The GlaxoSmithKline group of companies 205665

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

Title	:	Reporting and Analysis Plan for a randomized, open-label study to evaluate the effect of daprodustat on blood pressure in participants with anemia associated with chronic kidney disease on hemodialysis switched from a stable dose of an erythropoiesis-stimulating agent
Compound Number	:	Daprodustat (GSK1278863)
Effective Date	:	Refer to document date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205665.
- This RAP is intended to describe the final analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author(s)

Approver	Date
Lead PPD Statistician (FPD Clinical Statistics)	Refer to document date
Co-Author PPD Manager (Clinical Pharmacology, Modelling and Simulation)	Refer to document date

RAP Team Review Confirmations

(Method: E-mail)

Reviewer	Date
PPD Senior Programmer (FPD Clinical Programming)	16-JUN-2020
PPD Programming Manager (FPD Clinical Programming)	17-JUN-2020
PPD Director Clinical Development (Clinical Science Specialty)	09-JUN-2020
PPD Clinical Development Manager (GCSD Clinical Pharmacology)	15-JUN-2020
PPD Director Clinical Development (Clinical Science Nephrology)	16-JUN-2020
PPD Principal Clinical Data Manager (FPD PCPS)	09-JUN-2020

Clinical Statistics and Clinical Programming Line Approvals:

(Method: Pharma TMF eSignature)

Approver	Date
PPD Statistics Director (FPD Clinical Statistics)	Refer to document date
PPD Programming Manager (FPD Clinical Programming)	Refer to document date

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for GSK Document Number 2015N267693_04.

Revision Chronology:		
Protocol number:	Date:	Version:
2015N267693_00	02/Aug/2016	Original Protocol
2015N267693_01	21/Nov/2016	Protocol Amendment 1
This protocol amendment was written to clarify specific biomarkers being drawn, modify time points of biomarkers, clarify safety laboratory studies, and clarify day/time of assessments. An additional potential study visit was added.		
2015N267693_02	31/Jul/2017	Protocol Amendment 2
This protocol amendment was written to clarify the descriptive statistics and include them in the objectives and endpoints table(s) as well as remove one blood pressure measurement. Additional minor changes were made for clarity of study procedures.		
2015N267693_03	21/May/2018	Protocol Amendment 3
This protocol amendment was written to streamline recruitment of participants into the study and maintain appropriate Hgb levels while in the study. This includes removing study visits, altering entry requirements as well as stopping criteria, changing dosing and dose adjustments, and restructuring Hgb parameters.		
2015N267693_04	23/Oct/2019	Protocol Amendment 4
This protocol amendment was written to remove the interim analysis from the statistical section due to more rapid recruitment than anticipated. During the update, the objectives and endpoints were streamlined, the stratification variable of previous ESA dose was added to the models as it was inadvertently left out, the daprodustat dosing algorithm was updated, and exploratory endpoints were added to further clarify results. During this time the safety language was updated as well as clarification of inclusion/exclusion criteria in response to an internal audit.		

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Plasma concentrations and derived parameters including Cmax, tmax, t½ and AUC(0-24) as appropriate (to include erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II and metabolites, and noradrenalin)	• Plasma concentrations and derived parameters including Cmax, tmax, ~~t½~~ and AUC(0-24) as appropriate (to include erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II and metabolites, and noradrenalin)	• The derivation of t½ was removed since this parameter would be difficult to determine with or without treatment.
• Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1	• Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1 **and Day 57**	• Day 57 and for both treatments inadvertently left out of protocol
• Plasma concentrations of daprodustat and metabolites and derived pharmacokinetic parameters including maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), terminal phase half-life (t½) and area under concentration-time curve from time zero to 24 hours (AUC[0-24]) as appropriate	• Plasma concentrations of daprodustat and metabolites and derived pharmacokinetic parameters including maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), terminal phase half-life (t½), area under concentration-time curve from time zero to 24 hours (AUC[0-24]), and **area under concentration-time curve from time zero to infinity (AUC[0-inf])** as appropriate	• Added AUC (0-inf) as this was inadvertently left out of protocol
	• The daprodustat exposure (AUC) compared to the AUEC of SBP, DBP, MAP, and HR at Day 1 and Day 57	• To investigate if a relationship exists between daprodustat exposure and BP
	• The daprodustat exposure (AUC) compared to the biomarker AUEC at Day 1	• To investigate if a relationship exists between

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	and Day 57. Biomarkers included erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II (and metabolites), and noradrenalin.	daprodustat exposure and biomarkers of interest

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

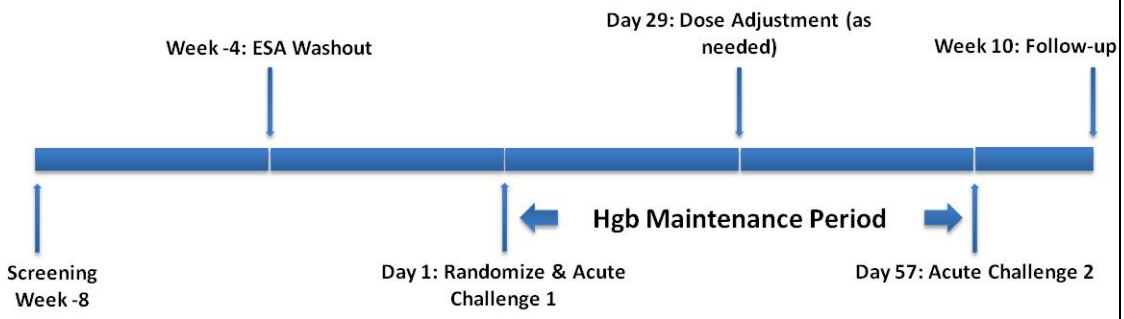
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare the effect of daprodustat to epoetin alfa on blood pressure (BP) after Acute Challenge 2 (8 weeks of hemoglobin [Hgb] maintenance therapy)	• Average of systolic blood pressure (SBP) as measured by ambulatory blood pressure monitoring (ABPM) over 6-hr post-dosing after 8 weeks of Hgb maintenance therapy
Secondary Objectives	**Secondary Endpoints**
• To compare the initial effect of daprodustat to epoetin alfa on BP after Acute Challenge 1 (2 weeks of erythropoiesis-stimulating agent [ESA] washout)	• Average of SBP, diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and heart rate (HR) as measured by ABPM over 6-hr post-dosing at Day 1 • Area under the effect curve (AUEC) of SBP, DBP, MAP, and HR as measured by ABPM over 24-hr post-dosing at Day 1
• To compare the effect of daprodustat to epoetin alfa on BP after Acute Challenge 2	• Average of DBP, MAP, and HR as measured by ABPM over 6 hr post-dosing at Day 57. • AUEC of SBP, DBP, MAP, and HR as measured by ABPM over 24-hr post-dosing at Day 57.
• To estimate the initial effect of daprodustat and epoetin alfa on SBP, DBP, HR and MAP after Acute Challenge 1 and 2	• Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1 and Day 57
• To characterize the pharmacokinetics of daprodustat	• Plasma concentrations of daprodustat and metabolites and derived pharmacokinetic parameters including maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), terminal phase half-life (t½) and area under concentration-time curve from time zero to 24 hours (AUC[0-24]) as appropriate
Safety Objectives	**Safety Endpoints**
• To assess the safety and tolerability of daprodustat	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Reasons for discontinuation of study treatment

Objectives	Endpoints
	• Absolute values and changes from baseline over time in laboratory parameters, electrocardiograms (ECGs) and vital signs
Exploratory Objectives	**Exploratory Endpoints**
• To investigate the effect of daprodustat and epoetin alfa on vasoactive mediators of blood pressure	• Plasma concentrations and derived parameters including Cmax, tmax, and AUC(0-24) as appropriate (to include erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II and metabolites, and noradrenalin)
• To summarize the effect of daprodustat and epoetin alfa on SBP after Acute Challenge 1 and Acute Challenge 2	• AUEC of SBP as measured by ABPM over 24-hr post-dosing
• To compare the effect of daprodustat to epoetin alfa on SBP after 8 weeks of Hgb maintenance therapy	• Change from Day 1 pre-dose SBP to Day 57 pre-dose
• To compare the effect of daprodustat to epoetin alfa on SBP at Cmax of the study treatment	• Change in SBP from pre-dose on Day 1 to Cmax of the study treatment on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 1 to Cmax of the study treatment on Day 57, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 57, as measured by ABPM
• To compare the effect of daprodustat to epoetin alfa on SBP at Cmax of the erythropoietin level	• Change in SBP from pre-dose on Day 1 to Cmax of erythropoietin on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 1 to Cmax of erythropoietin on Day 57, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 57, as measured by ABPM
• To investigate if an exposure-response relationship exists between daprodustat and BP	• The daprodustat exposure (AUC) compared to the AUEC of SBP, DBP, MAP, and HR at Day 1 and Day 57
• To investigate if an exposure-response relationship exists between daprodustat and biomarkers of interest	• The daprodustat exposure (AUC) compared to the biomarker AUEC at Day 1 and Day 57. Biomarkers included erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II (and metabolites), and noradrenalin.

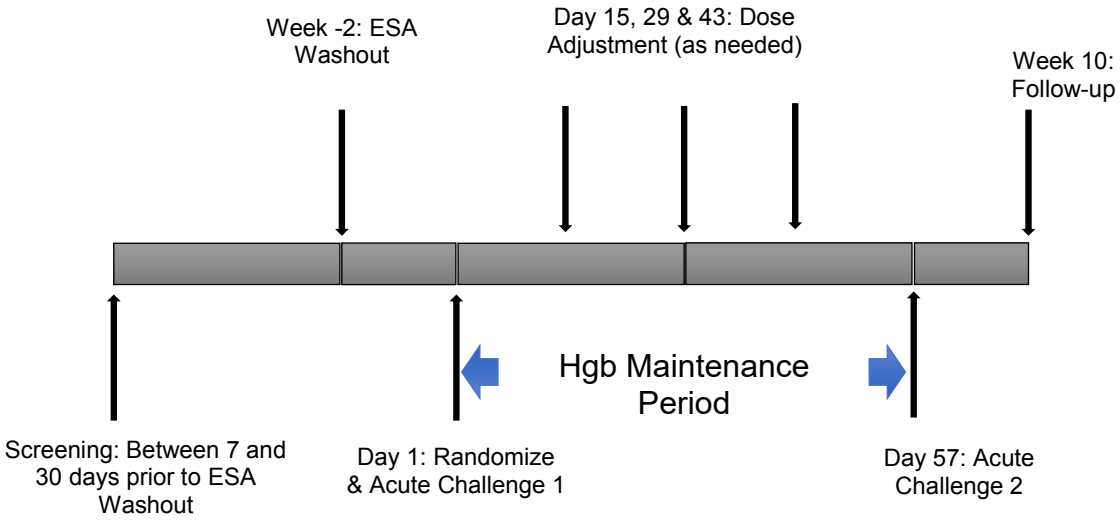
2.3. Study Design

Overview of Study Design and Key Features

Pre protocol amendment 3:



Post protocol amendment 3:



Design Features	• This study will be an open-label, randomized, parallel-group design in HD participants with anemia associated with CKD. • This study will randomise approximately 31 participants per treatment arm assuming that 25 participants per treatment arm will complete the study and therefore, undertake and pass QC for acute challenge 2. • There will be a 7-30 day screening period, a 2-week ESA washout period, an 8-week Hgb-maintenance period, two 24-hr acute challenges on Day 1 and Day 57 and a follow-up visit at 14±3 days after completing treatment. • ABPM blood pressure monitoring will be performed for the 24 hours following each acute challenge. If the ABPM data at acute challenge 2 do not meet the required quality standards, an additional acute challenge 2 will be performed • Blood samples will be collected for PK and biomarkers as detailed in the Time & Events table.

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Dosing</td><td>
The details of the study treatments are given below and the daprodustat dose will be adjusted based on the Hgb value using a pre-defined algorithm (Protocol Section 6.4.1).
<table>
<tr><th>Treatment Arm</th><th>Acute Challenge 1</th><th>Hgb Maintenance Phase</th><th>Acute Challenge 2</th></tr>
<tr><td>A</td><td>100 U/kg IV epoetin alfa</td><td>IV epoetin alfa according to label</td><td>100 U/kg IV epoetin alfa</td></tr>
<tr><td>B</td><td>24 mg daprodustat</td><td>QD daprodustat according to dose adjustment algorithm (Protocol Section 6.4.1)</td><td>24 mg daprodustat</td></tr>
</table>
</td></tr>
<tr><td>Time & Events</td><td>[Refer to Appendix 2: Schedule of Activities]</td></tr>
<tr><td>Treatment Assignment</td><td>Randomization & Acute Challenge 1 (Day 1): Participants will be randomized 1:1 to two treatment arms and will begin a 24-hr Acute Challenge where the acute BP effects of daprodustat and epoetin alfa will be evaluated. This challenge will be initiated promptly following the participant's dialysis session.
Hgb Maintenance Period: Participants randomized to daprodustat will start an 8-week Hgb maintenance period based on a starting dose and dose adjustment algorithm. Participants randomized to epoetin alfa will begin an 8-week Hgb maintenance period where Hgb will be managed in accordance with local labelling.
Acute Challenge 2: At the end of the 8-week Hgb maintenance period (Day 57) participants will repeat the procedures of Acute Challenge 1 utilizing the same treatment administered in Acute Challenge 1. This challenge will be initiated promptly following the participant's dialysis session.</td></tr>
<tr><td>Interim Analysis</td><td>No interim analyses are currently planned for this study.</td></tr>
</table>

2.4. Statistical Hypotheses

The primary objective of this study is to compare the effect of daprodustat to epoetin alfa on BP after Acute Challenge 2 (8 weeks of Hgb maintenance therapy). Specifically, the primary endpoint is the average of SBP as measured by ABPM over 6-hr post-dosing after 8 weeks of Hgb maintenance therapy. The estimand of interest is the effect of 8 weeks of randomized treatment on the primary endpoint.

- **Null Hypothesis**: The difference between 24 mg daprodustat versus 100 U/kg epoetin alfa on 6 hr average SBP under a background of treatment (i.e., during Acute Challenge 2) is zero.

- **Alternative Hypothesis**: The difference between 24 mg daprodustat versus 100 U/kg epoetin alfa on 6-hr average SBP under a background of treatment (i.e. during Acute Challenge 2) is not zero.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analyses are currently planned for this study.

3.2. Final Analyses

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

1. All participants (N=50) have completed the study as defined in the protocol and have passed QC for acute challenges 1 and 2.
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	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Screen Failures
Enrolled	• All participants who enter washout. • Participants will be analyzed according to the treatment to which they were randomized, if randomized.	• Study Population, Safety
Safety	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant actually received.[1] • Note: Participants who were not randomized but received at least one dose of study treatment should be listed.	• Safety
Intent-To-Treat (ITT)	• All randomized participants [who received at least one dose of study treatment]. • This population will be based on the treatment the participant was randomized to. • Any participants who receives a treatment randomization number will be considered to have been randomized.	• Primary, secondary, and exploratory endpoints excluding PK endpoints
Per-Protocol (PP)	• All participants in the ITT population who comply with the protocol. • Protocol deviations that would exclude participants from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).	• Sensitivity analysis of primary endpoint

Population	Definition / Criteria	Analyses Evaluated
	• The PP set will not be analysed if this population comprises more than 90% of the ITT population.	
Pharmacokinetic (PK)	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• All PK endpoints

Refer to Appendix 12: List of Data Displays which details the population used for each display.

[1]: Only participants receiving incorrect randomized treatment for the duration of their study participation will be analyzed according to the treatment received. If participant received both treatments then analysis will be based on treatment received for the greatest number of days. Otherwise, participants will be analyzed according to the treatment to which they were randomized.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised 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 [13Apr2020 V5.0].

- 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 categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
[RandAll NG / FSO Randomization System]		Data Displays for Reporting	
Code	**Description**	**Description**	**Order in TLF**
A	IV epoetin alfa	rhEPO	2
B	Daprodustat	Dapro	1
-	-	Total	3

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

Dapro vs rhEPO

Within each treatment group/arm, the display descriptors for the study periods/visits will be as follows:

Pre-Protocol Amendment 3	Post-Protocol Amendment 3
Study Period (Visit)	**Study Period (Visit)**
Screening* (Week -8 to Week -4)	Screening* (7-30 days prior to Week -2)
ESA Washout* (Week -4 to Day 1)	ESA Washout* (Week -2 to Day 1)
Acute Challenge 1 (Day 1)	Acute Challenge 1 (Day 1)
Hgb Maintenance Phase (Day 2 to Day 56)	Hgb Maintenance Phase (Day 2 to Day 56)
Acute Challenge 2 (Day 57)	Acute Challenge 2 (Day 57)
Hgb Maintenance Phase (Day 58 to day before repeated AC2)	Hgb Maintenance Phase (Day 58 to day before repeated AC2)
Repeat Acute Challenge 2**	Repeat Acute Challenge 2**
Early Withdrawal	Early Withdrawal
Follow-up (Day 58 to Week 10)	Follow-up (Day 58 to Week 10)

*For these visits, the period will include the first visit up to but not including the last reference visit. For example, screening period for pre-protocol amendment 3 will defined as week -8 up to but not including the week -4 visit.

**For subjects with a repeat acute challenge 2, the follow-up period will be the day following this visit

5.2. Baseline Definitions and Derivations

5.2.1. Baseline Definitions

For all endpoints the baseline value will be the latest non-missing pre-dose assessment before Acute Challenge 1 as detailed in the following table. Pre-dose values following Acute Challenge 1 following the maintenance therapy will not be used as baseline.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Week -2	Day 1 (Pre-Dose)	
Pre-Acute Challenge 1				
ABPM Parameters			X	Post-HD/Pre-Acute Challenge 1
Vital signs (SBP, DBP and pulse rate)	X	X	X (post-HD)	Post-HD and Pre-Acute Challenge 1
Laboratory data	X		X	Day 1(Pre-dose)
ECG	X		X	Day 1(Pre-dose)
Biomarkers			X	Day 1(Pre-dose)
NOTES: Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.				

5.2.2. Derivations and Handling of Missing Baseline Data

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

Change from Baseline

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

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and the change from baseline value will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

Percent Change from Baseline

Ferritin and serum iron will be log-transformed. Instead of reporting change from baseline and mean, percent change from baseline and geometric mean will be reported.

To calculate a geometric mean for baseline measurement or at a specified timepoint, the following steps are used:

1. Log-transform the data points
2. Calculate the mean and standard error (SE) of the log-transformed data
3. Exponentiate the mean, (if required, the mean – SE, mean + SE) and the endpoints of the confidence interval back to the original scale in order to obtain the geometric mean, (the geometric mean – SE, the geometric mean + SE) and the confidence interval for the geometric mean.
4. Coefficient of variation will be calculated as

$$CV = \sqrt{\exp(Var_{\log scale}) - 1} \times 100\%$$

To calculate a geometric mean for the ratio of a specific timepoint to baseline (expressed as a percent change from baseline), the following steps are used:

1. Log-transform the data at both the baseline and the specified timepoint
2. For each participant, calculate a change from baseline using the log-transformed data
3. Calculate the mean and standard error (SE) of the log-transformed data
4. Exponentiate the mean, (if required, the mean – SE, the mean + SE) and the endpoints of the confidence interval, back to the original scale and then subtract 1, then multiply everything by 100% in order to express the geometric mean, (the geometric mean – SE, the geometric mean + SE) and the confidence interval (CI) as the percent change from baseline.

Geometric mean for percent change from baseline =

[Exp(∑ {log(value at specified time point_i) – log(baseline value_i) }/n) – 1] x 100,

Where i = participant, n= total number of participants, and ∑ represents the sum over all participants.

To calculate the minimum, median and maximum for the ratio of a specific timepoint to baseline (expressed as a percent change from baseline), the following steps are used:

1. Log-transform the data at both the baseline and the specified timepoint
2. For each participant, calculate a change from baseline using the log-transformed data
3. Calculate the minimum (median and maximum) of change from baseline using the log transformed data.
4. Exponentiate the minimum (median and maximum), back to the original scale and then subtract 1, then multiply everything by 100% in order to express the minimum (median and maximum) as the percent change from baseline.

Minimum percent change from baseline =

[Exp(min {log(value at specified time point_i) – log(baseline value_i) }) – 1] x 100,

Where i = participant.

Unless otherwise specified, the baseline definitions specified in Section 5.2.1 will be used for derivations for endpoints/parameters and indicated on summaries and listings. Unless otherwise specified, if baseline data is missing, no derivation will be performed and the % change from baseline value will be set to missing.

5.3. Multicentre Studies

In this multicentre study, enrolment will be presented by investigative site.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Strata	Prior treatment by ESA Dose (low ESA/high ESA)
Covariates	Treatment (daprodustat/epoetin alfa)
	Post_HD/pre-Acute Challenge 1 BP (SBP, DBP, MAP, HR)
	Difference in SBP between post-HD/pre-Acute Challenge 2 BP (SBP, DBP, MAP, HR)and post-HD/pre-Acute Challenge 1.

The pre-challenge SBP may change over time between Acute Challenge 1 and Acute Challenge 2 as a result of the maintenance therapy, and thus the pre-challenge SBP at Acute Challenge 2 is not a true pre-treatment covariate. Therefore, pre-Acute Challenge 2 SBP will not be used as a covariate. Instead, any impact on the SBP due to the covariate between Challenge 1 to Challenge 2 will be adjusted for using the covariate 'Difference in SBP between post-HD/pre-Acute Challenge 2 SBP and post-HD/pre-Acute Challenge 1'.

The primary model will include the interaction between treatment and 'difference in post-HD SBP between Acute Challenge 1 and 2'. As a result, the interpretation of the effect of the Acute Challenge 2 may be confounded by the impact of treatment phase on the covariate. Therefore, if the interaction term in this model is significant at the 0.10 level, then the primary model will be ANCOVA with terms for treatment, post-HD/pre-Acute Challenge 1 SBP, and prior ESA dose (low/high).

Stratification factor (previous ESA dose) will be used as a fixed factor in the model where indicated in Section 11. See details below:

Classification Name (Description)	Value	Code/Range
Treatment by ESA Dose (Treatment by Previous ESA Dose)	Low ESA Dose	1
	High ESA Dose	2

5.4.2. Examination of Subgroups

No subgroups will be examined.

5.5. Multiple Comparisons and Multiplicity

No multiplicity adjustments will be made for the final analysis of the secondary endpoints. Although the secondary and exploratory analyses will include statistical testing, these will be considered as exploratory and no Type I error adjustments will be made.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

6.2. Display Details

6.2.1. Participant Disposition

Participant Status and Reason for Study Withdrawal

The number and percentage of participants who completed the study as well as participants who withdrew from the study will be summarized by participant status and reason for withdrawal. The number of participants who completed the study for purpose of the disposition table will consist of all randomized participants who, as documented in the eCRF, Study Conclusion form, have completed all study periods through the Day 57 visit. This table will also include those subjects who entered washout but were never randomized.

A listing of reasons for study withdrawal will be provided for all participants who were withdrawn from the study. This listing will include treatment, site ID, unique subject ID, date of withdrawal, study day of withdrawal, primary reason for withdrawal from study, was a follow-up phone contact attempted 3 times, and was a follow-up certified letter mailed.

Treatment Status and Reasons for Discontinuation of Study Treatment

A summary of the number and percentage of participants who completed the study treatment as planned, as well as participants who stopped study treatment prematurely will be produced.

A listing of the randomized treatment discontinuation record will be provided for all participants who prematurely discontinued randomized treatment. This listing will include treatment, site ID, unique subject ID, date of last dose, study day of discontinuation, primary reason for discontinuation, and sub reasons for discontinuation, and related to study treatment.

Participant Disposition at Each Study Period

The number and percentage of participants who entered, withdrew from and completed screening, washout, HGB maintenance Period, and follow-up of the study will be summarized by treatment group and overall.

Pre-Protocol Amendment 3	Post-Protocol Amendment 3
Study Period (Visit)	**Study Period (Visit)**
Screening* (Week -8 to Week -4)	Screening* (7-30 days prior to Week -2)
ESA Washout* (Week -4 to Day 1)	ESA Washout* (Week -2 to Day 1)
Hgb Maintenance Phase (Day 1 to Day 57)	Hgb Maintenance Phase (Day 1 to Day 57)
Follow-up (Day 58 to Week 10)	Follow-up (Day 58 to Week 10)

*For these visits, the period will include the first visit up to but not including the last reference visit. For example, screening period for pre-protocol amendment 3 will defined as week -8 up to but not including the week -4 visit.

Screening Status and Reasons for Screen Failure

The number and percentage of participants who passed screening (i.e. enrolled) and who failed screening and therefore were not entered into the study will be summarized along with the reasons for failure will be summarized for those participants who failed screening. If a subject has been screened multiple times, the subject's latest screening information will be displayed. (Note that the reasons for rescreen participants who initially failed but subsequently enrolled are not included in the display.)

A listing of the screen failure record for all participants who failed screening and were not enrolled in the study will be produced. This listing will include site ID, unique subject ID, date of screen failure, reason term(s) for screen failure (including the specify text, if any).

Number of Participants by Site ID

The number and percentage of participants by Site ID will be summarized by treatment group and overall for the Enrolled population.

A listing of planned and actual treatments will be provided. This listing will include site ID, unique subject ID, randomization number, randomization date, randomized treatment, actual treatment and deviation.

6.2.2. Protocol Deviations

Important Protocol Deviations

The number and percentage of participants who had important protocol deviations (defined in protocol deviation management plan) will be summarized by category and by treatment group and overall.

A listing of important protocol deviations will be provided. The listing will include treatment, site ID, unique subject ID, date of deviation, study day of deviation, protocol deviation category, protocol deviation coded term, and protocol deviation description.

Participants with Inclusion/Exclusion Criteria Deviations

The number and percentage of participants who had inclusion/exclusion criteria deviations will be summarized by inclusion/exclusion type, criteria description and by treatment group and overall.

A listing of participants with inclusion/exclusion criteria deviations will be provided. The listing will include treatment, site ID, unique subject ID, inclusion/exclusion type, and criteria description.

6.2.3. Population Analysed

Study Populations

The number and percentage of screened participants in the Screened, Enrolled, Safety, ITT, PP, PK will be summarized by treatment group and overall.

Exclusion from Safety Population

The number and percentage of participants excluded from the Safety population will be summarized by reason, treatment group and overall in individual displays for each study population.

A listing of participants excluded from the Safety population will be provided. The listing will include the treatment arm, site ID, unique subject ID, date of deviation, study day of deviation, category, coded term and criteria which lead to exclusion.

6.2.4. Demographic and Baseline Characteristics

Demographic Characteristics

Demographic and baseline data will be summarized by treatment group and overall for ITT, Safety, and PP populations. PP only to be produced if used in sensitivity analysis.

A by-subject listing of demographic and baseline characteristics will also be produced. This listing will include treatment, site ID, unique subject ID, year of birth, age, sex, ethnicity, height, weight, and other demographic and baseline characteristics.

Age Ranges

A summary of age ranges will be produced based on the Enrolled population.

Race and Racial Combinations

Summaries of race and racial combinations will be produced for each treatment group and overall.

A listing of race details by participant will also be produced, which will include treatment, site ID, unique subject ID, race, and race detail.

6.2.5. Medical Conditions, Prior and Concomitant Medications

Medical Conditions

A summary of baseline medical conditions will be provided by treatment group and overall.

A listing of medical conditions will be produced, which will capture both pre-specified medical conditions and other medical conditions collected on the eCRF.

Concomitant Medications

For reporting purposes, medications will be classified as prior (pre-treatment), concomitant (on-treatment), and post-treatment using the associated start and stop dates recorded in the eCRF and relative to the first and last dose dates of IP (see Section 14.4.1). Medications will be coded using the GSK Drug coding dictionary (current version at the time of DBR).

The number and percentage of participants reporting the use of each concomitant medication will be summarized by GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1, 2, 3 (body system) and ingredient. Drugs that are composed of a combination of ingredients will be displayed according to the ATC classifications of the ingredients, not of the combination. Summaries of pre-treatment, on-treatment, and post-treatment medication will be provided separately. See Section 14.4.1.1 for a summary of study phases for concomitant medications.

A listing of all medications taken by participants, including any of which are only prior or post-treatment, will be produced. The relationship between ATC level 1, 2, 3, and ingredients and verbatim text for all medications in the study will be listed.

6.2.6. Exposure and Treatment Compliance

Months (or days) of exposure (see Section 14.6.2) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group and overall.

A listing of exposure data will be provided. This listing will include treatment, site ID, unique subject ID, dose start date, dose stop date, duration of time on dose, dose, dose units, dose form, route of administration, and dosing frequency.

Summary of percent compliance will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum.

A listing of compliance data will be provided. This listing will include treatment, site ID, unique subject ID, and percent compliance.

Compliance is only calculated for Daprodustat because rhEPO subjects are dosed at site.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

Efficacy is not evaluated for this study. The primary objective is Pharmacodynamic, the average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks, this is described in Section 11.

8. SAFETY ANALYSES

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

Objectives	Endpoints
Safety	
• To assess the safety and tolerability of daprodustat	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Reasons for discontinuation of study treatment • Absolute values and changes from baseline over time in laboratory parameters, electrocardiograms (ECGs) and vital signs

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of AEs of special interest (AESI), adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

Adverse Events

The number and percentage of participants reporting at least one AE will be provided for each treatment group. These events will be summarized by treatment group, primary system organ class, and preferred term. Pre-treatment, post-randomization, treatment emergent and follow-up AEs will be summarized separately, specifically the on treatment AEs will be separated by acute challenge 1, HGB maintenance, and acute challenge 2. HGB maintenance is defined as the dates between acute challenge 1 and 2.

Summaries of all AEs will be produced for the safety population.

A listing of AE records for all participants who reported AEs will be produced.

The number and percentage of participants reporting the most common treatment emergent AEs (those occurring in ≥ 2% of participants in any treatment group) will be summarized by preferred term and treatment group. Rounding is not applied, e.g. with a threshold of 2% then a preferred term occurring in 1.99% of subjects would not be included.

The number and percentage of participants reporting treatment emergent AEs assessed by the investigator to be related to the study drug will be summarized by treatment group, primary system organ class, and preferred term and separately by overall frequency.

The number and percentage of participants and the number of occurrences of common non-serious treatment emergent adverse events will be summarized by primary system organ class, preferred term, and treatment group and separately by overall frequency.

A listing of which participants reported specific adverse events will be produced.

The hierarchical relationship between MedDRA SOCs, PTs and verbatim text will be listed for all adverse events.

Adverse events occurring during the 24-hour acute challenge will be grouped in the appropriate acute challenge phase. Any AE occurring after AC2 but before repeat-AC2 will be grouped in the HGB maintenance phase.

Adverse events occurring after the last on treatment date will be grouped either in early withdrawal or follow-up depending on the final status of the subject,

Serious and Other Significant Adverse Events

The number and percentage of participants and the number of occurrences of SAEs will be provided for each treatment group. These events will be summarized by treatment group, primary system organ class, and preferred term. Pre-treatment, post-randomization, treatment emergent and follow-up SAEs will be summarized separately. Treatment emergent SAE preferred terms will also be summarized by treatment group and overall frequency.

A listing of reasons for considering as a SAE will be produced for all treatment emergent SAEs.

The number and percentage of participants and the number of occurrences of treatment emergent drug-related SAEs, and drug-related fatal SAEs will be summarized by treatment group.

A listing of treatment emergent fatal SAE records and a listing of treatment emergent non-fatal SAE records will be provided.

The number and percentage of participants reporting treatment emergent AEs leading to discontinuation of randomized treatment will be summarized by treatment group, primary system organ class, and preferred term.

A listing of treatment emergent AEs leading to discontinuation of randomized treatment will be provided.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. [Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.] The details of the planned displays are provided in Appendix 12: List of Data Displays. See Section 14.6.4 for complete list of AESIs

Summaries of AESIs will include the number, percentage and rate per 100 person-years of participants having at least one occurrence, the number of events, the number of participants by number of occurrence, the characteristics of the AE (serious, drug-related, etc.), outcome, maximum intensity, time to first onset/worsening, the duration of first, second, and third occurrence of the AE, and action taken summarized by treatment group. For each count, a participant will be summarized as follows:

- Serious/drug-related/severe/fatal: If any specific AE falls in the respective category, the participant will be counted in that category.
- Outcome: The participant will be counted within a category if there is at least one specific AE in that category.
- Maximum intensity: The specific AE with the maximum intensity will be counted for this purpose. For example, a participant will be counted in the 'severe' category if there is at least one specific AE with severe intensity. A participant will be counted in the 'moderate' category if there is at least one specific AE with moderate intensity and there is no specific AE with severe intensity.
- Time to first onset/worsening (days): The earliest of onset dates for the specific AE – treatment start + 1
- Duration of the occurrence (days): AE resolution date – AE onset date/AE worsening date + 1 for the occurrence

If the AE onset date/AE worsening and/or resolution date is missing or incomplete in the database for any occurrence of the specific AE, time to first onset/worsening and/or duration of the first, second, and third occurrence will be left missing for the participant. These summaries of special interest AEs will be provided for those AEs classified as treatment emergent, follow-up and post-randomization.

Kaplan-Meier plots may be produced for each special interest AE summarizing the time to first occurrence of the special interest AE by treatment group.

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays and include the following tests:

Laboratory Assessments	Parameters		
Hematology	Platelet Count	*RBC Indices:*	*WBC Count with Differential:*
	RBC Count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	MCHC	Monocytes
	WBC Count (absolute)	RDW	Eosinophils
	Reticulocyte Count	CHr	Basophils
Clinical Chemistry	Potassium	AST (SGOT)	Total and direct/indirect bilirubin
	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium (Albumin adjusted)	Alkaline Phosphatase
	Albumin	Phosphate	
Other Screening Tests	Serum hCG pregnancy test	Serum ferritin	Folate
	Estradiol	Serum iron	Vitamin B12
	FSH	Serum transferrin	UIBC
		TSAT	

The clinical chemistry tests performed in this study include ALT, AST and bilirubin. In addition to being summarized with the clinical chemistry values, these laboratory values will be included in some of the Hepatobiliary (liver) displays.

In addition to the visits listed for the laboratory assessments in the Schedule of Activities (see Section 14.2.1), any of these assessments can be performed at an unscheduled/retest visit or at the follow-up visit at the discretion of the investigator. See Section 14.5.2 for handling of unscheduled values. The laboratory's normal range values will be provided by the central laboratory and potential clinical importance thresholds are defined in Section 14.8.1.

In addition to the other screening tests, serum iron will also be collected and summarized similar to the parameters listed in the table above. Both ferritin and serum iron will be log transformed.

HGB will be summarized with both the central lab and local lab (Hemocue).

All of the tabular summaries described below will include summaries in SI units and conventional units for the following laboratory tests: hemoglobin, MCHC, albumin-adjusted calcium, phosphate, and albumin. Conversions from SI units to conventional units are included in Section 14.6.4.

The clinical laboratory safety analyses will be based on the Safety population and GSK Core Data Standards, unless otherwise specified. The details of the planned displays are in Appendix 12: List of Data Displays.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

The analyses of non-laboratory safety test results including vital signs, concomitant medications and meeting protocol defined stopping criteria (e.g., liver chemistry) will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

Vital signs and weight are assessed in this study according to the schedule outlined in the Time and Events table (see Section 14.2.1) and include the following assessments:

- Temperature
    - SBP
    - DBP
    - HR
    - MAP
    - Weight (pre- and post-dialysis)

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

Vital signs will be summarized for both pre and post dialysis recordings.

Vital sign values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit and for baseline and end of treatment by treatment group.

Vital sign change from baseline values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit.

A listing of all vital signs with PCI criteria for participants with on-treatment vital signs values outside of PCI criteria will be provided for the parameters listed in Section 14.8.

Reasons for early study withdrawal and for stopping randomized treatment will also be summarized by treatment group with Table 1.1 and Table 1.2 respectively under study population tables using the enrolled and ITT populations respectively.

Summaries of subjects affected by COVID-19 will be provided. These will include a summary of all treatment emergent adverse events. See Appendix 12: List of Data Displays for list of summary tables.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

There are no primary Pharmacokinetic analyses, only secondary. The primary objective is Pharmacodynamic, the average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks, this is described in Section 11.

9.2. Secondary Pharmacokinetic Analyses

9.2.1. Endpoint / Variables

• To characterize the pharmacokinetics of daprodustat	• Plasma concentrations of daprodustat and metabolites and derived pharmacokinetic parameters including maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), terminal phase half-life (t½), area under concentration-time curve from time zero to 24 hours (AUC[0-24]), and area under concentration-time curve from time zero to infinity (AUC[0-inf]) as appropriate

9.2.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Standards for Pharmacokinetic)

9.2.1.2. Derived Pharmacokinetic Parameters

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

Blood samples for pharmacokinetic (PK) analysis of daprodustat and its metabolites (GSK2391220 [M2], GSK2531403 [M3], GSK2487818 [M4], GSK2506102 [M5], GSK2531398 [M6], and GSK2531401 [M13]) will be collected at the time points indicated in Section 14.2.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM. If the participant is unable to provide a sufficient blood quantity per time point or there is significant concern for this by the participant or investigator, these serial blood draws may be omitted.

Plasma analysis will be performed under the control of Bioanalysis, Immunogenicity, and Biomarkers - In Vitro/In Vivo Translation Platform/Scinovo, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of daprodustat and its metabolites (GSK2391220 [M2], GSK2531403 [M3], GSK2487818 [M4], GSK2506102

[M5], GSK2531398 [M6], and GSK2531401 [M13]) will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

9.2.2. Summary Measure

All pharmacokinetic endpoints will be summarized in tabular form. Descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum) will be calculated for all pharmacokinetic endpoints by regimen. In addition, for AUC(0-24, AUC(0-inf), C_{max}, $t_{1/2}$, geometric means and geometric CVs (CVb(%)) will be calculated for each regimen. Geometric mean and geometric CV% will not be calculated for t_{max}.

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

9.2.3. Population of Interest

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

9.2.4. Strategy for Intercurrent (Post-Randomization) Events

Not required.

9.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Geometric mean=exp (mean on $\log_e$ scale)

CVb (%)=SQRT(exp(SD**2)-1)x100, where SD is the standard deviation of the $\log_e$-transformed data.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

10.1. Statistical Analyses / Methods

POPPK is not evaluated for this study. The primary objective is Pharmacodynamic, the average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks, this is described in Section 11.

11. PHARMACODYNAMIC AND BIOMARKER ANALYSES

11.1. Primary Pharmacodynamic Analyses

11.1.1. Endpoint / Variables

Primary Objectives	Primary Endpoints
• To compare the effect of daprodustat to epoetin alfa on blood pressure (BP) after Acute Challenge 2 (8 weeks of hemoglobin [Hgb) maintenance therapy)	• Average of systolic blood pressure (SBP) as measured by ambulatory blood pressure monitoring (ABPM) over 6-hr post-dosing after 8 weeks of Hgb maintenance therapy

The primary endpoint is average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks. Other variables used in the primary endpoint model include: treatment, prior ESA dose (low/high), post-HD/pre-Acute Challenge 1 SBP, difference between post-HD/pre-Acute Challenge 2 SBP and post-HD/pre-Acute Challenge 1 SBP, and treatment by (difference in post-HD SBP between Acute Challenge 1 and 2) interaction.

11.1.2. Summary Measure

Average of systolic blood pressure (SBP) as measured by ambulatory blood pressure monitoring (ABPM) over 6-hr post-dosing after 8 weeks (i.e. Day 57) of Hgb maintenance therapy.

11.1.3. Population of Interest

The primary pharmacodynamics analyses will be based on the Intent-To-Treat population, unless otherwise specified.

If there are protocol deviations that are thought to potentially impact the primary endpoints (defined as at least 10% of the ITT population being excluded from the PP population), an exploratory sensitivity analysis may be considered using the PP population.

Any such important protocol deviations will be identified before DBR and the subsequent sensitivity analysis on the PP population will be documented in the CSR.

11.1.4. Strategy for Intercurrent (Post-Randomization) Events

ABPM data is collected every 15 minutes for the first 6-hrs and then every 20 minutes thereafter until 24-hrs post dose. In order to reduce the extent of missing ABPM data due to device issues, the device is designed to retry measuring blood pressure if it fails to record a BP during the scheduled timepoint. In addition, after both Acute Challenge 1 and 2, the 24-hr ABPM results will be checked for data quality as defined in the Project Requirement Specification (PRS). If the ABPM fails the QC criteria following Acute Challenge 2, one additional Acute Challenge may be made in a subsequent, mid-week dialysis visit 1 week later if the participant agrees. This repeat Acute Challenge 2 would replace the failed QC Acute Challenge 2.

For these participants who have a failed QC of the ABPM for a given acute challenge day, the data that is available from the ABPM device will be used during a sensitivity analysis on the primary endpoint. For those participants that fail QC both Acute Challenge 2, and a repeat Acute Challenge 2, the repeat Acute Challenge 2 data will be utilized.

Since participants who discontinue randomized study medication are withdrawn from the study and would have already performed their Day 1 acute challenge, multiple imputation will be used to attempt to impute what the missing data would have been had the participant not stopped randomized study medication. These participants who are early withdrawn will have their missing Day 57 ABPM data imputed to be included in a sensitivity analysis on the primary endpoint. This sensitivity analysis will include those participants who both early withdrawal and have their ABPM data imputed as well as those participants whose ABPM data did not pass QC for a given day. Details of the multiple imputation can be found in Section 14.6.6.

11.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 11.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

11.1.5.1. Interim Analysis

No interim analyses are currently planned for this study.

11.1.5.2. Statistical Methodology Specification

Endpoint / Variables
• Average of systolic blood pressure (SBP) as measured by ambulatory blood pressure monitoring (ABPM) over 6-hr post-dosing after 8 weeks (i.e. Day 57) of Hgb maintenance therapy
Model Specification
• ANCOVA with terms for treatment, prior ESA dose (low/high), and post-HD/pre-Acute Challenge 1 SBP, difference between post-HD/pre-Acute Challenge 2 SBP and post-HD/pre-Acute Challenge 1 SBP, and treatment by (difference in post-HD SBP between Acute Challenge 1 and 2) interaction. Note that the pre-challenge SBP may change over time between Acute Challenge 1 and Acute Challenge 2 as a result of the maintenance therapy, and thus the pre-challenge SBP at Acute Challenge 2 is not a true pre-treatment covariate. As a result, the interpretation of the effect of the Acute Challenge 2 may be confounded by the impact of treatment phase on the covariate. Therefore, if the interaction term in this model is significant at the 0.10 level, then the primary model will be ANCOVA with terms for treatment, prior ESA dose (low/high), and post-HD/pre-Acute Challenge 1 SBP.
Model Checking & Diagnostics
• Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance

will be assessed by plotting the residuals against the predicted values for the model. If assumptions are grossly violated, alternative analyses will be considered.
Model Results Presentation
• The point estimate, two-sided 95% CI and p-value for the difference between treatment groups will be presented from the selected final model for the superiority assessment. Superiority will be established if the p-value is <0.05.
Sensitivity and Supportive Analyses
• If there are protocol deviations that are thought to potentially impact the primary endpoints (defined as at least 10% of the ITT population being excluded from the PP population), an exploratory sensitivity analysis will be completed. The analysis used for the primary endpoint will be repeated and similar results will be presented. • Participants who discontinue randomized study medication early will have their missing Day 57 AC2 ABPM data imputed; a sensitivity analysis will be run on the primary endpoint including these participants. • The primary endpoint will analyse using a 6-hour average of BP from ABPM device, sensitivity analyses using 8, 12, and 24-hour averages will be analysed using the primary model explained above in the model specification section.

11.2. Secondary Pharmacodynamic Analyses

11.2.1. Endpoint / Variables

Secondary Objectives	Secondary Endpoints
• To compare the initial effect of daprodustat to epoetin alfa on BP after Acute Challenge 1 (2 weeks of erythropoiesis-stimulating agent [ESA] washout)	• Average of SBP, diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and heart rate (HR) as measured by ABPM over 6-hr post-dosing at Day 1 • Area under the effect curve (AUEC) of SBP, DBP, MAP, and HR as measured by ABPM over 24-hr post-dosing at Day 1
• To compare the effect of daprodustat to epoetin alfa on BP after Acute Challenge 2	• Average of DBP, MAP, and HR as measured by ABPM over 6 hr post-dosing at Day 57. • AUEC of SBP, DBP, MAP, and HR as measured by ABPM over 24-hr post-dosing at Day 57.
• To estimate the initial effect of daprodustat and epoetin alfa on SBP, DBP, HR and MAP after Acute Challenge 1 and 2	• Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1 and Day 57

11.2.2. Summary Measure

Secondary Endpoints	Summary Measure
• Average of SBP, diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and heart rate (HR) as measured by ABPM over 6-hr post-dosing at Day 1	• Average SBP, DBP, MAP, and HR over 6 hours post-dosing on Day 1 • AUEC for SBP, DBP, MAP, and HR over 24 hours post-dosing on Day 1

Secondary Endpoints	Summary Measure
• Area under the effect curve (AUEC) of SBP, DBP, MAP, and HR as measured by ABPM over 24-hr post-dosing at Day 1	
• Average of DBP, MAP, and HR as measured by ABPM over 6 hr post-dosing at Day 57. • AUEC of SBP, DBP, MAP, and HR as measured by ABPM over 24-hr post-dosing at Day 57.	• Average DBP, MAP, and HR over 6 hours post-dosing on Day 57 • AUEC for SBP, DBP, MAP, and HR over 24 hours post-dosing on Day 57
• Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1 and Day 57	• Mean change in SBP, DBP, HR, and MAP at each timepoint on Day 1 and Day 57

11.2.3. Population of Interest

The secondary pharmacodynamics analyses will be based on the ITT population, unless otherwise specified.

11.2.4. Strategy for Intercurrent (Post-Randomization) Events

If the primary sensitivity analysis for missing data differs with the primary endpoint, further sensitivity analyses on the secondary endpoints will be analysed. These potential, additional sensitivity analyses will follow how the primary endpoint sensitivity analysis was analysed, see Section 11.1.4 and Section 14.6.6 for details.

11.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 11.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

11.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• Average of SBP, DBP, HR, and MAP • AUEC of SBP, DBP, HR, and MAP • Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1 and Day 57
Model Specification
• For the first secondary endpoint, Average SBP over 6 hr post-dose in Acute Challenge 1 will be analyzed using ANCOVA with terms for treatment, prior ESA dose (low/high), and post-HD/pre-Acute Challenge 1 SBP. Similar analyses will be performed for DBP, MAP, and HR. • ANCOVA using the primary model will be used for the analysis of average DBP, MAP, and HR over 6 hr post-dose in Acute Challenge 2 replacing SBP terms with the analogous measurement for DBP, MAP, and HR respectively. o ANCOVA with terms for treatment, prior ESA dose (low/high), and post-HD/pre-Acute Challenge 1 ABPM (DBP/MAP/HR), difference between post-HD/pre-Acute Challenge 2 ABPM (DBP/MAP/HR) and post-HD/pre-Acute Challenge 1 ABPM (DBP/MAP/HR), and treatment by (difference in post-HD ABPM (DBP/MAP/HR) between Acute

Challenge 1 and 2) interaction. Note that the pre-challenge ABPM (DBP/MAP/HR) may change over time between Acute Challenge 1 and Acute Challenge 2 as a result of the maintenance therapy, and thus the pre-challenge ABPM (DBP/MAP/HR) at Acute Challenge 2 is not a true pre-treatment covariate. As a result, the interpretation of the effect of the Acute Challenge 2 may be confounded by the impact of treatment phase on the covariate. Therefore, if the interaction term in this model is significant at the 0.10 level, then the primary model will be ANCOVA with terms for treatment, prior ESA dose (low/high), and post-HD/pre-Acute Challenge 1 ABPM (DBP/MAP/HR). • For the second secondary endpoint, AUEC of SBP, DBP, HR, and MAP post-acute challenge 1 and 2 will be analyzed using an ANCOVA model with terms for treatment and prior ESA dose (low/high). • The AUEC for ABPM will only be analysed if a subject has ABPM data up to hour 24. o For example if the subject has ABPM data up to hour 23, the subject will be excluded from the ABPM AUEC analysis. o If more than 25% of subjects are excluded from the ABPM AUEC analysis because the subject is missing any of the 3 possible hour 24 ABPM measurements, then an extrapolation technique of average hour 23 measurement carried forward to hour 24 may be utilized as a sensitivity analysis for AUEC ABPM.
Model Checking & Diagnostics
• Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If assumptions are grossly violated, alternative analyses will be considered. • Section 14.6.6 outlines any transformation of data as needed.
Model Results Presentation
• The point estimate, two-sided 95% CI and p-value for the difference between treatment groups will be presented from all ANCOVA models for the superiority assessment. Superiority will be established if the p-value is <0.05. • Plot of hourly average ABPM will be created for SBP, DBP, MAP, and HR for both AC1 and AC2. • Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1 and Day 57will be summarized in a table.
Sensitivity and Supportive Analyses
• If more than 25% of subjects are excluded from the ABPM AUEC analysis because the subject is missing any of the 3 possible hour 24 ABPM measurements, then an extrapolation technique of average hour 23 measurement carried forward to hour 24 may be utilized as a sensitivity analysis for AUEC ABPM. o This will be only for the AC2 SBP, other sensitivity analyses may be considered.

11.3. Exploratory Pharmacodynamic and Biomarker Analyses

11.3.1. Endpoint / Variables

Exploratory Objectives	Exploratory Endpoints
• To investigate the effect of daprodustat and epoetin alfa on vasoactive mediators of blood pressure	• Plasma concentrations and derived parameters including Cmax, tmax, and AUC(0-24) as appropriate (to include erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II and metabolites, and noradrenalin)

Exploratory Objectives	Exploratory Endpoints
• To summarize the effect of daprodustat and epoetin alfa on SBP after Acute Challenge 1 and Acute Challenge 2	• AUEC of SBP as measured by ABPM over 24-hr post-dosing
• To compare the effect of daprodustat to epoetin alfa on SBP after 8 weeks of Hgb maintenance therapy	• Change from Day 1 pre-dose SBP to Day 57 pre-dose
• To compare the effect of daprodustat to epoetin alfa on SBP at Cmax of the study treatment	• Change in SBP from pre-dose on Day 1 to Cmax of the study treatment on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 1 to Cmax of the study treatment on Day 57, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 57, as measured by ABPM
• To compare the effect of daprodustat to epoetin alfa on SBP at Cmax of the erythropoietin level	• Change in SBP from pre-dose on Day 1 to Cmax of erythropoietin on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 1 to Cmax of erythropoietin on Day 57, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 57, as measured by ABPM

11.3.1.1. Statistical Methodology Specification

Endpoint / Variables
• Cmax, tmax, and AUC(0-24) for erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II and metabolites, and noradrenalin • AUEC of SBP, comparing Day 57 vs Day 1 • Change in pre-dose SBP from Day 1 to Day 57 • Change in SBP from pre-dose on Day 1 to Cmax of the study treatment on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 57, as measured by ABPM • Change in SBP from pre-dose on Day 1 to Cmax of erythropoietin on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 1, as measured by ABPM • Change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 57, as measured by ABPM
Overview of exploratory endpoints
• For each acute challenge, the concentration of erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II and metabolites, and noradrenalin will be summarized by treatment group at each timepoint. Descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum) will be calculated for all biomarkers endpoints by regimen. In addition, for AUC, Cmax, tmax, baseline adjusted AUC and baseline adjusted Cmax; geometric means and geometric CVs (CVb(%)) will be calculated for each regimen. Geometric mean and geometric CV% will not be calculated for tmax. Line graphs of this information will be provided by treatment group for

each acute challenge. Cmax, tmax, AUC(0-24), baseline adjusted AUC and baseline adjusted Cmax will all be summarized by treatment arm and for each acute challenge day.

- Change in AUEC of SBP from Day 57 to Day 1 for each treatment arm will be summarized in a table.
- The difference in SBP between pre-dose in Acute Challenge 1 and pre-dose in Acute Challenge 2 will be summarized by treatment group. Similar summaries of DBP, MAP, and HR will be performed.
- For each acute challenge, change from pre-challenge in SBP, DBP, MAP, and HR will be summarized by treatment group at each timepoint. In addition, for each acute challenge, SBP, DBP, MAP, and HR will be summarized by treatment group at each timepoint. Line graphs of this information will be provided by treatment group for each acute challenge.
- For the following endpoints, an ANCOVA model will be used with terms for baseline SBP, treatment, and prior ESA dose (low/high):
    - Change in SBP from pre-dose on Day 1 to Cmax of the study treatment on Day 1, as measured by ABPM
    - Change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 1, as measured by ABPM
    - Change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 57, as measured by ABPM
    - Change in SBP from pre-dose on Day 1 to Cmax of erythropoietin on Day 1, as measured by ABPM
    - Change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 1, as measured by ABPM
    - Change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 57, as measured by ABPM

Model Checking & Diagnostics

- Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If assumptions are grossly violated, alternative analyses will be considered.

Presentation of Exploratory Endpoints

- Line graphs for each acute challenge and each biomarker by treatment group
- Table summaries for AUEC of SBP, comparing Day 57 vs Day 1, and change in pre-dose SBP from Day 1 to Day 57
- Plot of hourly average ABPM will be created for SBP, over-lay for both AC1 and AC2.
- The point estimate, two-sided 95% CI and p-value for the difference between treatment groups will be presented from all ANCOVA models.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

12.1. Primary Pharmacokinetic / Pharmacodynamic Analyses

There are no primary Pharmacokinetic / Pharmacodynamic Analyses, only exploratory. The primary objective is Pharmacodynamic, the average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks, this is described in Section 11.

12.2. Secondary Pharmacokinetic / Pharmacodynamic Analyses

There are no secondary Pharmacokinetic / Pharmacodynamic Analyses, only exploratory. The primary objective is Pharmacodynamic, the average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks, this is described in Section 11.

12.3. Exploratory Pharmacokinetic / Pharmacodynamic Analyses

12.3.1. Endpoint / Variables

• To investigate if an exposure-response relationship exists between daprodustat and BP	• The daprodustat exposure (AUC) compared to the AUEC of SBP, DBP, MAP, and HR at Day 1 and Day 57
• To investigate if an exposure-response relationship exists between daprodustat and biomarkers of interest	• The daprodustat exposure (AUC) compared to the biomarker AUEC at Day 1 and Day 57. Biomarkers included erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II (and metabolites), and noradrenalin.

12.3.2. Summary Measure

To investigate if an exposure-response relationship exists between daprodustat and average systolic blood pressure (SBP), the daprodustat exposure (AUC) and SBP, DBP, MAP and HR AUEC from Days 1 and 57 will be plotted to determine if further modelling is required. Similar plot analyses (daprodustat AUC vs. biomarker AUEC on Days 1 and 57) will be explored to determine if a daprodustat exposure-response relationships exist with: erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II (and metabolites), and noradrenalin to determine if further modelling is deemed necessary.

These figures will be created for Day 1 and Day 57 visits. The x-axis will be the AUC of Daprodustat for each subject and the y-axis will be the AUEC of either BP or biomarkers for that subject. The figures will be scatter plots.

12.3.3. Population of Interest

The exploratory Pharmacokinetic / Pharmacodynamic Analyses will be based on the PK population, unless otherwise specified.

12.3.4. Strategy for Intercurrent (Post-Randomization) Events

Not required.

12.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

13. REFERENCES

GlaxoSmithKline Document Number 2015N267693_04, GSK1278864, A randomized, open label study to evaluate the effect of daprodustat on blood pressure in subjects with anemia associated with chronic kidney disease on hemodialysis switched from a stable dose of an erythropoiesis-stimulating agent (ASCEND-BP). 23-OCT-2019

Iverson C, Christiansen S, Flanagin A, et al. *AMA Manual of Style: A Guide for Authors and Editors*. 10th ed. New York, NY: Oxford University Press; 2007.

Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons, 1987.

14. APPENDICES

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

14.1.1. Exclusions from Per Protocol Population

A participant meeting any of the following criteria will be excluded from the Per Protocol population as detailed in the PDMP V5.0:

Number	Exclusion Description
01	Signed informed consent/assent not available on site
02	Wrong informed consent/assent version signed
03	Informed consent/assent not signed and/or dated by participant (parent/Legally Acceptable representative, if applicable)
04	Informed consent/assent not signed and/or dated by appropriate site staff.
05	Informed consent/assent not signed prior to any study procedure
06	Other informed consent/assent deviations
07	Meets Hgb stopping criteria
08	Receives a blood transfusion
09	Receives a kidney transplant
10	Becomes pregnant
11	Misses 2 consecutive dialysis sessions
12	Need for chronic use of prohibited medication
13	Myocardial infarction or acute coronary syndrome
14	Stroke or transient ischemic attack
15	New diagnosis of heart failure
16	Active chronic inflammatory disease that could impact erythropoiesis
17	Any new diagnosis of hematological disease
18	Active GI bleeding
19	Medication, excluded by the protocol, was administered*
20	Wrong study treatment or assignment administered
21	Assessment not properly performed*
22	Missed visit/phone contact*

NOTES:

- * Case by case basis.
- The list may be updated to reflect any amendments to the PDMP

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

Table 3 Study Procedures and Assessments

Procedure[1]	Screening	Washout	Treatment Period[2]					Follow-up[2]	
			Day 1	Day 15	Day 29	Day 43	Day 57	Early WD	Week 10
Informed Consent	X								
Entry Criteria	X								
Physical, Medical History, Demography	X								
HemoCue Hgb	X	X	X[4]	X	X	X	X[4]	X	X
Enrolment		X							
IVWRS			X	X	X	X			
Randomization			X						
Acute Challenge			X[4]				X[4]		
ABPM Assessment			X[4]				X[4]		
Dose Adjustment				X	X	X			
Females Only: Serum Pregnancy Test	X		X		X		X		X
Females Only: Estradiol & FSH (if required)[3]	X								
ECG	X		X[4]				X[4]		X
Vital signs & weight (Pre- & Post-dialysis)	X	X	X[4]		X		X[4]		X
Clinical Chemistry	X		X		X		X		X
Hematology	X		X		X		X		X
Folate and Vitamin B12	X								
Ferritin, transferrin, total iron, TSAT, UIBC	X								
Pharmacokinetic/Biomarker Assessments			X[4]				X[4]		
Hgb Maintenance Period[5]			←==========				==========→		
Adverse Events Assessment	X[6]	X	X[4]	X	X	X	X[4]		X
Review Concomitant Medications	X	X	X[4]	X	X	X	X[4]		X

1 All assessments should be done predialysis/predose except as noted.
2 Allowable time window ±2 days EXCEPT Follow-up Visit which is ±3 days.
3 As detailed in Inclusion Criteria.
4 Detailed timings for assessments on Acute Challenge Days are given in Table 4.
5 From the end of Acute Challenge 1 to the beginning of Acute Challenge 2.
6 Only SAEs assessed as related to study participation are collected at this visit. See Section 12.4 of the protocol for additional details.

Table 4 Study Procedures and Assessments on Acute Challenge Days (Treatment Period Day 1 and Day 57)

Procedure	Pre-Dialysis	Post-Dialysis	Predose	Time (in hours relative to dosing)										
				0	0.5	1	2	3	4	6	8	12	16	24
HemoCue Hgb[1]			X											X
IWRS			X											
ABPM Assessment[1, 3]			←==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========→
Administer Study Treatment[1]				X										
Serum Pregnancy Test[1]			X											
ECG[1]			X											X
Vital Signs and Weight[1]	X	X						X				X		X
Clinical Chemistry			X											
Hematology			X											
Pharmacokinetics[4]			X		X	X	X	X	X	X	X	X	X	X
Erythropoietin			X		X	X	X	X	X	X	X	X	X	X
Endothelin-1			X			X	X		X	X	X			X
Nitric Oxide			X			X	X		X	X	X			X
Asymmetric dimethylarginine			X			X	X		X	X	X			X
Renin			X			X	X		X	X	X			X
Angiotensin-II			X			X	X		X	X	X			X
Noradrenalin			X			X	X		X	X	X			X
Adverse Events Assessment[1]			X		X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications[1]			X											X
Initiate Hgb maintenance dosing[2]														X

1 Procedures to be repeated if Acute Challenge 2 fails quality control criteria
2 Applies to Acute Challenge 1 only
3 Timing of ABPM measurements does not correlate with specified time points in Table 4
4 PK to be drawn from daprodustat participants only

14.3. Appendix 3: Assessment Windows

14.3.1. Definitions of Assessment Windows for Analyses

Data for continuous variables will be summarized according to the scheduled visit time period for which they were recorded in the eCRF. Unscheduled assessments will not be slotted to a particular time point, but will remain as unscheduled if they are either summarized or listed unless otherwise specified.

14.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

14.4.1. Study Phases

Assessments and events will be classified according to time of occurrence relative to the treatment start and stop dates.

Treatment States **Treatment State**	**Definition**
Pre-Treatment	Date < Treatment Start Date
On-Treatment	Treatment Start Date <= Date ≤ Treatment Stop Date + 1 day
Post-Treatment	Date > Treatment Stop Date + 1 day

NOTES:

- If the treatment stop date is missing and the treatment start date is non-missing, then the assessment will be considered to be On-Treatment

14.4.1.1. Study Phases for Concomitant Medication

Pre-treatment medications are those taken (i.e., started) before the start date of randomized treatment. On-treatment medications are those taken (i.e., started or continued) at any time between the randomized treatment start date and the last non-zero dose date + 1 day, inclusive. Pre-treatment medications that were continued during this on-treatment period are also considered to be on-treatment medications. Post-treatment medications are those taken (i.e., started or continued) at any time after the last non-zero dose date + 1 day. On-treatment medications that were continued during this post-treatment period are also considered to be post-treatment medications.

It will be assumed that the medication has been taken on the date in which it is reported as started or stopped. Also, for any medication starting on the same date as randomized treatment, it will be assumed that the medication was taken after the participant started taking randomized treatment.

Illustrations of the pre-treatment, on-treatment, and post-treatment treatment states are included below:

	Pre-treatment	On-treatment			Post-treatment		Pre-treatment medication	On-treatment medication	Post-treatment medication
		Randomized Treatment Start Date		Last Non-zero Dose Date + 1 Day	Last Non-zero Dose Date + 2 Days				
(a)	x———x						Y	N	N
(b)	x———		———x				Y	Y	N
(c)	x———		———			———x	Y	Y	Y
(d)			x———x				N	Y	N
(e)			x———			———x	N	Y	Y
(f)						x———x	N	N	Y
(g)	?——— x						Y	N	N
(h)	?———		———x				Y*	Y	N
(i)	?———		———			———x	Y*	Y*	Y
(j)	x———		———			———?	Y	Y**	Y**
(k)			x———			———?	N	Y	Y**
(l)						x———?	N	N	Y
(m)	?—— ———		———			———?	Y***	Y***	Y***
(n)	x———	x					Y	Y	N
(o)	?—— ———	x					Y*	Y	N
(p)		x	———x				N	Y	N
(q)		x	———	x			N	Y	N
(r)				x	—	———x	N	Y	Y
(s)				x	—	———?	N	Y	Y**
(t)					x	———x	N	N	Y
(u)					x	———?	N	N	Y
(v)			x———	——	x		N	Y	Y

x = start/stop date of medication

? = missing start/stop date of medication

* If a medication is stopped On-treatment or Post-treatment and no start date is recorded it will be assumed that the medication was ongoing from the Pre-treatment phase

** If a medication is started Pre-treatment or On-treatment and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study

*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the Pre-treatment phase to the Post-treatment phase

14.4.2. Treatment Emergent Flag for Adverse Events

All AEs (non-serious AEs and serious AEs) will be collected and recorded on the eCRF from the start of treatment, including washout period, until the follow-up visit at the time points specified in the SoA from Appendix 2. Serious AEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded on the eCRF from the time a participant consents to participate in the study up to and including any follow-up contact.

Treatment State	Definition
Pre-treatment	• For participants with a non-missing screen failure date, if AE onset is on or before the screen failure date: AE Start Date ≤ Screen Failure Date • For randomized participants with a missing treatment start date, all AEs are considered pre-treatment • For randomized subjects with a non-missing treatment start date, if AE onset date is before treatment start date: AE Start Date < Treatment Start Date
Post-randomization	If AE onset date or AE worsening date is on or after the randomization date Randomization date ≤ AE Start Date Randomization date ≤ AE Worsening Date
Treatment emergent	If AE onset date or AE worsening date is on or after treatment start date & on or before the last non-zero dose date plus 1 day. Treatment Start Date ≤ AE Start Date ≤ Last Non-Zero Dose Date + 1 day Treatment Start Date ≤ AE Worsening Date ≤ Last Non-Zero Dose Date + 1 day
Follow-up	If AE onset date or AE worsening date is after the last non-zero dose date plus 1 day. AE Start Date > Last Non-Zero Dose Date + 1 day AE Worsening Date > Last Non-Zero Dose Date + 1 day
Onset /Worsening Time Since 1st 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 If Treatment Start Date > AE Worsening Date = AE Worsening Date - Treatment Start Date If Treatment Start Date ≤ AE Worsening Date = AE Worsening Date - Treatment Start Date +1 Missing otherwise.
Onset/Worsening Time Since Last Dose (Days)	If Last Non-Zero Dose Date < AE onset date: AE onset date – last non-zero dose date If Last Non-Zero Dose Date ≥ AE onset date: AE onset date – last non-zero dose date If Last Non-Zero Dose Date < AE worsening date: AE worsening date – last non-zero dose date If Last Non-Zero Dose Date ≥ AE worsening date: AE worsening date – last non-zero dose date Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date/AE Worsening Date + 1
Drug-related	If relationship is marked 'YES' on eCRF or if the value is missing.

NOTES:

- AEs that occur or worsen during interruptions of randomized study treatment will be classified as treatment emergent and post-randomization.
- If the treatment stop date is missing and the treatment start date is non-missing and the AE onset date or AE worsening date is on or after the treatment start date, then the AE will be considered to be treatment emergent.
- If AE onset date or AE worsening date is missing and AE resolution date is before the treatment start date, then the AE will be classified as Pre-treatment.
- If AE onset date or AE worsening date is missing and AE resolution date is either missing or on or after treatment start date, then the AE will be classified as treatment emergent and post-randomization.

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software, Version 9.2 (or higher) will be used for all analyses unless otherwise specified. Additionally, R Version 3.1.0 or higher may be used for analysis and the production of graphics.	
Reporting Area	
HARP Server	: us1salx00259
HARP Compound	: gsk1278863/mid205665
Analysis Datasets	
• Analysis datasets will be created according to clinical data interchange standards consortium (CDISC) standards: study data tabulation model (SDTM) implementation guide (IG) Version 3.1.3 with some updates from Version 3.2, Analysis data model (ADaM) IG Version 1.1, and GSK ADaM specification template. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from system independent (SI) to SDTM.	
Generation of RTF Files	
• Rich text format (RTF) files will be generated for Tables.	

14.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings
• In all displays (TFLs) the term “Subjects” will be used to refer to the “Participants”.

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

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.

• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables, with the following exceptions: o If the table includes a row for all post-baseline assessments, unscheduled visits will be included in this row. All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

14.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
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.
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.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 14.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Treatment Day

• Calculated as the number of days from treatment start date:
  • Treatment Start Date = Missing → Treatment Day = Missing
  • Ref Date < Treatment Start Date → Treatment Day = Ref Date – Treatment Start Date
  • Ref Data ≥ Treatment Start Date → Treatment Day = Ref Date – (Treatment Start Date) + 1

Randomization Date
• Date subject was randomized
Study Day

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

Study Completion/Withdrawal Date
• Date of withdrawal for subjects withdrawing (i.e., subjects who actively withdraw or are deemed lost to follow-up) from study or date of completion of study for subjects who complete the study. • Early withdrawal subjects during washout will be calculated if the subject has a withdrawal date but no randomization date
First Study Contact Date
• First study contact with the subject while on the study is defined as consent date   ○ If subject has been re-screened, latest consent date will be used
Last Study Contact Date
• Last study contact with subject (clinic, telephone or other contact with subject) with the subject while on the study

Time Definitions (per GSK standard principles)

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

Last Non-Zero Dose Date

- Date of last actual dose of randomized study treatment from the IP Discontinuation eCRF form.
    - The dose steps used by the dosing algorithm described in the protocol include a dose hold or a zero dose. If participants are assigned by the algorithm to a zero dose, they do not receive randomized treatment for that period. Hence, it would be possible for a participant to complete the study, while still following the dosing algorithm, but not actually taking any actual randomized treatment. The last non-zero dose date then captures the latest date in the study that a participant physically took a dose of randomized treatment.
- The eCRF allows for the possibility of partial or missing dates to be recorded for the last actual dose of randomized study treatment on the IP Discontinuation form (i.e., missing day, or day and month, or day and month and year). In such a case, or in case of a missing IP Discontinuation form, the following conventions will be applied in order to impute a last non-zero dose date:
    - Missing day:
        - The last day of the month will be used, unless the treatment stop date also occurs in the same month; in this case, the treatment stop date will be used.
    - Missing day and month;
        - '31' will be used for the day and 'Dec' will be used for the month, unless the treatment stop date also occurs in the same year; in this case the treatment stop date will be used.
    - Missing day, month, and year:
- Treatment stop date will be used only for participants who have a non-missing treatment start date.

Screening and Washout visits

Screening

- Screening is an average of all screening values. For subject's pre-protocol amendment 3, this is the average of the week -8 up to but not including the week -4 visits. For subject's post-protocol amendment 3, this is the average of the 7-30 days prior to week -2 visit but not including the week -2 visits.
- Rescreened subjects data will only be counted once, the latest visit will only be summarized.

Washout

- Washout is the average of all washout visit values. For subject's pre-protocol amendment 3, this is the average of the week -4 up to but not including the Day 1 visits. For subject's post-protocol amendment 3, this is the average of the week -2 up to but not including Day 1 visits

Day 57 Repeat visits

How to summarize data

- For subjects with a repeat Day 57 visit, data such as vital signs and ECG will be summarized under the Day 57 table heading.
    - Day 57 data will be replaced with day 57 repeat visit data

14.6.2. Study Population

Demographics
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]^2
Race Groups
• Geographic ancestry data will be combined into categories as provided by the United States (US) Food and Drug Administration (FDA) and summarized as FDA race group: o American Indian or Alaskan Native o Asian (Asian-East Asian Heritage, Asian-Japanese Heritage, Asian-Central/South Asian Heritage, Asian-South East Asian Heritage, Asian-Mixed Race) o Black (African American/African Heritage) o Native Hawaiian or Other Pacific Islander o White (White-Arabic/North African Heritage, White-White/Caucasian/European Heritage, White – Mixed Race) o Mixed Race (Multiple races are selected, but excludes Asian – Mixed Race and White – Mixed Race) Note: Asian – Mixed Race includes subjects who have more than one Asian category selected, but no other categories. White – Mixed Race includes subjects who have more than one White category selected, but no other categories.

Study Withdrawal
• Time to Study Withdrawal (days) = Study withdrawal date – Randomization date +1
• Time To Study Withdrawal (days), subjects withdrawn during washout = Study withdrawal date – Week -2 Visit date +1, if subject was consented after protocol amendment 3 • Time To Study Withdrawal (days), subjects withdrawn during washout = Study withdrawal date – Week -4 Visit date +1, if subject was consented before protocol amendment 3

Treatment Compliance

- Treatment compliance will be calculated based on the formula:
  - Daprodustat:
    - **Compliance (%) = [(Total # of tablets actual taken) / (Total # of tablets planned taken)] * 100**
      - Where:
        - Total # of tablets actual taken = Sum of (Numbers of Tablets Taken at Each Visit)
        - Total # of tablets planned taken = Sum of [(Treatment Stop Date – Treatment Start Date + 1 day) x Planned # of tablet / day in Each Visit]
          - Exclude any dose hold days from sum if able to calculate dose hold days.
  - rhEPO:
    - **For rhEPO subjects, compliance will not be calculated since the data is not being collected. These subjects are dosed within the clinic during their visit.**
- Planned Treatment Duration is defined as day 1 to day 57 (day 57 repeat if applicable)

Extent of Exposure

- Number of days of exposure to study drug will be calculated based on the formula:
  - **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1**
- Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.
- The cumulative dose will be based on the formula:
  - **Cumulative Dose = Sum of (Each dose taken recorded in the eCRF)**

14.6.3. Efficacy

No Efficacy analyses being performed

14.6.4. Safety

Adverse Events
AEs of Special Interest
Adverse events of special interest are classified as follows: • Death, MI, stroke, heart failure, PE, DVT, thromboembolic events, thrombosis of vascular access • Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis • Cardiomyopathy • Pulmonary artery hypertension • Cancer-related mortality and tumor progression and recurrence • Esophageal and gastric erosions • Proliferative retinopathy, macular edema, choroidal neovascularization • Exacerbation of rheumatoid arthritis • Worsening of hypertension The above list text can be shortened for displays as follows: • Fatal, CV, and thromboembolic events • Excessive erythropoiesis sequelae • Cardiomyopathy • Pulmonary artery hypertension • Cancer progression or recurrence • Esophageal and gastric erosions • Retinal and choroidal neovascularization • Exacerbation of rheumatoid arthritis • Worsening of hypertension

Thrombosis and tissue ischemia events will be considered to be secondary to excessive erythropoiesis if during the window of [AE start date – 30 days, AE start date +15 days] any one of the following 3 events occurs:

- Any Hgb value >= 13 g/dL (measured pre-dialysis)
- Hgb increase > 2 g/dL over 2 weeks
- Hgb increase > 4 g/dL over 4 weeks

Note: Scheduled central laboratory Hgb values will be used, unless a scheduled central laboratory Hgb value is missing, in which case, a corresponding non-missing scheduled HemoCue Hgb value will be used. Unscheduled Hgb values will also be used in the assessment of secondary to excessive erythropoiesis as follows:

- If an unscheduled central laboratory Hgb value and an unscheduled HemoCue Hgb value are on the same date, only the central laboratory Hgb value will be used.
- If there is only one unscheduled Hgb value available on an individual date, then that value will be used regardless of the data source (i.e., either central laboratory or HemoCue).

Potential AESIs will be identified through a pre-defined terms of interest process in which predefined lists of AE preferred terms corresponding with each AESI will be used to identify events considered to be potential AESIs. Sites will be prompted via query to complete any necessary additional information for these AESIs in the eCRF.

For the category of thrombosis and/or tissue ischemia secondary to excessive erythropoiesis, after the terms of interest list has been applied, the additional Hgb criteria described above will be applied to identify only those events that are considered to be secondary to excessive erythropoiesis as meeting the AESI definition for thrombosis and/or tissue ischemia secondary to excessive erythropoiesis.

General Definitions

- For the analysis of the time to AE onset/worsening, if the AE onset/worsening date is missing then the time to AE onset/worsening will be counted as 1 day.

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 significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1
- 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' is present, then the corresponding numeric value will be set equal to x.
- If there is more than one laboratory value on the same date for the same laboratory test, then the laboratory values associated with scheduled visits will be used.
- The following will be used to convert laboratory values from SI units to conventional units if the specific lab value is not already in this format. [Iverson, 2007]:
  - Hemoglobin, MCHC and Albumin: Divide the g/L value by 10 to get the g/dL value.
  - Albumin-adjusted calcium: Divide the mmol/L value by 0.25 to get the mg/dL value.

Laboratory Parameters
• Phosphate: Divide the mmol/L value by 0.323 to get the mg/dL value. • Lab values that are converted will be reported in place of original value
• Heart rate and pulse rate can be used interchangeably • Total calcium and calcium can be used interchangeably • Total protein and protein can be used interchangeably • Total bilirubin and bilirubin can be used interchangeably • TSAT and transferrin saturation can be used interchangeably
• Baseline HGB will be based either on the pre-dose value on Day 1 or screening value. Any unscheduled HGB values taken after the pre-dose value on Day 1 will not be used.
Normal Range Categories, PCI Criteria Categories and Worst Case Values
• Normal range categories are: To Low, To Normal or No Change, To High • PCI criteria categories are: To Low, To w/in Range or No Change, To High • Subjects with a missing baseline value are to be assumed to have a normal/within range baseline value. • The determination of the worst-case post baseline value takes into account both planned and unscheduled assessments. • Worst case can be either High or Low. o If a subject has both a decrease 'To Low' and an increase 'To High', then the subject is counted in both the 'To Low' and 'To High' categories. o If a subject was High at baseline and decreases to Low during the time interval, then the subject is counted in the 'To Low' category. Likewise, if a subject was low at baseline and increases to high during the time interval, then the subject is counted in the 'To High' category. o Subjects are only counted in the 'To Normal or No Change' or 'To w/in Range or No Change' category if their values are: ▪ When using normal ranges: Normal at baseline and have no high and no low values; When using PCI ranges: Within range at baseline and have no high and no low values ▪ High at baseline and do not change to low ▪ Low at baseline and do not change to high

14.6.5. Pharmacokinetic

Parameter	Parameter Description
AUC(0-τ)	Area under the concentration-time curve from time zero to the end of the dosing interval τ, where τ=24 h will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z** (Day 1 only)
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.

Parameter	Parameter Description
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z** (Day 1 only)
Percent drug related material (%DRM)	For parent as well as each metabolite, where the denominator is the sum of the exposures of all analytes. The AUCs will be corrected for the molecular weight (MW) of each compound. Example: $\%DRM_{daprodustat} = 100^* (AUC_{daprodustat} / MW_{daprodustat}) / ((AUC_{daprodustat} / MW_{daprodustat}) + (AUC_{M2} / MW_{M2}) + (AUC_{M3} / MW_{M3}) + (AUC_{M4} / MW_{M4}) + (AUC_{M5} / MW_{M5}) + (AUC_{M6} / MW_{M6}) + (AUC_{M13} / MW_{M13}))$ Parameters to be used in this calculation are: Day 1: AUC(0-τ), AUC(0-∞) Day 57 AUC(0-τ)

NOTES:

- Additional parameters may be included as required.
- Lambda_z is the terminal phase rate constant.

Compound	Molecular Weight (MW) (g/mol)
daprodustat	393.442
M2	425.442
M3	425.442
M4	425.442
M5	425.442
M6	425.442
M13	441.442

14.6.6. Pharmacodynamic and Biomarker

Pharmacodynamic and Biomarker
ABPM Data

• Only subjects whose ABPM data QC passes will be included in the PD TLFs
• ABPM data will be recorded during the challenge agents on Day 1, Day 57, and repeat Day 57 if applicable.
• The pre-acute challenge measurement will come from ABPM data if the first included ABPM measurement is within ± 10 min of the adjusted start time of the ABPM device.
  ○ Else, the pre-acute challenge measurement will be taken from the vitals dataset, post-dialysis measurement only. This is for Day 1, Day 57, repeat Day 57. If day 1 is missing from the vitals dataset, then week-2 or screening can be used.
  ▪ The time used for replacing excluded ABPM measurement with a vitals measurement will remain the adjusted start time of the ABPM device.

Pharmacodynamic and Biomarker

- If there is an additional ABPM data for Day 57, this means the subjects original Day 57 ABPM data failed QC and this data will not be included for any analysis
- 6, 8, 12, and 24-hour averages will be calculated using the following method:
  - Each hour will be averaged (up to 4 measurements per hour for the first 6 hours)
  - Then average the 6, 8, 12, and 24 hour measurements
  - This applies for ABPM data (SBP, DP, MAP, HR)
  - Missing or data that has been deemed not of good quality based on QC criteria, will be flagged with an excluded flag. These data will not be used when averaging ABPM.
  - This will be calculated for 6, 8, 12 and 24 hours
  - Example:

Hour	ABPM				
	1st Measurement	2nd Measurement	3rd Measurement	4th Measurement	Average
0-1	***, not used for average ABPM, being used as baseline BP value unless baseline comes from vitals	112	116	115	= (112+116+115)/3 = 114.33
1-2	120	118	121	X, missing	= (120+118+121)/3 = 119.67
2-3	120	118	121	125	= (120+118+121 + 125)/4 = 121
3-4	120	118	121	125	121
4-5	120	118	121	125	121
5-6	120	118	121	125	121
6 Hour Average					(114.33 +119.67+121+121 +121+121)/6 = 119.67

- X represents missing data

Post HD Pre Acute Challenge Variable

- The Post HD Pre Acute Challenge Variable data point will come from the SBP/DBP/HR/MAP reading recorded from the ABPM data. The zero time, first recorded measurement from the ABPM device, will be used as the post HD pre acute challenge variable
  - If the data is missing from the ABPM data, the eCRF vital signs data will be used
    - Post-dialysis measurement will be used
  - If MAP variable is needed from eCRF, MAP will be calculated the following way:
    - MAP = (SBP + 2(DBP)) / 3

Difference between post-HD/pre-Acute Challenge 2 and post-HD/pre-Acute Challenge 1

Difference between post-HD/pre-Acute Challenge 2 and post-HD/pre-Acute Challenge 1

Pharmacodynamic and Biomarker

= post-HD/pre- Acute challenge 2– post-HD/pre-Acute challenge 1

- This applies for SBP, DBP, HR, and MAP

AUEC Secondary Endpoints

- Baseline, or time zero, for AUEC of ABPM data will be defined as the first ABPM measurement. If the first ABPM measurement is missing or excluded, then BP data from vitals will be used.
  - For these subjects, if the recorded time of vitals measurement is > 24 hours before the last ABPM measurement, then last ABPM measurement time is used in place of baseline time.
- AUEC will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
- AUEC timepoints will be converted to be on the hourly scale
  - For example, if the second measurement is listed as 00:15, then this will be converted to the hourly scale of 0.25
- The AUEC for ABPM will only be analysed if a subject has ABPM data up to hour 24.
  - For example if the subject has ABPM data up to hour 23, the subject will be excluded from the ABPM AUEC analysis.
  - If more than 25% of subjects are excluded from the ABPM AUEC analysis because the subject is missing any of the 3 possible hour 24 ABPM measurements, then an extrapolation technique of average hour 23 measurement carried forward to hour 24 may be utilized as a sensitivity analysis for AUEC ABPM.
- If the AUEC data appears to be skewed, then the data will be log-transformed. Instead of reporting mean and standard deviation, the geometric mean and CV will be reported

Change from pre-dose in SBP, DBP, HR, and MAP at each timepoint at Day 1

- Each timepoint is defined as every 15 minutes for the first 6 hours, then every 20 minutes after.
- The first measurement will be defined as pre-acute challenge and will not be used when calculating the averages.
- The calculation will look like the following:
  - Change = Measurement – Pre-acute challenge measurement

Hour	Measurement 1 Chg	Measurement 2 Chg	Measurement 3 Chg	Measurement 4 Chg	Average
0-1	***, not used for average ABPM, being used as baseline BP value	121-115=6	122-115=7	120-115=5	(6+7+5)/3=6
…					
5-6	120-115=5	121-115=6	122-115=7	missing	(5+6+7)/3=6
6-7	120-115=5	121-115=6	122-115=7	No data possible	(5+6+7)/3=6
…					
23-24	120-115=5	121-115=6	missing	No data possible	(5+6)/2=5.5

Pharmacodynamic and Biomarker	
Change from pre-dose at Day 1	(6+…+6+6+…+5.5)/24=5.875

- This will be calculated only for the Daprodustat treated arm and will be done for SBP, DBP, HR, and MAP on Day 1

Pharmacodynamic and Biomarker

Multiple Imputation

- A sensitivity analysis will be performed on the primary endpoint to include those subjects who stop randomized treatment and those participants who fail any QC for their acute challenge.
    - The first group are those participants who stop randomized treatment. These participants will have their Day 57 6hr average SBP ABPM data imputed to assess what would have happened had the participant not stopped IP. Since these participants would have been randomized, there will be data for acute challenge 1, however acute challenge 2 data will need to be imputed.
        - Post-HD/pre-Acute Challenge 2 SBP will also be imputed.
    - The second group are those participants who have QC failed either their Day 1 or Day 57 acute challenge, or QC failed both acute challenges. For this group no data imputation will be performed, instead the data that is available from the ABPM device will be used to calculate what the 6hr average is.
        - Like for the primary endpoint, post-HD/pre-Acute Challenge SBP will be taken from the first measurement on the ABPM device. If missing, then the vital signs BP will be used instead.

- Multiple imputation for the first group, those participants who stop randomized treatment, will be done under the assumption of a multivariate normal distribution using the Markov Chain Monte Carlo (MCMC) procedure assuming missing at random.
    - Both the pre AC2 SBP and Day 57 6hr average SBP will be imputed
    - The first step will be to calculate the number of missing data points to see what the missing pattern is
    - Next the imputation phase will fill in values for the missing data points
        - Seed code of 205665 will be used
        - Burn in iterations and maximum iterations are set to default, 200
        - This will result in 1,000 imputations being calculated
        - Trace plots and autocorrelation figures will be used to assess the imputations
        - Variables to be included for imputation:
            - Day 1 6 hr average SBP from ABPM
            - Day 1 baseline SBP
            - Day 57 baseline SBP
            - Day 57 6 hr average SBP from ABPM
            - Add treatment and prior esa dose as by variables in proc mi
                - If there are error and or warning messages related to the by statement, try by randomized treatment only until no error/warning messages.
            - Next the imputed dataset will be used to calculate the difference between the pre AC1 and pre AC2 SBP, now using the imputed pre AC2 SBP.

Pharmacodynamic and Biomarker

- The analysis phase will then calculate what the parameter estimates are using the same model as the primary endpoint, ANCOVA model with terms for treatment, prior ESA dose (low/high), pre AC1 SBP, difference between pre AC1 and pre AC2 SBP, and interaction of treatment and difference between pre AC1 and pre AC2 SBP.
  - if the interaction term in this model is significant at the 0.10 level, then the model will be an ANCOVA with terms for treatment, prior ESA dose (low/high), and pre AC1 SBP, just like the primary endpoint
- The pooling phase will then pool all 1,000 model's parameter estimates.

- After the sensitivity analysis pooled parameter estimates are calculated, output will be compared with original non-imputed model (primary endpoint).
  - Day 57 6hr average SBP values will be computed and compared across treatment groups using the primary ANCOVA model described above. Rubin's rules [Rubin, 1987] will be used to combine results of the imputed datasets using SAS PROC MIANALYZE procedure. As a result, a single estimated treatment difference and its standard error will be produced, with which a 95% CI will be calculated.
  - For each parameter, the estimate, 95% CI, and p-value will be compared
  - If the results of the primary endpoint differs when compared with this sensitivity analysis, then further secondary endpoint sensitivity analyses will be analysed in a similar fashion.

Biomarker Derivations

- Nitrate umol/L = Nitrite Total - Nitrite Endogenous
  - The Nitrate concentration is an indirect method to estimate Nitric Oxide.
  - Nitric Oxide label will be used in place of nitrate concentration

- Geometric mean=exp (mean on loge scale)
- CVb (%)=SQRT(exp(SD**2)-1)x100, where SD is the standard deviation of the loge-transformed data.
- Natural Log-transformation, (Ln), of biomarker data will not be done for Tmax
- AUC(baseline corrected) = Calculated AUC - (baseline level*time)
  - Where baseline level is defined as the pre-dose measurement for each visit
  - Where time is the last time measurement, for most subjects this would be 24 hours.
  - To be done on a by subject level then summarized by treatment for each visit
- Cmax(baseline corrected) = Cmax - baseline level
  - Where baseline level is defined as the pre-dose measurement for each visit
  - To be done on a by subject level then summarized by treatment for each visit

Parameter	Parameter Description
AUC(0-24)	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. o If subject is missing pre-dose or 24-hour data, then exclude from AUC calculation.
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data.

Pharmacodynamic and Biomarker

Tmax	Time to reach Cmax, determined directly from the concentration-time data.

Exploratory endpoints

- For exploratory endpoints utilizing ANCOVA models:
  - Baseline SBP data point will come from the SBP/DBP/HR/MAP reading recorded from the ABPM data. The zero time, first recorded measurement from the ABPM device, will be used as the post HD pre acute challenge variable as per the guidelines under ABPM data.
    - If the data is missing from the ABPM data, the eCRF vital signs data will be used
      - Post-dialysis measurement will be used
    - If MAP variable is needed from eCRF, MAP will be calculated the following way:
    - MAP = (SBP + 2(DBP)) / 3
  - Change from baseline will be defined as average of the BP from ABPM device, within $\pm$ 20 min from tmax, minus the baseline SBP data point.
    - Discrete timepoints will be used
    - If no ABPM data is available with the $\pm$ 20 min window, then the calculated average will be marked as "." to indicate missing since no ABPM data is available within that window.
  - If repeat day 57 data is available, then the Cmax data will be based on the non-repeat visit and the ABPM data will be based on the repeated visit.
  - If more than one tmax is listed for a given cmax, only the first tmax will be used.
- For Daprodustat subjects, the tmax from treatment and the tmax from epoetin alfa data will be used
- For rhEPO subjects, the tmax from epoetin alfa will be used for both endpoints analysing tmax of ABPM data.

Plot of ABPM Data

- Hourly average of each of the four ABPM measurements (SBP, DBP, MAP, and HR) for AC1 and AC2 will be generated for each subject
  - Hourly averages defined as follows:

Hour	Measurement 1	Measurement 2	Measurement 3	Measurement 4	Average
0-1	121	115	122	120	(121+115+122+120)/4 =119.5
…					
5-6	121	115	122	Missing	(121+115+122)/3 =119.3
6-7	121	115	122	No data possible	(121+115+122)/3 =119.3
…					
23-24	120	121	missing	No data possible	(120+121)/2=120.5

- The treatment arm averages of these hourly averaged subject values will then be plotted

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as a participant who has completed all phases of the study including the follow-up visit. • Participants that withdraw prior to the Acute Challenge 2 assessment or subjects who do not pass QC for Acute Challenge 2 will be replaced so that 25 participants per treatment arm complete and pass QC for Acute Challenge 2. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

14.7.2. 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 participant 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 participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant 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 study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ 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.
Concomitant Medications/ Medical History	• 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

Element	Reporting Detail
	○ 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.

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hemoglobin	G/DL		<8.5 G/DL	>11 G/DL
Platelet Count	GI/L		< 80 GI/L	> 500 GI/L
Neutrophils	GI/L		< 0.5x LLRR	
Lymphocytes	GI/L		< 0.5x LLRR	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Potassium	mmol/L		> 0.5 mmol/L below LLRR	> 1.0 mmol/L above ULRR
Albumin	g/dL		< 3.0 g/dL	> 5.5 g/dL
AST (SGOT)	IU/L			>= 3x ULRR
ALT (SGPT)	IU/L			>= 3x ULRR
Calcium (Albumin adjusted)	mg/dL		< 7.48 mg/dL	> 10.24 mg/dL
Phosphate	mg/dL		< 2.50 mg/dL	> 5.47 mg/dL
Total bilirubin	µmol/L			>= 2x ULRR
Serum ferritin	ng/mL		< 100 ng/mL	> 800 ng/mL
TSAT	%		<15%	> 40%
Sodium	mmol/L		< 130 mmol/L	> 150 mmol/L
Glucose	mmol/L		<3.9 mmol/L	>22 mmol/L

14.8.2. Vital Signs

Vital Sign Parameter (Absolute)	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	<= 80 mmHg	>= 160 mmHg
Diastolic Blood Pressure	mmHg	<= 50 mmHg	>= 100 mmHg
Pulse Rate	bpm	<= 40 bpm	>= 110 bpm

Notes:

- At visits where BP and HR are assessed more than once, the average of the values will be used to assess PCI criteria.
- For participants who undergo in-clinic dialysis, the post-dialysis BP and HR values will be used to assess PCI criteria, unless otherwise specified.

14.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

PopPK is not evaluated for this study. The primary objective is Pharmacodynamic, the average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks, this is described in Section 11.

14.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

PK/PD is not evaluated for this study. The primary objective is Pharmacodynamic, the average systolic blood pressure (SBP) over 6-hr post-dosing after 8 weeks, this is described in Section 11.

14.11. Appendix 11: Abbreviations & Trade Marks

14.11.1. Abbreviations

Abbreviation	Description
ABPM	Ambulatory blood pressure monitoring
AC	Acute challenge
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse event of special interest
AIC	Akaike's Information Criteria
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under curve
AUEC	Area under effect curve
A&R	Analysis and Reporting
BP	Blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CHF	Chronic heart failure
CHR	Reticulocyte hemoglobin content
CI	Confidence Interval
CKD	Chronic kidney disease
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBP	Diastolic blood pressure
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
DR	Dry run
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
HD	Hemodialysis-dependent
HR	Heart rate
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee

Abbreviation	Description
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MAP	Mean arterial blood pressure
MCH	Mean corpuscular hgb
MCHC	Mean corpuscular hgb concentration
MCV	Mean corpuscular volume
MI	Myocardial Infarction
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RC	Reticulocyte count
RDW	Red blood cell distribution width
SAC	Statistical Analysis Complete
SAE	Serious adverse event
SBP	Systolic blood pressure
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
WBC	White blood cell count

14.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
HemoCue
SAS

14.12. Appendix 12: List of Data Displays

14.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.19	-
Safety	2.01 to 2.35	-
Pharmacokinetic	3.01 to 3.2	3.01 to 3.21
Pharmacodynamic and Biomarker	4.01 to 4.42	4.01 to 4.12
Pharmacokinetic / Pharmacodynamic	-	5.01-5.02
Section	**Listings**	
ICH Listings	1 to 30	
Other Listings	31 to 35	

All tables and figures will start with numbering scheme like “X.01, X.02, etc”.

14.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Pharmacodynamic and Biomarker	PDF1	PDT1 - PDT10	PDL1
Pharmacokinetic / Pharmacodynamic	PKPDF1	-	-

NOTES:

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

14.12.3. Deliverables

Delivery	Description
DR	Dry Run
SAC	Final Statistical Analysis Complete

14.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	Enrolled	ES1	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, FDAAA, EudraCT No sub reason	DR, SAC
1.2.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3 No sub reason	DR, SAC
1.3.	Screened	PDT10	Summary of Participant Disposition at Each Study Period	ICH E3 Add footnote: Withdrawn subjects may be greater than entered for no treatment due to subject's first follow-up visit occurring after second screen failure.	DR, SAC
1.4.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	DR, SAC
1.5.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	DR, SAC
Protocol Deviation					
1.6.	ITT	DV1	Summary of Important Protocol Deviations	ICH E3	DR, SAC
1.7.	ITT	IE1	Summary of Inclusion/Exclusion Criteria Deviations	ICH E3	DR, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Population Analysed					
1.8.	Screened	SP1	Summary of Study Populations	IDSL, all populations to be used (Screened, enrolled, safety, ITT, PP, PK)	DR, SAC
1.9.	ITT	SP2	Summary of Exclusions from the Safety Population	IDSL	DR, SAC
1.10.	ITT	SP2	Summary of Exclusions from the Per Protocol Population	IDSL	DR, SAC
Demographic and Baseline Characteristics					
1.11.	ITT	DM1	Summary of Demographic Characteristics - ITT	ICH E3, GSK CTR, FDAAA, EudraCT Footnote: Age is imputed from year and month of birth	DR, SAC
1.12.	Safety	DM1	Summary of Demographic Characteristics - Safety	ICH E3, GSK CTR, FDAAA, EudraCT Footnote: Age is imputed from year and month of birth	DR, SAC
1.13.	Enrolled	DM11	Summary of Age Ranges	EudraCT Footnote: Age is imputed from year and month of birth	DR, SAC
1.14.	ITT	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, GSK CTR, FDAAA, EudraCT	DR, SAC
Prior and Concomitant Medications					
1.15.	ITT	MH1	Summary of Medical Conditions	ICH E3	DR, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.16.	ITT	CM1	Summary of Concomitant Medications (Pre-treatment)	ICH E3	DR, SAC
1.17.	ITT	CM1	Summary of Concomitant Medications (On-treatment)	ICH E3	DR, SAC
1.18.	ITT	CM1	Summary of Concomitant Medications (Post-treatment)	ICH E3	DR, SAC
Exposure and Treatment Compliance					
1.19.	Safety	EX1	Summary of Exposure and Compliance to Study Treatment	ICH E3, add line for average percent compliant for each treatment group. Total column not needed. Add the following footnote if unable to calculate dose hold days: Compliance calculation assumed dose hold days and missed doses to be the same. Add footnote, daprodustat only, rhEPO done at site so no compliance to calculate	DR, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Additional Study Population Tables					
1.20.	PP	DM1	Summary of Demographic Characteristics - PP	ICH E3, GSK CTR, FDAAA, EudraCT Footnote: Age is imputed from year and month of birth Only produce if PP used in sensitivity analyses	SAC

14.12.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
2.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3, by treatment, then summarized by pre-treatment, post-randomization, treatment emergent, and follow-up.	DR, SAC
2.2.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term by Phase	Treatment AEs will be separated by AC1, HGB maintenance, and AC2.	DR, SAC
2.3.	Safety	AE3	Summary of Common (>=2%) Adverse Events by Overall Frequency	ICH E3, by preferred term and treatment group, includes treatment emergent AEs	DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.4.	Safety	AE5A	Summary of Common (>=2%) Adverse Events by Maximum Intensity	ICH E3, by treatment, includes treatment emergent AEs	DR, SAC
2.5.	Safety	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3, by treatment, includes treatment emergent AEs	DR, SAC
2.6.	Safety	AE1	Summary of All Serious Drug-Related Adverse Events by System Organ Class and Preferred Term	By treatment, includes treatment emergent AEs	DR, SAC
2.7.	Safety	AE1	Summary of All Non-Serious Drug-Related Adverse Events by System Organ Class and Preferred Term	By treatment, includes treatment emergent AEs	DR, SAC
2.8.	Safety	AE15	Summary of Common (>=2%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT, by treatment group, includes treatment emergent AEs	DR, SAC
2.9.	Safety	AE5A	Summary of Common (>=2%) Drug Related Adverse Events by Maximum Intensity	ICH E3, by treatment group, includes treatment emergent AEs	DR, SAC
2.10.	Safety	AE5A	Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	ICH E3, by treatment, then summarized by pre-treatment, post-randomization, treatment emergent, and follow-up.	SAC
2.11.	Safety	AE1	Summary of AEs of Special Interest	By treatment	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serious and Other Significant Adverse Events					
2.12.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT, by treatment, then summarized by pre-treatment, post-randomization, treatment emergent, and follow-up.	DR, SAC
2.13.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL, by treatment	DR, SAC
Laboratory: Chemistry					
2.14.	Safety	PDT9	Summary of chemistry lab values	ICH E3 Includes: sodium, glucose, potassium, phosphate, calcium, ALT, AST, ALP, albumin, total protein, and total and indirect/direct bilirubin	DR, SAC
2.15.	Safety	LB1	Summary of change from baseline in chemistry lab values	ICH E3 Includes: sodium, glucose, potassium, phosphate, calcium, ALT, AST, ALP, albumin, total protein, and total and indirect/direct bilirubin	DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Hematology					
2.16.	Safety	PDT9	Summary of hematology lab values	ICH E3 Includes: platelets, WBC count, basophils, eosinophils, lymphocytes, monocytes, neutrophils, haematocrit, RDW, CHr, HGB, Mean Hemocue HGB, MCHC, RBC, Reticulocyte, MCH, MCV, neutrophils segmented Basophils/leukocytes (%), eosinophils/ leukocytes (%), lymphocytes/leukocytes (%), monocytes/ leukocytes (%), neutrophils/leukocytes (%), neutrophils segmented/ leukocytes (%)	DR, SAC
2.17.	Safety	LB1	Summary of change from baseline in hematology lab values	ICH E3 Includes: platelets, WBC count, basophils, eosinophils, lymphocytes, monocytes, neutrophils, haematocrit, RDW, CHr, HGB, Mean Hemocue HGB, MCHC, RBC, Reticulocyte, MCH, MCV, neutrophils segmented Basophils/leukocytes (%), eosinophils/ leukocytes (%), lymphocytes/leukocytes (%), monocytes/ leukocytes (%), neutrophils/leukocytes (%), neutrophils segmented/ leukocytes (%)	DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Other Screening Tests					
2.18.	Safety	PDT9	Summary of other screen test lab values	ICH E3 Includes: Serum hCG pregnancy test, Serum ferritin, Folate, Estradiol, Serum iron, Vitamin B12, FSH, Serum transferrin, UIBC, TSAT Display only screening visits, query DM if other parameters are found at screening	DR, SAC
2.19.	Safety	PDT9	Summary of other screen test lab values, log transformed	ICH E3 Includes: Log transformed Serum ferritin and Serum iron Display only screening visits	DR, SAC
ECG					
2.20.	Safety	EG2	Summary of ECG values	IDSL Includes: QTc, QTcB, QRS duration, and PR interval ECG mean heart rate, QT interval, QTcF	DR, SAC
2.21.	Safety	EG2	Summary of change from baseline in ECG values	IDSL Includes: QTc, QTcB, QRS duration, and PR interval ECG mean heart rate, QT interval, QTcF	DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Vital Signs					
2.22.	Safety	PDT9	Summary of vital signs values	ICH E3 Includes: temperature, heart rate, SBP, and DBP	DR, SAC
2.23.	Safety	VS1	Summary of change from baseline in vital signs	ICH E3 Includes: temperature, heart rate, SBP, and DBP	DR, SAC
Additional Safety Tables					
2.24.	Safety	AE5A	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	ICH E3, by treatment, then summarized by pre-treatment, post-randomization, treatment emergent, and follow-up.	SAC
2.25.	Safety	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline		SAC
2.26.	Safety	LB17	Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline		SAC
2.27.	Safety	VS7	Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline		SAC
2.28.	Safety	EG1	Summary of ECG Findings		SAC
2.29.	Safety	PAN1	Summary of COVID-19 Assessment		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.30.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time		SAC
2.31.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time by Region		SAC
2.32.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time by Age		SAC
2.33.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time by Gender		SAC
2.34.	Safety	PAN11	Summary of Exposure Adjusted Incidence Rate for Common (>=5%) Adverse Events		SAC

14.12.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.1.	PK	PK01	Summary of Daprodustat and Metabolite Plasma Concentrations (ng/mL) by Scheduled Time for Each Acute Challenge Day	Have column for analyte (daprodustat, M2, M3, M4, M5, M6, M13) N, mean, sd, 95% CI, median, min, max	DR, SAC
3.2.	PK	PK04	Summary of Daprodustat and Metabolite Plasma Pharmacokinetic Parameters for Each Acute Challenge Day	Paginate by analyte (daprodustat, M2, M3, M4, M5, M6, M13) N, mean, 95% CI, sd, median, min, max, geometric mean, 95% CI based on geometric mean, sd (ln), CV Include log transformed descriptive statistics	DR, SAC

14.12.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Individual Plots					
3.1.	PK	PK16A	Individual Plasma Daprodustat Concentration-Time Plots – by Subjects and Acute Challenge Day (Linear and Semi-Log)	1. x-axis should display actual relative time 2. Include line for LLQ with footnote defining LLQ value. 3. Include values below LLQ. 4. Can do both challenge days on one page by adding legends. Overlay of Day 1 and day 57	DR, SAC
3.2.	PK	PK16A	Individual Plasma GSK2391220 (M2) Concentration-Time Plots – by Subjects and Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.3.	PK	PK16A	Individual Plasma GSK2531403 (M3) Concentration-Time Plots – by Subjects and Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.4.	PK	PK16A	Individual Plasma GSK2487818 (M4) Concentration-Time Plots – by Subjects and Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.5.	PK	PK16A	Individual Plasma GSK2506102 (M5) Concentration-Time Plots – by Subjects and Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.6.	PK	PK16A	Individual Plasma GSK2531398 (M6) Concentration-Time Plots – by Subjects and Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.7.	PK	PK16A	Individual Plasma GSK2531401 (M13) Concentration-Time Plots – by Subjects and Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
Mean Plots					
3.8.	PK	PK17	Mean (± SD) Plasma daprodustat Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	1. Include bars for SD. 2. x-axis displays planned relative time. 3. Include line for LLQ with footnote defining LLQ value. 4. Can do both challenge days on one page by adding legends. Overlay of Day 1 and day 57	DR, SAC
3.9.	PK	PK17	Mean (± SD) Plasma GSK2391220 (M2) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.10.	PK	PK17	Mean (± SD) Plasma GSK2531403 (M3) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.11.	PK	PK17	Mean (± SD) Plasma GSK2487818 (M4) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.12.	PK	PK17	Mean (± SD) Plasma GSK2506102 (M5) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.13.	PK	PK17	Mean (± SD) Plasma GSK2531398 (M6) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.14.	PK	PK17	Mean (± SD) Plasma GSK2531401 (M13) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
Median Plots					
3.15.	PK	PK18	Median (range) Plasma daprodustat Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	1. Include bars for range. 2. x-axis displays planned relative time. 3. Include line for LLQ with footnote defining LLQ value. 4. Can do both challenge days on one page by adding legends. Overlay of Day 1 and day 57	DR, SAC
3.16.	PK	PK18	Median (range) Plasma GSK2391220 (M2) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.17.	PK	PK18	Median (range) Plasma GSK2531403 (M3) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.18.	PK	PK18	Median (range) Plasma GSK2487818 (M4) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.19.	PK	PK18	Median (range) Plasma GSK2506102 (M5) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.20.	PK	PK18	Median (range) Plasma GSK2531398 (M6) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC
3.21.	PK	PK18	Median (range) Plasma GSK2531401 (M13) Concentration-Time Plots (Linear and Semi-log) by Acute Challenge Day (Linear and Semi-Log)	Overlay of Day 1 and day 57	DR, SAC

14.12.8. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ABPM Summary Tables					
4.1.	ITT	PDT1	Summary of ABPM SBP by Treatment Group and Visit		DR, SAC
4.2.	ITT	PDT1	Summary of ABPM DBP by Treatment Group and Visit		DR, SAC
4.3.	ITT	PDT1	Summary of ABPM HR by Treatment Group and Visit		DR, SAC
4.4.	ITT	PDT1	Summary of ABPM MAP by Treatment Group and Visit		DR, SAC
Primary Endpoint					
4.5.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM SBP post-AC2	Primary ANCOVA model output	DR, SAC
Secondary Endpoints					
4.6.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM SBP post-AC1	Secondary ANCOVA model output	DR, SAC
4.7.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM DBP post-AC1	Secondary ANCOVA model output	DR, SAC
4.8.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM MAP post-AC1	Secondary ANCOVA model output	DR, SAC
4.9.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM HR post-AC1	Secondary ANCOVA model output	DR, SAC
4.10.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM DBP post-AC2	Secondary ANCOVA model output	DR, SAC
4.11.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM MAP post-AC2	Secondary ANCOVA model output	DR, SAC
4.12.	ITT	PDT3	Summary of Analysis of Average 6hr ABPM HR post-AC2	Secondary ANCOVA model output	DR, SAC
4.13.	ITT	PDT4	Summary of Analysis of AUEC SBP over 24hr post-AC1		DR, SAC
4.14.	ITT	PDT4	Summary of Analysis of AUEC DBP over 24hr post-AC1		DR, SAC
4.15.	ITT	PDT4	Summary of Analysis of AUEC MAP over 24hr post-AC1		DR, SAC
4.16.	ITT	PDT4	Summary of Analysis of AUEC HR over 24hr post-AC1		DR, SAC
4.17.	ITT	PDT4	Summary of Analysis of AUEC SBP over 24hr post-AC2		DR, SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.18.	ITT	PDT4	Summary of Analysis of AUEC DBP over 24hr post-AC2		DR, SAC
4.19.	ITT	PDT4	Summary of Analysis of AUEC MAP over 24hr post-AC2		DR, SAC
4.20.	ITT	PDT4	Summary of Analysis of AUEC HR over 24hr post-AC2		DR, SAC
4.21.	ITT	PDT5	Summary of change from pre-dose SBP	At each timepoint on day 1 and day 57 by treatment	DR, SAC
4.22.	ITT	PDT5	Summary of change from pre-dose DBP	At each timepoint on day 1 and day 57 by treatment	DR, SAC
4.23.	ITT	PDT5	Summary of change from pre-dose MAP	At each timepoint on day 1 and day 57 by treatment	DR, SAC
4.24.	ITT	PDT5	Summary of change from pre-dose HR	At each timepoint on day 1 and day 57 by treatment	DR, SAC
Exploratory Endpoints					
4.25.	ITT	PDT6	Summary of Change from Day 1 AUEC of 24hr SBP to Day 57 AUEC of 24hr SBP		DR, SAC
4.26.	ITT	PDT7	Summary of change from Day 1 pre-dose SBP to Day 57 pre-dose		DR, SAC
4.27.	ITT	PDT3	Summary of Analysis of change in SBP from pre-dose on Day 1 to Cmax of the study treatment on Day 1, as measured by ABPM		DR, SAC
4.28.	ITT	PDT3	Summary of Analysis of change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 1, as measured by ABPM		DR, SAC
4.29.	ITT	PDT3	Summary of Analysis of change in SBP from pre-dose on Day 57 to Cmax of the study treatment on Day 57, as measured by ABPM		DR, SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.30.	ITT	PDT3	Summary of Analysis of change in SBP from pre-dose on Day 1 to Cmax of erythropoietin on Day 1, as measured by ABPM		DR, SAC
4.31.	ITT	PDT3	Summary of Analysis of change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 1, as measured by ABPM		DR, SAC
4.32.	ITT	PDT3	Summary of Analysis of change in SBP from pre-dose on Day 57 to Cmax of erythropoietin on Day 57, as measured by ABPM		DR, SAC
Biomarker Concentration Table, Exploratory Endpoints					
4.33.	ITT	PK01	Summary of Biomarker Plasma Concentration-Time Data		DR, SAC
Biomarker Derived Parameters, Exploratory Endpoints					
4.34.	ITT	PK06	Summary of Derived Biomarker Plasma Parameters (Non-Transformed)	Parameters with units Include baseline adjusted AUC and CMAX	DR, SAC
4.35.	ITT	PK06	Summary of Derived Biomarker Plasma Parameters (Ln-Transformed)	Parameters with units Include baseline adjusted AUC and CMAX	DR, SAC
Sensitivity Analyses					
4.36.	PP	PDT3	Summary of Analysis of Average 6hr ABPM SBP post-AC2, Per Protocol	Use PP population if at least 10% of the ITT population is excluded from PP population	DR, SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.37.	ITT	PDT8	Summary of Analysis of Average 6hr ABPM SBP post-AC2, Imputed Data	Use imputed missing values for AC2 for early withdrawal subjects, calculate 6hr averages for those subjects who failed QC for any AC. For subjects who AC2 failed QC, 6hr average SBP will be calculated without imputation	DR, SAC
4.38.	ITT	PDT3	Summary of Analysis of Average 8hr ABPM SBP post-AC2		DR, SAC
4.39.	ITT	PDT3	Summary of Analysis of Average 12hr ABPM SBP post-AC2		DR, SAC
4.40.	ITT	PDT3	Summary of Analysis of Average 24hr ABPM SBP post-AC2		DR, SAC
4.41.	ITT	PDT4	Summary of Analysis of AUEC SBP over 24hr post-AC2, Imputed Data	• If more than 25% of subjects are excluded from the ABPM AUEC analysis then this sensitivity analysis will be performed for the AC2 SBP AUEC model • If during dry-run less than 25% of subjects are excluded, then table is not needed for dry-run	SAC
Additional PD tables					
4.42.	ITT	PDT10	Summary of Subjects who QC Pass Acute Challenges	Column by treatment, row by Day 1 and Day 57, where Day 57 includes repeat AC2	SAC

14.12.9. Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Secondary Endpoints					
4.1.	ITT	PDF1	Mean (95% CI) Hourly ABPM SBP over 24hr post-AC1	1. Include bars for 95% CI. 2. x-axis displays planned relative time. 3. Separate by treatment group	DR, SAC
4.2.	ITT	PDF1	Mean (95% CI) Hourly ABPM DBP over 24hr post-AC1	Same comments as Figure 4.1	DR, SAC
4.3.	ITT	PDF1	Mean (95% CI) Hourly ABPM MAP over 24hr post-AC1	Same comments as Figure 4.1	DR, SAC
4.4.	ITT	PDF1	Mean (95% CI) Hourly ABPM HR over 24hr post-AC1	Same comments as Figure 4.1	DR, SAC
4.5.	ITT	PDF1	Mean (95% CI) Hourly ABPM SBP over 24hr post-AC2	Same comments as Figure 4.1	DR, SAC
4.6.	ITT	PDF1	Mean (95% CI) Hourly ABPM DBP over 24hr post-AC2	Same comments as Figure 4.1	DR, SAC
4.7.	ITT	PDF1	Mean (95% CI) Hourly ABPM MAP over 24hr post-AC2	Same comments as Figure 4.1	DR, SAC
4.8.	ITT	PDF1	Mean (95% CI) Hourly ABPM HR over 24hr post-AC2	Same comments as Figure 4.1	DR, SAC
Exploratory Endpoints					
4.9.	ITT	PDF1	Mean (95% CI) Hourly ABPM SBP over 24hr post-AC2 post-AC1 comparison	Same comments as Figure 4.1 Overlay AC1 and AC2 on the same figure Page by treatment	DR, SAC
Individual Concentration Plots					
4.10.	ITT	PK16A	Individual Biomarker Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Paginate by analyte	DR, SAC

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Mean / Median Concentration Plots					
4.11.	ITT	PK17	Mean (± SD) Biomarker Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	1. Include bars for SD. 2. x-axis displays planned relative time. 3. Include line for LLQ with footnote defining LLQ value. 4. Paginate by analyte	DR, SAC
4.12.	ITT	PK18	Median (range) Biomarker Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)		DR, SAC

14.12.10. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Secondary Endpoints					
5.1	PK	PKPDF1	Scatterplot of Daprodustat AUC and BP AUEC	Page by visit (Day 1, Day 57) and by BP (SBP, DBP, MAP, and HR) For Daprodustat subjects only	SAC
5.2	PK	PKPDF1	Scatterplot of Daprodustat AUC and Biomarker AUEC	Page by visit (Day 1, Day 57) and by Biomarker (erythropoietin, endothelin-1, nitric oxide, asymmetric dimethylarginine, renin, angiotensin-II (and metabolites), and noradrenalin.) For Daprodustat subjects only	SAC

14.12.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	DR, SAC
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal	ICH E3	DR, SAC
3.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	DR, SAC
4.	ITT	TA1	Listing of Planned and Actual Treatments	IDSL	DR, SAC
Protocol Deviations					
5.	ITT	DV2	Listing of Important Protocol Deviations	ICH E3	DR, SAC
6.	ITT	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	DR, SAC
Populations Analysed					
7.	Screened	SP3	Listing of Participants Excluded from Any Population	ICH E3	DR, SAC
Demographic and Baseline Characteristics					
8.	ITT	DM2	Listing of Demographic Characteristics	ICH E3 Footnote: Age is imputed from year and month of birth	DR, SAC
9.	ITT	DM9	Listing of Race	ICH E3	DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
10.	ITT	CM10	Listing of Concomitant Medications	IDSL	DR, SAC
11.	ITT	CM6	Relationship between ATC Level 1, 2, 3, Ingredient and Verbatim Text	IDSL	DR, SAC
Exposure and Treatment Compliance					
12.	Safety	EX3	Listing of Exposure and Treatment Compliance Data	ICH E3, include % treatment compliance for each subject	DR, SAC
Adverse Events					
13.	Safety	AE8	Listing of All Adverse Events - Safety	ICH E3	DR, SAC
14.	Enrolled	AE8	Listing of All Adverse Events - Enrolled	ICH E3	DR, SAC
15.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	DR, SAC
16.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	DR, SAC
Serious and Other Significant Adverse Events					
17.	Safety	AE8	Listing of Fatal Serious Adverse Events	ICH E3	DR, SAC
18.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	DR, SAC
19.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	DR, SAC
20.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	DR, SAC
Hepatobiliary (Liver)					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
21.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	DR, SAC
22.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	DR, SAC
All Laboratory					
23.	Safety	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3 Include abnormal ranges	DR, SAC
24.	Safety	LB5	Listing of Laboratory Values of Potential Clinical Importance	Include abnormal ranges	DR, SAC
25.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	DR, SAC
ECG					
26.	Safety	EG3	Listing of All ECG Values for Participants	IDSL	DR, SAC
27.	Safety	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	DR, SAC
28.	Safety	EG5	Listing of Abnormal ECG Findings	IDSL	DR, SAC
Vital Signs					
29.	Safety	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	DR, SAC
30.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	DR, SAC

14.12.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
31.	ITT	MH2	Listing of Medical Conditions		DR, SAC
32.	PK	PK07	Listing of Daprodustat and Metabolites Plasma Pharmacokinetic Concentration-Time Data	Please list all the concentration data including unscheduled Have column for analyte (daprodustat, M2, M3, M4, M5, M6, M13)	DR, SAC
33.	PK	PK07	Listing of Derived Daprodustat and Metabolites Plasma Pharmacokinetic Parameters	Parameters with units Have column for analyte (daprodustat, M2, M3, M4, M5, M6, M13)	DR, SAC
Pharmacodynamic and Biomarkers					
34.	ITT	PDL1	Listing of ABPM data		DR, SAC
35.	ITT	PK07	Listing of Biomarker data		DR, SAC

14.13. Appendix 13: Example Mock Shells for Data Displays

Example mock shells for data displays are developed as separate documents.

Signature Page for 205665 TMF-1832793 v1.0

Reason for signing: Approved	Name: PPD Role: Author Date of signature: 23-Jul-2020 16:25:49 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 29-Jul-2020 18:16:21 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 29-Jul-2020 18:22:03 GMT+0000

Reason for signing: Approved	Name: PPD Role: Author Date of signature: 29-Jul-2020 18:26:13 GMT+0000

Signature Page for TMF-1832793 v1.0