteria Post-Baseline Relative to Baseline		SAC
Electrocardiograms					
2.13	Safety	EG1	Summary of ECG Findings		SAC
2.14	Safety	EG2	Summary of ECG Values		SAC
2.15	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC
2.16	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
2.17	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
Vital Signs					
2.18	Safety	VS1	Summary of Vital Signs		SAC
2.19	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC

10.10.5 Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Table					
3.1	PK	PKCT1	Summary of Daprodustat and Metabolites Plasma Pharmacokinetic Concentration-Time Data		SAC
3.2	PK	PKCT1	Summary of Daprodustat Unbound Plasma Pharmacokinetic Concentration-Time Data		SAC
PK Derived Parameters					
3.3	PK	PKPT4	Summary of Derived Daprodustat and Metabolites Plasma Pharmacokinetic Parameters (Non-Transformed)	Parameters with units	SAC
3.4	PK	PKPT4	Summary of Derived Daprodustat Unbound Plasma Pharmacokinetic Parameters (Non-Transformed)	Parameters with units	SAC
3.5	PK	PKPT4	Summary of Derived Daprodustat and Metabolites Plasma Pharmacokinetic Parameters (Ln-Transformed)	Parameters with units	SAC
3.6	PK	PKPT4	Summary of Derived Daprodustat Unbound Plasma Pharmacokinetic Parameters (Ln-Transformed)	Parameters with units	SAC
PK Analysis Tables					
3.7	PK	PKPT3	Statistical Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters: Analysis of Variance (ANOVA)	AUC(0-t), AUC(0-∞), Cmax, t½, free AUC(0-t), free AUC(0-∞) and free Cmax	SAC
3.8	PK	PKPT3	Sensitivity Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters: Analysis of Covariance (ANCOVA)	AUC(0-t), AUC(0-∞), Cmax, t½, free AUC(0-t), free AUC(0-∞) and free Cmax	SAC
3.9	PK	PK_T1	Statistical Analysis of Daprodustat and Metabolites Tmax		SAC

10.10.6 Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1	PK	PKCF1P	Individual Daprodustat and Metabolites Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Paginate by cohort and analyte	SAC
Mean / Median Concentration Plots					
3.2	PK	PKCF2	Mean Daprodustat and Metabolites Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	SAC
3.3	PK	PKCF3	Median Daprodustat and Metabolites Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	SAC

10.10.7 Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PD Concentration Data					
4.1	PD	PKCT1	Summary of Erythropoietin Plasma Pharmacodynamic Concentration-Time Data		SAC
PD Derived Parameter					
4.2	PD	PKPT4	Summary of Derived Erythropoietin Plasma Pharmacodynamic Parameters	Parameters with units	SAC

10.10.8 Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
4.1	PD	PKCF1P	Individual Erythropoietin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Paginate by cohort	SAC
Mean / Median Concentration Plots					
4.2	PD	PKCF2	Mean Erythropoietin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	SAC
4.3	PD	PKCF3	Median Erythropoietin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	SAC

10.10.9 ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1	Safety	ES2	Listing of Reasons for Study Withdrawal		SAC
2	Screened	ES7	Listing of Reasons for Screen Failure		SAC
3	Enrolled	DV2	Listing of Important Protocol Deviations		SAC
4	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Demography					
5	Safety	SAFE_L1	Listing of Child-Pugh Classification and Treatment Assignment		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6	Safety	DM2	Listing of Demographic Characteristics		SAC
7	Safety	DM9	Listing of Race		SAC
8	Enrolled	SP3	Listing of Subjects Excluded from Any Population		SAC
Medical/Surgical History & Concomitant Medications					
9	Safety	MH2	Listing of Medical Conditions		SAC
10	Safety	CM3	Listing of Concomitant Medications		SAC
Exposure					
11	Safety	EX3	Listing of Exposure Data		SAC
Adverse Events					
12	Safety	AE2	Listing of Relationship between System Organ Class and Verbatim Text		SAC
13	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
14	Safety	AE8CP	Listing of All Adverse Events		SAC
15	Safety	AE8CP	Listing of Drug-Related Adverse Events		SAC
16	Safety	AE8CPA	Listing of Serious Adverse Events (Fatal & Non-Fatal)		SAC
17	Safety	AE8CP	Listing of Adverse Events Leading to Withdrawal from Study		SAC
18	Safety	AE8CP	Listing of Liver Adverse Events	Conditional display	SAC
19	Safety	AE8CP	Listing of Cardiovascular Adverse Events	Conditional display	SAC
20	Safety	AE8CP	Listing of Adverse Events of Special Interest	Conditional display	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory Measurements					
21	Safety	LB13	Listing of Laboratory Tests and Associated Reference Ranges		SAC
22	Safety	LB5	Listing of Chemistry Values of Potential Clinical Importance		SAC
23	Safety	LB5	Listing of All Chemistry Data for Subjects with Any Value of Potential Clinical Importance		SAC
24	Safety	LB5	Listing of Haematology Values of Potential Clinical Importance		SAC
25	Safety	LB5	Listing of All Haematology Data for Subjects with Any Value of Potential Clinical Importance		SAC
26	Safety	UR2A	Listing of Urinalysis Data		SAC
Electrocardiograms					
27	Safety	EG5	Listing of Abnormal ECG Findings		SAC
28	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC
29	Safety	EG3	Listing of ECG Values of Potential Clinical Importance		SAC
30	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
Vital Signs					
31	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance		SAC
32	Safety	VS4	Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Liver Events					
33	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional display	SAC
34	Safety	SU2	Listing of Alcohol Intake for Subjects with Liver Stopping Events	Conditional display	SAC
35	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Conditional display	SAC
36	Safety	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score	Conditional display	SAC
37	Safety	LIVER7	Listing of Liver Biopsy Details	Conditional display	SAC
38	Safety	LIVER8	Listing of Liver Imaging Details	Conditional display	SAC
Pharmacokinetic					
39	PK	PKCL1P	Listing of Daprodustat and Metabolites Plasma Pharmacokinetic Concentration-Time Data	Please list all the concentration data including unscheduled	SAC
40	PK	PKCL1P	Listing of Daprodustat Unbound Plasma Pharmacokinetic Concentration-Time Data	Please list all the concentration data including unscheduled	SAC
41	PK	PKPL1P	Listing of Derived Daprodustat and Metabolites Plasma Pharmacokinetic Parameters	Parameters with units	SAC
42	PK	PKPL1P	Listing of Derived Daprodustat Unbound Plasma Pharmacokinetic Parameters	Parameters with units	SAC
43	PK	N/A	RAW SAS Output from Statistical Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters		SAC
44	PK	N/A	RAW SAS Output from Sensitivity Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
45	PK	N/A	RAW SAS Output from Statistical Analysis of Daprodustat and Metabolites Tmax		SAC
Pharmacodynamic					
46	PD	PKCL1P	Listing of Erythropoietin Plasma Pharmacodynamic Concentration-Time Data	Please list all the concentration data including unscheduled	SAC
47	PD	PKPL1P	Listing of Derived Erythropoietin Plasma Pharmacodynamic Parameters	Parameters with units	SAC

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function
Compound Number	:	GSK1278863
Effective Date	:	15-SEP-2018

Description:

- The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in Clinical Pharmacology Study Report for Protocol 200231.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.
- This version of the RAP includes amendments to the originally approved RAP (22-Nov-2017)

RAP Author(s):

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the Reporting and Analysis Plan
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe: • The planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol 200231. This RAP is intended to describe the safety and pharmacokinetic (PK) analyses required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC).
Protocol	• This RAP is based on amended protocol (Dated: [15-Nov-2017]) for study 200231 [GlaxoSmithKline Document Number: 2016N305941_01].
Primary Objectives	• To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), and GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI). • To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat and its metabolites in plasma
Primary Endpoints	• Daprodustat and its metabolites in plasma area under the concentration-time curve from time zero (predose) extrapolated to infinite time [AUC (0-∞)], percentage of AUC (0-∞) obtained by extrapolation (%AUCex), time zero (predose) to time of last quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life ($t_{½}$), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat. • Unbound concentration and unbound fraction in plasma of daprodustat and its metabolites at 3, 12 and 24 h post dose (as data permit)
Secondary Objectives	• To characterize the effect of hepatic impairment on the pharmacodynamics (PD) effect of daprodustat. • To assess the safety and tolerability of a single 6 mg dose of daprodustat.
Secondary Endpoints	• Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and erythropoietin area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable erythropoietin concentration [AUC (0-t, EPO)]. • Safety and tolerability parameters, including adverse events and clinical laboratory tests.

Overview	Key Elements of the Reporting and Analysis Plan
Study Design	A phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with moderate (Part 1) and either mild or severe (Part 2) hepatic impairment and matched, healthy control participants with normal hepatic function. **Part 1**: Part 1 will include 2 cohorts. Cohort 1 includes participants with moderate hepatic impairment, and Cohort 2 includes matched healthy control participants. Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (n=8; Child-Pugh score of 7-9). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 1 of the study. **Part 2**: Part 2 will include 2 cohorts. Cohort 3 includes participants with either mild or severe hepatic impairment, and Cohort 4 includes matched healthy control participants. Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with either mild impairment (Child-Pugh score of 5-6) or participants with severe impairment (Child-Pugh score of 10-13) (n=8). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 2 of the study. All participants' total involvement with the study will be up to 7 weeks.
Planned Analyses	• An informal interim analysis of the primary PK endpoints of AUC (0-∞), AUC(0-t) and Cmax will be conducted for completion of Part 1 of the study. • The final planned analyses will be performed, as defined in this RAP document, after database freeze has been declared. • Safety and PK/PD data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Overview	Key Elements of the Reporting and Analysis Plan
Analysis Population	• Screened Population: All participants who were screened will be considered for this population. This population will be used for summarizing screening status. • Enrolled Population: All participants who were successfully screened and enrolled for the trial and for whom a record exists on the study database. This population will be used for summarize number of subjects by Country and Site ID and age ranges. • Safety Population: All participants who received at least 1 dose of study medication. This will be the primary population for the safety analyses. • PK Population: All participants in the 'Safety Population' for whom a PK sample has been obtained and analyzed will be included in the PK population. This population will be used in the evaluation of PK data. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PK data. • PD Population: All participants in the 'Safety Population' who had at least 1 PD assessment. PD samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PD data.
Hypothesis	No formal hypotheses will be tested.
Interim Analyses	An informal interim analysis of the primary PK endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria: ➢ If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to the healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group. ➢ If a ⩾ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to the healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

1.1. RAP Amendments

RAP Section	Amendment Details
Reporting and Analysis Plan_Study200231_Final_V1 [22-Nov-2017]	
Reporting and Analysis Plan_Study200231_Amendment_Final_V1 [Insert Date]	
Section 2.1	• Second primary objective and associate endpoint adds daprodustat AND its metabolites to plasma protein binding and unbound concentration in plasma. • Secondary PD endpoint is revised to say Cmax, EPO instead of Emax; and specifies AUC(0-t, EPO) instead of AUC(last)
Section 10.9.1	• Cmax, EPO added
Section 7.2.1.2.2	• Added text determining if there is concentration-dependent protein binding. “If data suggest appreciable differences existing in the results obtained based on the observed total and unbound daprodustat PK plasma concentration data, and if deemed appropriate, the bound fraction (1-Fu) at 3 h, 12 h and 24 h will be analysed using paired t-test comparing 12h versus 3h, 24 h versus 3h and 24 h versus 12h”.
Section 10.4.1	• Updated heading to match with latest updates in TA and TE. Removed Treatment in heading. Study Treatment & Display Descriptors to Study Displays Descriptors.
Section 10.7.1	• PCI laboratory values added for hepatic impairment subjects and updated units for Albumin and Creatinine.

2. SUMMARY OF KEY PROTOCOL INFORMATION

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare plasma PK parameters of daprodustat and its six metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), and GSK2531401 (M13)) in participants with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI).	• Daprodustat and its metabolites plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC (0-∞)], percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time zero (pre-dose) to last time of quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax) following a single oral dose of daprodustat, apparent terminal phase half-life ($t_{1/2}$), and time of occurrence of Cmax (Tmax) following a single oral dose of daprodustat.
• To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of daprodustat and its metabolites in plasma.	• Unbound concentration and unbound fraction in plasma of daprodustat and its metabolites at 3, 12 and 24 h post dose (as data permit).
Secondary Objectives	**Secondary Endpoints**
• To characterize the effect of hepatic impairment on the PD effect of daprodustat.	• Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and erythropoietin area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable concentration [AUC (0-t, EPO)].
• To assess the safety and tolerability of a single 6 mg dose of daprodustat.	• Safety and tolerability parameters, including adverse events and clinical laboratory tests.

2.2. Study Design

Overview of Study Design and Key Features	
Design Features	A phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with moderate (Part 1) and either mild or severe (Part 2) hepatic impairment and matched, healthy control participants with normal hepatic function. **Part 1**: Part 1 will include 2 cohorts. Cohort 1 includes participants with moderate hepatic impairment, and Cohort 2 includes matched healthy control participants. Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with moderate hepatic impairment (n=8; Child-Pugh score of 7-9). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 1 of the study. **Part 2**: Part 2 will include 2 cohorts. Cohort 3 includes participants with either mild or severe hepatic impairment, and Cohort 4 includes matched healthy control participants. Healthy control participants (n=8) will be matched in gender, age (±10 years), and BMI (±15%) to participants with either mild impairment (Child-Pugh score of 5-6) or participants with severe impairment (Child-Pugh score of 10-13) (n=8). All participants will receive 6 mg of daprodustat as a single oral dose in the fasted state. Up to 16 participants (8 in each cohort, excluding possible replacements) will be recruited into Part 2 of the study. All participant's total involvement with the study will be up to 7 weeks.
Dosing	**Part 1** All participants will be administered 6 mg of daprodustat as a single oral dose, with assessments conducted for up to 48 h post dosing (Please refer to Appendix 2)

Overview of Study Design and Key Features	
	Part 2 If conducted, all participants will be administered 6 mg of daprodustat as a single oral dose, with assessments conducted for up to 48 h post dosing.
Treatment Assignment	• Part 1 consists of up to 16 participants (8 in each cohort, excluding possible replacements). • Part 2 consists of up to 16 participants (8 in each cohort, excluding possible replacements). • All participants will receive the same treatment of a single oral 6 mg dose of daprodustat.
Interim Analyses	• An informal interim analysis of the primary PK endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria: ➢ If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group. ➢ If a ⩾ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

2.3. Statistical Hypotheses

No formal hypotheses will be tested for this study. An estimation approach will be used to evaluate the effect of hepatic impairment (i.e., moderate and potentially either mild or severe) on the PK of daprodustat. The primary comparisons of interest are the single dose PK parameters, including Cmax and AUC of daprodustat in each hepatic impaired cohort compared to the normal hepatic function cohort.

The point estimates of the geometric least squares (GLS) mean ratio for the PK parameters and associated 90% confidence intervals (CIs) will be provided for cohort comparisons (hepatically impaired : healthy participants). The PK parameters will be log-transformed prior to analysis and cohort comparisons will be expressed as ratios on the original scale. %AUCex and Tmax and will be summarized descriptively.

3. PLANNED ANALYSES

3.1. Interim Analyses

An informal interim analysis of the primary endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

- If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group.

- If a ≥ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

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 and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Endpoint(s) Evaluated
Screened Population	• All participants who were screened will be considered for this population. This population will be used for summarizing screening status.	• Screen Failure
Enrolled Population	• All participants who were successfully screened and enrolled for the trial and for whom a record exists on the study database. This population will be used for summarize number of subjects by Country and Site ID and age ranges.	• Study Population
Safety Population	• All participants who received at least one dose of study medication. This will be the primary population for the safety analyses.	• Study Population • Safety
PK Population	• All participants in the 'Safety Population' for whom a PK sample has been obtained and analyzed will be included in the PK population. This population will be used in the evaluation of PK data. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PK data.	• PK
PD Population	• All participants in the 'Safety Population' who had at least 1 PD assessment. PD samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded from the analyses of PD data.	• PD

NOTES:

- Please refer to Appendix 10 which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant 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 and deviations which may lead to exclusion from the analysis are captured and categorized on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Treatment States
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
10.7	Appendix 7: Values of Potential Clinical Importance
10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population displays will be based on the "Safety" population, unless otherwise specified.

Table 2 provides an overview of the planned study population displays, with full details of data displays being presented in Appendix 10: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated	
	Table	Listing
Subject Disposition		
Subject Disposition	Y	
Reasons for Screening Failures [1]	Y	Y
Reasons for Withdrawals		Y
Important Protocol Deviations	Y	Y
Inclusion and Exclusion Criteria Deviations		Y
Demography		
Demographic Characteristics	Y	Y
Race & Racial Combinations	Y	Y
Study Populations	Y	Y
Summary of Number of Subjects by Country and Site ID	Y	
Summary of Age Ranges	Y	
Summary of Child-Pugh score	Y	Y
Medical/Surgical History & Concomitant Medications		
Medical/Surgical History		Y
Concomitant Medication	Y	Y
Exposure and Treatment Compliance		
Exposure to Study Treatment		Y

NOTES:

- Y = Yes display generated.

[1] Conditional displays, if data is available table and listing will be generated.

7. PRIMARY STATISTICAL ANALYSES

7.1. Interim Analyses

An informal interim analysis of the primary PK endpoints AUC (0-∞), AUC(0-t) and Cmax will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

- If a < 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with severe hepatic impairment and a healthy, matched control group.

- If a ≥ 2-fold change in daprodustat exposure (AUC) is observed in participants with moderate hepatic impairment compared to healthy matched control group, the study may enrol participants with mild hepatic impairment and a healthy, matched control group.

7.2. Pharmacokinetic Analyses

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of Clinical Pharmacology Sciences and Study Operations (CPSSO), GlaxoSmithKline.

The merge of PK concentration data and CRF data will be performed by PPD Programming under the direct auspices of Clinical Programming, GlaxoSmithKline.

Derivation of PK parameters will be performed by PPD PK group under the direct auspices of Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline.

Statistical analysis of PK data and parameters will be performed by PPD Statistics and Programming under the direct auspices of Clinical Statistics, GlaxoSmithKline.

7.2.1. Overview of Planned Pharmacokinetic Analyses

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

Table 3 provides an overview of the planned non-compartmental PK analyses of daprodustat and its six metabolites, (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6) and GSK2531401 (M13)) with full details being presented in Appendix 10: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK Concentrations				Y[3]	Y[1] [2]	Y[1]	Y[3]							
Plasma PK Parameters	Y[4]			Y			Y	Y[4]		Y	Y			

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- 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.

[1] Linear and Semi-Logarithmic plots will be created on the same display.
[2] Separate mean and median plots will be generated.
[3] Unbound PK Concentrations for Daprodustat and its metabolites will be summarized on a separate display.
[4] Supportive SAS Output from Statistical Analysis.

7.2.1.1. Drug Concentration Measures

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

7.2.1.2. Pharmacokinetic Parameters

7.2.1.2.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.4.3. Reporting Process & Standards).
- Plasma concentration-time data for daprodustat and its six predominant metabolites will be analysed by non-compartmental methods according to current working practices with WinNonlin 6.4 or higher.
- Non-compartmental analysis will be performed in accordance with GSK PK Guidance document GUI_51487.
- All calculations of non-compartmental parameters will be based on actual sampling times recorded during the study.
- PK parameters described in Table 4 will be determined from plasma concentration-time data as data permits.

Table 4 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (daprodustat and its six metabolites).
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity calculated as: **AUC(0-∞) = AUC(0-t) + C(t) / lambda_z** (daprodustat and its six metabolites) where C(t) is the last measurable concentration.
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: **[AUC (0-∞) – AUC(0-t)] / AUC (0-∞) x 100** (daprodustat and its six metabolites)
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data. (daprodustat and its six metabolites)
Lambda_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve. (daprodustat and its six metabolites)
Tmax	Time to reach Cmax, determined directly from the concentration-time data. (daprodustat and its six metabolites)
t½	Apparent terminal phase half-life will be calculated as: **t½ = ln2 / Lambda_z** (daprodustat and its six metabolites)
fu	Unbound fraction (fu) of daprodustat and its metabolites will be calculated using the total and unbound plasma concentration of daprodustat and its metabolites generated at 3, 12 and 24 h post dose for both normal and hepatic impaired participants using the following formula: **Fu=Cunbound/Ctotal**
free AUC(0-t)	AUC(0-t) * fu (daprodustat)

Parameter	Parameter Description
free AUC(0-∞)	AUC(0-∞) * fu (daprodustat)
free Cmax	Cmax * fu (daprodustat)

7.2.1.2.2. Statistical Analysis of Pharmacokinetic Parameters

For each of the parameters AUC (AUC(0-∞), AUC (0-t) and %AUCex)-total and free, t½, Tmax and Cmax-total and free the following summary statistics will be calculated and tabulated by each cohort:

- **Untransformed Data:** N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum and maximum.
- **Log_e-transformed Data:** Geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and between subject geometric coefficient of variation (%CVb).
- If data suggest appreciable differences existing in the results obtained based on the observed total and unbound daprodustat PK plasma concentration data, and if deemed appropriate, the bound fraction (1-Fu) at 3 h, 12 h and 24 h will be analysed using paired t-test comparing 12h versus 3h, 24 h versus 3h and 24 h versus 12h.

The following PK statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined plasma profiles). Pharmacokinetic analysis and Statistical analyses of the PK parameter data will be the responsibility of PPD.

Planned Pharmacokinetic Statistical Analyses
Endpoint(s)
• Plasma primary PK endpoints include AUC (0-t), AUC (0-∞), Cmax and t½, as data permit
Model Specification
• The log-transformed AUC(0-t), AUC (0-∞), Cmax and t½ values for daprodustat and metabolites will be analyzed separately using analysis of variance (ANOVA) as appropriate to the study design, fitting a fixed effect term for cohort. Point estimates and 90% CIs for the differences of interest (hepatically impaired versus healthy participants) will be constructed using the residual variance.
Model Checking & Diagnostics
• Refer to Appendix 8 : Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Statistical analysis by ANOVA will be presented in tabular format with geometric mean ratios for the hepatically impaired versus healthy participants and 90% CI for the ratios of AUC (0-t), AUC (0-∞), Cmax and t½ for daprodustat and metabolites.

Planned Pharmacokinetic Statistical Analyses
Endpoint(s)
• Tmax
Model Specification
• If data permit, Tmax will be analyzed nonparametrically using the Mann Whitney U test (Wilcoxon rank sum test). The point estimates and 90% CI for the median differences will be derived for hepatic impairment and healthy participants based on Hodges-Lehmann estimation.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The point estimates and 90% confidence intervals for the median differences will be calculated for the cohort difference (hepatically impaired – healthy participants).

Sensitivity Pharmacokinetic Statistical Analyses
Endpoint(s)
• AUC(0-t), AUC(0-∞), Cmax and t1/2
Model Specification
• The log-transformed AUC(0-t), AUC(0-∞), Cmax and t½ values for daprodustat and metabolites will be analyzed separately using analysis of covariance (ANCOVA) as appropriate to the study design, fitting fixed effect terms for cohort, gender, age and BMI. Point estimates and 90% CIs for the differences of interest (hepatically impaired versus healthy participants) will be constructed using the residual variance.
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Statistical analysis by ANCOVA will be presented in tabular format with geometric mean ratios for the difference between participants with hepatically impairment and healthy participants, and 90% CI for the ratios of AUC(0-t), AUC(0-∞), Cmax and t½ for daprodustat and metabolites.

7.3. Pharmacodynamic Analyses

7.3.1. Overview of Planned Pharmacodynamic Analyses

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

Table 5 provides an overview of the planned PD analyses, with full details being presented in Appendix 10: List of Data Displays.

Table 5 Overview of Planned Pharmacodynamic Analyses

Display Type	Untransformed													
	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PD Concentrations				Y	Y[1][2]	Y[1]	Y							
PD Parameters				Y	Y		Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Linear and Semi-Logarithmic plots will be created on the same display.

[2] Separate mean and median plots will be generated.

7.3.1.1. Pharmacodynamic Parameters

7.3.1.1.1. Deriving Pharmacodynamic Parameters

- Although erythropoietin (EPO) is an endogenous substance, the plasma concentrations of erythropoietin will not be corrected for baseline endogenous levels Pharmacodynamic analysis will be performed on uncorrected (absolute erythropoietin concentrations) data only.

- Maximum observed erythropoietin concentration (Cmax, EPO), Time of the maximum observed erythropoietin concentration (Tmax, EPO) and area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable erythropoietin concentration [AUC (0-t, EPO)] will be listed and summarised if data is available.

- Pharmacodynamic parameters described in Table 6 will be determined from plasma absolute erythropoietin concentration-time data as data permits.

Table 6 Derived Pharmacodynamic Parameters

Parameter	Parameter Description
Cmax, EPO	Maximum observed EPO concentration
Tmax, EPO	Time of the maximum observed EPO concentration
AUC (0-t, EPO)	Area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable erythropoietin concentration

8. SAFETY ANALYSES

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

8.1. Overview of Planned Adverse Events Analyses

Adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary and summarized by cohort.

Counting of AEs will be based on the number of subjects – not the number of AEs. For example, if a subject experiences the same AE (i.e. same preferred term) more than once, they are counted only once under the count for the preferred term. If a subject experiences more than one AE in a particular system organ class (SOC), they will only be included once in the count for the SOC, but will appear in the count for each appropriate preferred term within the SOC. Therefore, the sum of the numbers of subjects with each preferred term event within a SOC may exceed the total number of subjects with at least one event.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 7 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs	Y		Y
Serious AEs	Y		Y
Drug Related AEs	Y		Y
AEs leading to withdrawal	Y		Y
Summary of Common (>=25%) Non-serious Adverse Events by System Organ Class and Preferred Term	Y		
Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Y		
Relationship Between System Organ Class and Verbatim Text			Y
Subject Numbers for Individual Adverse Events			Y
AEs of special interest [1]			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- 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.

[1] Conditional displays, if data is available listing will be generated.

8.2. Overview of Planned Clinical Laboratory Analyses

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 8 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Clinical Chemistry	Y		Y	Y		
Clinical Chemistry (Values Outside the PCI Range)			Y			
Haematology						
Haematology	Y		Y	Y		
Haematology (Values Outside the PCI Range)			Y			
Urinalysis						
Urinalysis			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- 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.

8.3. Overview of Planned Other Safety Analyses

Table 9 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays

Table 9 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ 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		
ECG Values Outside the PCI Range			Y			
Maximum QTc Values Post-Baseline Relative to Baseline by Category				Y		
Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category				Y		
Vital Signs						
Vitals Values	Y		Y	Y		
Vital Signs Measurements Outside the PCI Range			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.

9. REFERENCES

GlaxoSmithKline Document Number 2016N305941_00 (Original – 23-MAY-2017): A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function.

GlaxoSmithKline Document Number 2016N305941_01 (Amended – 15-NOV-2017): A Phase 1, open-label, non-randomized, parallel group, single-dose adaptive study in adults with hepatic impairment and matched, healthy control participants with normal hepatic function.

GUI_137354, Information for Authors: Reporting and Analysis Plan (RAP), Global. 2018

GUI_51487, Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global. Date: 21-AUG-2018.

SOP_54838, Development, Review & Approval of Reporting & Analysis Plan (RAP), Global. Date: 22-Aug-2018.

10. APPENDICES

Section	Appendix
RAP Section 4: Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Treatment States
Section 10.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.5	Appendix 5: Derived and Transformed Data • General • Study Population • Safety • Pharmacokinetic • Pharmacodynamic

Section 10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
	• Premature Withdrawals
	• Handling of Missing Data
	  ○ Handling of Missing Dates
	  ○ Handling of Partial Dates

Section 10.7	Appendix 7: Values of Potential Clinical Importance • Laboratory Values • ECG • Vital Signs
Section 10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.9	Appendix 9 Abbreviations & Trade Marks
Section 10.10	Appendix 10: List of Data Displays

10.1. Appendix 1: Protocol Deviation Management

There are no pre-defined categories leading to exclusion from the PK population but all protocol deviations will be reviewed on a case-by-case basis.

No subjects will be excluded from the safety population.

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Informed Consent	X																	
Inclusion & Exclusion Criteria	X	X																
Demography	X																	
Full physical exam	X																	
Medical history	X																	
Past/current medications	X																	
Laboratory assessments[3]	X																X	X
Drug/Alcohol Screen	X	X																
12-lead ECG	X	X															X	X
Vital Signs and Weight	X	X															X	X
Pregnancy Test	X[4]	X[4]																
Females only: Estrogen and FSH[5]	X																	

Procedure	Screening[1]	Day -1	Pre-Dose	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Follow-up[2]
Admission to Unit		X																
Brief Physical Exam		X															X	X
Administration of daprodustat				X														
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Protein binding sample			X						X					X	X			
EPO blood sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X												X		X	X
Discharge from Unit																	X	

[1] All participants will undergo screening assessments within 28 days of enrolment.

[2] A follow-up visit will occur 10-14 days after the dose of study treatment.

[3] Laboratory assessment guidance can be found in Protocol Appendix 3.

[4] For women of childbearing potential that are not using an approved method of contraception (see Protocol Appendix 6), one negative pregnancy test between Day -7 and Day -4 AND another negative pregnancy test on Day -1 is required. Additional guidance can be found in Protocol Section 9.5.5.

[5] All females are to have estrogen and FSH measured at screening.

10.3. Appendix 3: Treatment States

10.3.1. Treatment States for AE Data

Assessments and events will be classified according to date of occurrence relative to the start and/or stop date of the study treatment.

Treatment State	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before the treatment stop date 2 days Study Treatment Start Date ⩽ AE Start Date ⩽ Study Treatment Stop Date + 2 days
Post-Treatment	If AE onset date is after the treatment stop date + 2 days AE Start Date > Study Treatment Stop Date + 2 days
AE Onset Time Since First Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ⩽ AE Onset Date = AE Onset Date - Treatment Start Date +1 day Missing otherwise
AE Duration (Days)	AE Resolution Date – AE Onset Date + 1 day
AE 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 On-Treatment.

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Study Display Descriptors

Study Display Descriptions			
Study Part	Cohort		Data display for reporting
	Code	Description	Description [2]
1	1	Moderate Hepatic Impairment	Cohort 1
1	2	Matched Healthy Controls for Moderate Hepatic Impairment	Cohort 2
2	3	Mild Hepatic Impairment / Severe Hepatic Impairment[1]	Cohort 3
2	4	Matched Healthy Controls for Mild Hepatic Impairment / Matched Healthy Controls for Severe Hepatic Impairment[1]	Cohort 4

[1] Either Mild or Severe Hepatic Impairment participants will be selected based on part 1 results.

[2] The word "Cohort" may be omitted from displays in order to limit wrapping

10.4.2. Baseline Definition & Derivations

10.4.2.1. Baseline Definitions

For all endpoints (except as noted in Table 9) the baseline value will be the latest non-missing pre-dose assessment. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used, unless otherwise stated.

Table 10 Baseline Definitions

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
12 Lead ECG & Vital Signs	X	X		Day -1
Haematology	X			Screening
Clinical Chemistry	X			Screening
Pharmacodynamic				
EPO blood sampling			X	Pre-Dose

10.4.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.4.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries. Unless otherwise stated, if baseline data is missing or post-dose data is missing no derivation will be performed.
- The baseline definition will be footnoted on all change from baseline displays.

10.4.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS 9.3 or latest software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: arenv/arprod/GSK1278863/mid200231/final
QC Spreadsheet	: arenv/arwork/GSK1278863/mid200231/final/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & AdaM IG Version 1.0). • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated only for SAC.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: ○ 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
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • 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.

Reporting Standards	
• 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: o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. o 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 (see Section 4.1). • Reporting for Data Listings: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings. o Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables, unless otherwise stated. • Unscheduled visits will not be included in 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, %
Reporting of Pharmacokinetic and Pharmacodynamic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 and Standards for the Transfer and Reporting of PK and PD Data using HARP. For NQ values, refer to GUI_51487.
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics. (Log_e Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log transformed data and %CVb will be reported. CVb (%) = $\sqrt{\ }$ (exp(SD^2) - 1) * 100 [NOTE: SD = SD of log_e transformed data]
Parameters Not Being Log_e Transformed	%AUCex and Tmax
Summary Tables	Cmax, Tmax, AUC(0-t), AUC (0-∞), t1/2, and %AUCex as data permit. The following PK parameters will not be summarised: first point, last point, and number of points used in the determination of λz.
Summary of Statistical analysis	Geometric mean ratio of hepatic impaired : healthy, point estimate and an associated 90% CI.

Reporting Standards	
Listings	Include PK Parameters Cmax, Tmax, AUC(0-t), AUC (0-∞), and t1/2 as data permit. Include the first point, last point and number of points used in the determination of λz.
Reporting of Pharmacodynamic Parameters	
Descriptive Summary Statistics	N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum and maximum
Parameters	Cmax, EPO, Tmax, EPO and AUC (0-t, EPO)
Summary Tables	Cmax, EPO, Tmax, EPO and AUC (0-t, EPO) as data permit
Listings	Include PD Parameters Cmax, EPO, Tmax, EPO and AUC (0-t, EPO) as data permit
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13 and Standards for the Transfer and Reporting of PK and PD Data using HARP.	

10.5. Appendix 5: Derived and Transformed Data

10.5.1. General

Multiple Measurements at One 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. • The worst finding/interpretation associated with multiple measurements as the finding/interpretation for that time point. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits 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 Treatment start date:
  • Ref Date = Missing → Day = Missing
  • Ref Date < Treatment start Date → Study Day = Ref Date – Treatment start Date
  • Ref Data ≥ Treatment start Date → Study Day = (Ref Date – Treatment start Date) + 1

10.5.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

10.5.3. Safety

Laboratory Parameters

• 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 decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  • Example 1: 2 Decimal Places = '< x' becomes x – 0.01
  • Example 2: 1 Decimal Places = '> x' becomes x + 0.1

Laboratory Parameters
• Example 3: 0 Decimal Places = '< x' becomes x – 1

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive. • Machine read values of RR should not be replaced with derived values.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

AEs
AEs OF Special Interest
• Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis • Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular Access • Cardiomyopathy • Pulmonary artery hypertension • Cancer-related mortality and tumour progression and recurrence • Esophageal and gastric erosions • Proliferative retinopathy, macular edema, choroidal neovascularization • Exacerbation of rheumatoid arthritis

10.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

10.6.1. Premature Withdrawals

Element	Reporting Detail
General	• A completed subject is one who has completed all phases of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study. • All subjects who withdraw prematurely from the study will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). • All available data collected up until the point of withdrawal, and the follow-up visits will be used in the analyses and will be listed and all available planned data will be included in the summaries according to the populations defined in Section 4 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: • 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. • Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects 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 Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows 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 may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: • Missing Start Day: First of the month will be used unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered On-treatment as per

Element	Reporting Detail
	Appendix 3: Treatment States). • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • AEs with entirely missing or unknown start dates will be assumed to be on-treatment for reporting. • AEs with missing end dates are not anticipated to affect reporting.

10.6.2.2. Handling of Partial Dates

Element	Reporting Detail

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • 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 recorded partial date will be displayed in listings.

Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made for calculating the time to onset and the duration of the event:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month, unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered on-treatment as per Appendix 3: Treatment States).
	  • 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, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• The recorded partial date will be displayed in listings.

10.6.2.3. Handling of PK Concentration Data

Element	Reporting Detail
General	• The PK population will be used for the concentration listing, summaries and plotting of the individual concentration-time profiles. • PK assay results from samples collected from a subject with vomiting occurring within 2 times the median Tmax will not be considered as evaluable. • For missing and NQ values, refer to GUI_51487.

10.6.2.4. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Imputation	• No imputation will be performed for missing data

10.7. Appendix 7: Values of Potential Clinical Importance

10.7.1. Laboratory Values

Laboratory Values of Potential Clinical Importance **(Healthy subjects)**

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	>0.075	
Hemoglobin	g/L	Male		180
		Female		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
While Blood Cell Count (WBC)	$x10^9$/ 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	umol/L	Δ from BL		> 44.2
Glucose	mmol/L		3	9
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

Laboratory Values of Potential Clinical Importance **(Hepatic Impaired Subjects)**

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	>0.075	
Hemoglobin	g/L	Male		180
		Female		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
While Blood Cell Count (WBC)	$x10^9$/ 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	umol/L	Δ from BL		> 44.2
Glucose	mmol/L		3	9
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	≥ 3x ULN
AST/SGOT	U/L	High	≥ 3x ULN
AlkPhos	U/L	High	≥ 3x ULN
T Bilirubin	µmol/L	High	≥ 2xULN
T. Bilirubin + ALT	µmol/L U/L	High	2xULN T. Bilirubin + ≥ 3x ULN ALT

10.7.2. ECG

ECG Values of Potential Clinical Importance **(Healthy subjects)**

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

ECG Values of Potential Clinical Importance **(Hepatic Impaired Subjects)**

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 480
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 Values of Potential Clinical Importance **(Healthy Subjects)**

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

Vital Sign Values of Potential Clinical Importance **(Hepatic Impaired Subjects)**

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 90	> 160
Diastolic Blood Pressure	mmHg	< 45	> 95
Heart Rate	bpm	< 50(females) and <45(males)	> 100

10.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

Endpoint(s)	• PK End points AUC(0-t), AUC (0-∞), Cmax, and t½
Analysis	• ANOVA (primary) and ANCOVA (sensitivity)

Assumptions:

- For the Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored.
- Non-parametric analyses will be conducted if the normality assumption does not hold.

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

λz	Terminal phase rate constant
ADaM	Analysis Data Model
AE	Adverse Event
Ae	Excretion of unchanged drug
AIC	Akaike's Information Criteria
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC (0-∞)	Area under the concentration-time curve 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
AUC0-t, EPO	Area under the EPO concentration-time curve from time zero (pre-dose) to last time of quantifiable EPO concentration within a subject across all treatments
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CKD	Chronic kidney disease
Cmax	Maximum observed concentration
Cmax, EPO	Maximum observed EPO concentration
CPMS	Clinical Pharmacology Modelling and Simulation
CPSR	Clinical Pharmacology Study Report
CPSSO	Clinical Pharmacology Sciences and Study Operations
CRF	Case Report Form
CV_b	Coefficient of Variation (Between)
DBR	Database Release
DP's	Decimal places
ECG	Electrocardiogram
Emax	Maximum observed effect
EPO	Erythropoietin
FSH	Follicle stimulating hormone
fu	Fraction unbound in plasma
GSK	GlaxoSmithKline
h	Hour
HARP	Harmonized Analysis and Reporting Process
Hg	Mercury
HI	Hepatic Impairment
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library

kg	Kilogram
L	Litres
mg	Milligram
mL	Millilitre
mm	Millimetre
MM	Mixed Model
nm	Nanometer
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamic
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development
QSI	Quantitative Sciences India
QTc	Electrocardiogram QT interval corrected for heart rate
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables, Figures & Listings
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPDS	Statistics, Programming and Data Sciences
t½	Terminal phase half-life
Tmax	Time of occurrence of Cmax
Tmax, EPO	Time of occurrence of Cmax, EPO
ULN	Upper Limit of Normal

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
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10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.11	N/A
Safety	2.1 to 2.19	N/A
Pharmacokinetic	3.1 to 3.10	3.1 to 3.3
Pharmacodynamic	4.1 to 4.2	4.1 to 4.3
Section	**Listings**	
ICH Listings	1 to 47	

10.10.2. Deliverable

Delivery	Description
DR	Dry Run Complete
SAC	Final Statistical Analysis Complete

10.10.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record		DR, SAC
1.2	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		DR, SAC
1.3	Enrolled	DV1	Summary of Important Protocol Deviations		DR, SAC
Demography					
1.4	Safety	SAFE_T1	Summary of Child-Pugh Score		DR, SAC
1.5	Safety	DM1	Summary of Demographic Characteristics		DR, SAC
1.6	Enrolled	DM11	Summary of Age Ranges		DR, SAC
1.7	Safety	DM5	Summary of Race and Racial Combinations		DR, SAC
1.8	Safety	DM6	Summary of Race and Racial Combination Details		DR, SAC
1.9	Enrolled	SP1A	Summary of Study Population		DR, SAC
1.10	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		DR, SAC
Medical/Surgical History & Concomitant Medications					
1.11	Safety	CM1	Summary of Concomitant Medications		DR, SAC

10.10.4. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term		DR, SAC
2.2	Safety	AE1CP	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term		DR, SAC
2.3	Safety	AE1CP	Summary of Adverse Events Leading to Withdrawal from Study		DR, SAC
2.4	Safety	AE1CP	Summary of Serious Adverse Events by System Organ Class and Preferred Term		DR, SAC
2.5	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		DR, SAC
2.6	Safety	AE15	Summary of Common (>=25%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		DR, SAC
Laboratory Measurements					
2.7	Safety	LB1	Summary of Chemistry Values		DR, SAC
2.8	Safety	LB1	Summary of Chemistry Changes from Baseline		DR, SAC
2.9	Safety	LB17	Summary of Worst Case Chemistry Results Relative to Potential Clinical Importance Criteria Post-Baseline Relative to Baseline		DR, SAC
2.10	Safety	LB1	Summary of Haematology Values		DR, SAC
2.11	Safety	LB1	Summary of Haematology Changes from Baseline		DR, SAC
2.12	Safety	LB17	Summary of Worst Case Haematology Results Relative to Potential Clinical Importance Criteria Post-Baseline Relative to Baseline		DR, SAC

Safety : Tables					
Electrocardiograms					
2.13	Safety	EG1	Summary of ECG Findings		DR, SAC
2.14	Safety	EG2	Summary of ECG Values		DR, SAC
2.15	Safety	EG2	Summary of Change from Baseline in ECG Values		DR, SAC
2.16	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		DR, SAC
2.17	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		DR, SAC
Vital Signs					
2.18	Safety	VS1	Summary of Vital Signs		DR, SAC
2.19	Safety	VS1	Summary of Change from Baseline in Vital Signs		DR, SAC

10.10.5. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Table					
3.1	PK	PKCT1	Summary of Daprodustat and Metabolites Plasma Pharmacokinetic Concentration-Time Data		DR, SAC
3.2	PK	PKCT1	Summary of Daprodustat and Metabolites Unbound Plasma Pharmacokinetic Concentration-Time Data		DR, SAC
PK Derived Parameters					
3.3	PK	PKPT4	Summary of Derived Daprodustat and Metabolites Plasma Pharmacokinetic Parameters (Non-Transformed)	Parameters with units	DR, SAC
3.4	PK	PKPT4	Summary of Derived Daprodustat Unbound Plasma Pharmacokinetic Parameters (Non-Transformed)	Parameters with units	DR, SAC
3.5	PK	PKPT4	Summary of Derived Daprodustat and Metabolites Plasma Pharmacokinetic Parameters (Ln-Transformed)	Parameters with units	DR, SAC
3.6	PK	PKPT4	Summary of Derived Daprodustat Unbound Plasma Pharmacokinetic Parameters (Ln-Transformed)	Parameters with units	DR, SAC
PK Analysis Tables					
3.7	PK	PKPT3	Statistical Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters: Analysis of Variance (ANOVA)	AUC(0-t), AUC(0-∞), Cmax, t½, free AUC(0-t), free AUC(0-∞) and free Cmax	DR, SAC
3.8	PK	PKPT3	Sensitivity Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters: Analysis of Covariance (ANCOVA)	AUC(0-t), AUC(0-∞), Cmax, t½, free AUC(0-t), free AUC(0-∞) and free Cmax	DR, SAC
3.9	PK	PK_T1	Statistical Analysis of Daprodustat and Metabolites Tmax		DR, SAC
3.10	PK	PKPT3	Statistical Analysis of Daprodustat Bound Fraction (1-Fu) in Plasma		SAC

10.10.6. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1	PK	PKCF1P	Individual Daprodustat and Metabolites Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Paginate by cohort and analyte	DR, SAC
Mean / Median Concentration Plots					
3.2	PK	PKCF2	Mean Daprodustat and Metabolites Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	DR, SAC
3.3	PK	PKCF3	Median Daprodustat and Metabolites Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	DR, SAC

10.10.7. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PD Concentration Data					
4.1	PD	PKCT1	Summary of Erythropoietin Plasma Pharmacodynamic Concentration-Time Data		DR, SAC
PD Derived Parameter					
4.2	PD	PKPT4	Summary of Derived Erythropoietin Plasma Pharmacodynamic Parameters	Parameters with units	DR, SAC

10.10.8. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
4.1	PD	PKCF1P	Individual Erythropoietin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Paginate by cohort	DR, SAC
Mean / Median Concentration Plots					
4.2	PD	PKCF2	Mean Erythropoietin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	DR, SAC
4.3	PD	PKCF3	Median Erythropoietin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	All cohorts on one page	DR, SAC

10.10.9. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1	Safety	ES2	Listing of Reasons for Study Withdrawal		DR, SAC
2	Screened	ES7	Listing of Reasons for Screen Failure		DR, SAC
3	Enrolled	DV2	Listing of Important Protocol Deviations		DR, SAC
4	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		DR, SAC
Demography					
5	Safety	SAFE_L1	Listing of Child-Pugh Classification and Treatment Assignment		DR, SAC
6	Safety	DM2	Listing of Demographic Characteristics		DR, SAC
7	Safety	DM9	Listing of Race		DR, SAC
8	Enrolled	SP3	Listing of Subjects Excluded from Any Population		DR, SAC
Medical/Surgical History & Concomitant Medications					
9	Safety	MH2	Listing of Medical Conditions		DR, SAC
10	Safety	CM3	Listing of Concomitant Medications		DR, SAC
Exposure					
11	Safety	EX3	Listing of Exposure Data		DR, SAC
Adverse Events					
12	Safety	AE2	Listing of Relationship between System Organ Class and Verbatim Text		DR, SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
13	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		DR, SAC
14	Safety	AE8CP	Listing of All Adverse Events		DR, SAC
15	Safety	AE8CP	Listing of Drug-Related Adverse Events		DR, SAC
16	Safety	AE8CPA	Listing of Serious Adverse Events (Fatal & Non-Fatal)		DR, SAC
17	Safety	AE8CP	Listing of Adverse Events Leading to Withdrawal from Study		DR, SAC
18	Safety	AE8CP	Listing of Liver Adverse Events	Conditional display	DR, SAC
19	Safety	AE8CP	Listing of Cardiovascular Adverse Events	Conditional display	DR, SAC
20	Safety	AE8CP	Listing of Adverse Events of Special Interest	Conditional display	DR, SAC
Laboratory Measurements					
21	Safety	LB13	Listing of Laboratory Tests and Associated Reference Ranges		DR, SAC
22	Safety	LB5	Listing of Chemistry Values of Potential Clinical Importance		DR, SAC
23	Safety	LB5	Listing of All Chemistry Data for Subjects with Any Value of Potential Clinical Importance		DR, SAC
24	Safety	LB5	Listing of Haematology Values of Potential Clinical Importance		DR, SAC
25	Safety	LB5	Listing of All Haematology Data for Subjects with Any Value of Potential Clinical Importance		DR, SAC
26	Safety	UR2A	Listing of Urinalysis Data		DR, SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Electrocardiograms					
27	Safety	EG5	Listing of Abnormal ECG Findings		DR, SAC
28	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		DR, SAC
29	Safety	EG3	Listing of ECG Values of Potential Clinical Importance		DR, SAC
30	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		DR, SAC
Vital Signs					
31	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance		DR, SAC
32	Safety	VS4	Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance		DR, SAC
Liver Events					
33	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional display	DR, SAC
34	Safety	SU2	Listing of Alcohol Intake for Subjects with Liver Stopping Events	Conditional display	DR, SAC
35	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Conditional display	DR, SAC
36	Safety	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score	Conditional display	DR, SAC
37	Safety	LIVER7	Listing of Liver Biopsy Details	Conditional display	DR, SAC
38	Safety	LIVER8	Listing of Liver Imaging Details	Conditional display	DR, SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic					
39	PK	PKCL1P	Listing of Daprodustat and Metabolites Plasma Pharmacokinetic Concentration-Time Data	Please list all the concentration data including unscheduled	DR, SAC
40	PK	PKCL1P	Listing of Daprodustat and Metabolites Unbound Plasma Pharmacokinetic Concentration-Time Data	Please list all the concentration data including unscheduled	DR, SAC
41	PK	PKPL1P	Listing of Derived Daprodustat and Metabolites Plasma Pharmacokinetic Parameters	Parameters with units	DR, SAC
42	PK	PKPL1P	Listing of Derived Daprodustat Unbound Plasma Pharmacokinetic Parameters	Parameters with units	DR, SAC
43	PK	N/A	RAW SAS Output from Statistical Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters		DR, SAC
44	PK	N/A	RAW SAS Output from Sensitivity Analysis of Daprodustat and Metabolites Plasma Pharmacokinetic Parameters		DR, SAC
45	PK	N/A	RAW SAS Output from Statistical Analysis of Daprodustat and Metabolites Tmax		DR, SAC
Pharmacodynamic					
46	PD	PKCL1P	Listing of Erythropoietin Plasma Pharmacodynamic Concentration-Time Data	Please list all the concentration data including unscheduled	DR, SAC
47	PD	PKPL1P	Listing of Derived Erythropoietin Plasma Pharmacodynamic Parameters	Parameters with units	DR, SAC