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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for a randomized, repeat dose, open label, parallel group, multi-center study to evaluate the effect of daprodustat compared to darbepoetin alfa on forearm blood flow in participants with anemia of chronic kidney disease that are not dialysis dependent
Compound Number	:	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 GlaxoSmithKline Document Number 2016N291495_02.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol GlaxoSmithKline Document Number 2016N291495_02.

Revision Chronology:		
Protocol number:	Date:	Version:
2016N291495_00	17/Nov/2017	Original Protocol
2016N291495_01	28/Jan/2018	Protocol Amendment 1
This protocol amendment was written as the study team was required per regulatory agencies to change the protocol to include serum pregnancy testing at screening. During the amendment process, minor updates were made for study optimization.		
2016N291495_02	07/Aug/2019	Protocol Amendment 2
This protocol amendment was written becase a challenge agent suddenly became commercially unavailable with no immediate ability to reobtain this. The study has been modified to allow flexibility for the forearm blood flow testing to be performed with this agent if it becomes available again, and to be performed without it if not. During this time the safety language was updated as well.		

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**
• 10.1.2 Sample Size Re-estimation	• Sample size re-estimation will not be performed	• The study was terminated
• 10.3.3 Other Analyses (Pharmacodynamic)	• No statistical analyses will be performed; only summary statistics will be reported. We will not perform exploratory analyses and sensitivity analysis.	• Since the study was terminated and we have only 4 completed subjects to report. Therefore, statistical analysis will not be performed.

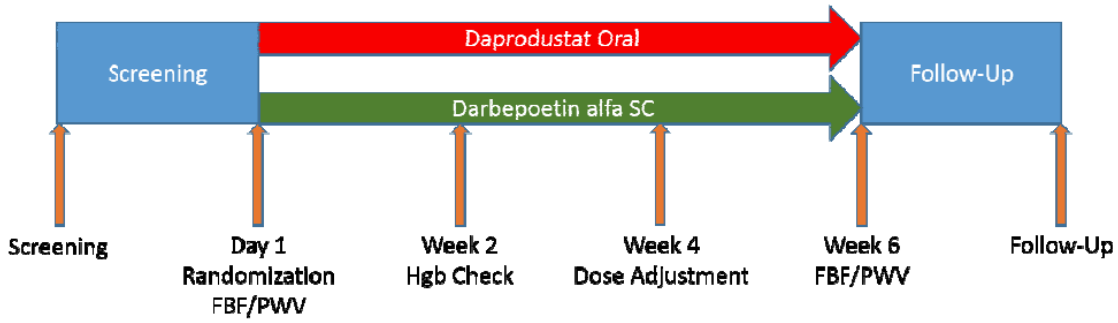
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• 10.3.4 Interim Analyses	• Interim analyses will not be performed	• The study was terminated
• Enrolled population is not defined in the protocol	• Enrolled population added in the RAP with the below definition. "All Randomized Participants"	• This population is required for data disclosure displays
• 10.2. Pharmacodynamic Per-Protocol (PDPP) Population: "All randomized participants who provide pharmacodynamic (PD) data at Day 1 and Day 42 that meets the QC criteria (See Section 9.6.1.3 of Protocol) and completes the protocol without important deviations will be included in the PDPP population. This population will be used in the evaluation of all endpoints with the exception of safety endpoints."	• PDPP definition updated with adding RAP section number of exclusions of per proptocol population. "All randomized participants who provide pharmacodynamic (PD) data at Day 1 and Day 42 that meets the QC criteria (See Section 9.6.1.3 of Protocol) and completes the protocol without important deviations **(exclusions are populated under Section 10.1.1 of RAP)** will be included in the PDPP population. This population will be used in the evaluation of all endpoints with the exception of safety endpoints."	• To exclude all participants based on the Protocol Deviation Management Plan (PDMP) definitions, as not all important deviations are criticial for analysis population exclusion. In efforts to maximize the number of participants in the analysis, only the important deviations **(exclusions are populated under Section 10.1.1 of RAP)** will be considered exclusionary for the analysis.
• Non-Contact, Optical Forearm Plethysmography (NC-OFP) Sub-Study	• Sub-study will not be performed	• The study was terminated, and no subjects recruited for sub-study

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

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To compare the effect of daprodustat to darbepoetin alfa on endothelial function	- Change in FBF ratio from Day 1 to Day 42 in response to acetylcholine
Principle Secondary	**Principle Secondary Endpoint**
To further compare the effect of daprodustat to darbepoetin alfa on endothelial function	- Change in the absolute FBF from Day 1 to Day 42 in response to acetylcholine
Secondary Objectives	**Secondary Endpoints**
To compare the effect of daprodustat to darbepoetin alfa on endothelium-independent vasodilation	- Change in FBF ratio from Day 1 to 42 in response to sodium nitroprusside (SNP)

Objectives	Endpoints
	- Change in the absolute FBF from Day 1 to Day 42 in response to SNP
To compare the effect of daprodustat to darbepoetin alfa on basal endothelial NO synthesis	- Change in FBF ratio from Day 1 to Day 42 in response to L-N^G-monomethyl arginine citrate (L-NMMA) - Change in the absolute FBF from Day 1 to Day 42 in response to L-NMMA
To compare the effect of daprodustat on the FBF response to acetylcholine, SNP and L-NMMA between Day 42 and Day 1	- Change in FBF ratio in response to each individual challenge agent at Day 42 vs Day 1 in participants treated with daprodustat - Change in the absolute FBF in response to each individual challenge agent at Day 42 vs Day 1 in participants treated with daprodustat
To compare the effect of darbepoetin alfa on the FBF response to acetylcholine, SNP and L-NMMA between Day 42 and Day 1	- Change in FBF ratio in response to each individual challenge agent at Day 42 vs Day 1 in participants treated with darbepoetin alfa - Change in the absolute FBF in response to each individual challenge agent at Day 42 vs Day 1 in participants treated with darbepoetin alfa
To compare the effect of daprodustat to darbepoetin alfa on vascular compliance	- Change in Augmentation Index (an indicator of arterial stiffness) as estimated by radial arterial pulse contours from Day 1 to 42 - Change in pulse wave velocity (PWV) from Day 1 to Day 42
Safety	**Safety Endpoints**
Assess safety and tolerability	- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest - Reasons for discontinuation of randomized study treatment - Absolute values and changes from baseline in clinical laboratory parameters, ECG parameters, blood pressure (BP) and heart rate (HR)
Exploratory Objective	**Exploratory Endpoint**
To explore the relationship between diabetes status and endothelial function	- FBF response to each individual challenge agent in relation to diabetes status

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This study will use a randomized, repeat dose, open label, parallel group design, in adult, ND, male and female participants with anemia of CKD that are currently not treated with rhEPOs (i.e. no rhEPO use within the 12 weeks prior to the screening visit and through Day 1). • The study will comprise three study periods: a screening period starting up to 30 days prior to Day 1, a Day 42 (6 week) treatment period with 4 visits starting at Day 1, and a follow-up visit up to 14 days later. The total duration of participant involvement is up to 14 weeks. • Participants will be randomized to either daprodustat or darbepoetin alfa. A central randomization approach will be used with stratification by center. • All participants will be treated with the goal of achieving a Hgb level within the range of 10.0 to 12.0 g/dL, consistent with national guidelines (Medicines and Healthcare Products Regulatory Agency, 2007). • FBF and PWV will be conducted at the beginning (Day 1) and end (Day 42) of the treatment period.
Number of Participants	• As defined in the protocol a sufficient number of participants will be enrolled such that at least 50 evaluable participants comprise the Pharmacodynamic Per-Protocol (PDPP) Population. Since, the study was terminated the number of evaluable participants is not applicable here.
Dosing	• The dose of darbepoetin and daprodustat is administered using a dosing steps algorithm which is based on the HemoCue Hgb value to ensure consistency of treatment across the study. The doses of each treatment including starting dose and criteria for dose adjustments are detailed in the protocol (Section 7, protocol).
Time & Events	• [Refer to Appendix 2: Schedule of Activities]
Treatment Assignment	• Study treatments (darbepoetin and daprodustat) are randomized to participants using a pre-planned randomization schedule stratified by center

2.4. Statistical Hypotheses

The primary endpoint is to compare the effect of daprodustat to darbepoetin alfa on change in FBF ratio from Day 1 to Day 42 in response to acetylcholine. The estimand of interest is the effect of 6 weeks of randomized treatment on the primary endpoint.

Null: The difference between daprodustat and darbepoetin alfa on the acetylcholine-induced change (from Day 1) in FBF ratio at Day 42 is 0.

Alternative: The difference between daprodustat and darbepoetin alfa on the acetylcholine-induced change (from Day 1) in FBF ratio at Day 42 is not 0.

3. PLANNED ANALYSES

3.1. Interim Analyses

The study was terminated, hence no interim analysis will be performed.

3.2. Final Analyses

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

1. All participants have completed the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who signed an ICF to participate in the clinical trial. This population will be used for summarizing screening failure rates and reasons for screening failure.	• Screen Failures
Safety	• All randomized participants who receive at least one dose of study treatment will be included in the safety population. • This population will be used in the evaluation of all safety analyses • Particpants will be analyzed according to the treatment received.[1]	• Study population • Safety and tolerability
Pharmacodynamic Per-Protocol (PDPP) Population	• All randomized participants who provide pharmacodynamic (PD) data at Day 1 and Day 42 that meets the QC criteria (See Section 9.6.1.3 of Protocol) and completes the protocol without important deviations (exclusion are populated under	• Primary, secondary endpoints

Population	Definition / Criteria	Analyses Evaluated
	Section 10.1.1 of RAP) will be included in the PDPP population. • This population will be used in the evaluation of all endpoints with the exception of safety endpoints. • Participants will be analyzed according to the treatment received.[1]	
Enrolled	• All randomized participants	• Study population

[1]: Only participants receiving incorrect randomized treatment for the duration of their study participation will be analysed according to the treatment received. Otherwise, participants will be analyzed according to the treatment to which they were randomized.

Refer to Appendix 10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [28Aug2018 V2.0].

- Data will be reviewed prior to unblinding and 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 listing of all inclusion/exclusion criteria deviations will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG System		**Data Displays for Reporting**	
Code	**Description**	**Description**	**Order in TLF**
A	Darbepoetin alfa	rhEPO	2
B	Daprodustat	Dapro	1

5.2. Baseline Definitions

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

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Primary Endpoint				
FBF ratio			X	Day 1/Repeat Day 1[1]
Secondary Endpoints				
FBF ratio			X	Day 1/Repeat Day 1[1]
Absolute FBF			X	Day 1/Repeat Day 1[1]
Augmentation index			X	Day 1/Repeat Day 1[1]
PWV			X	Day 1/Repeat Day 1[1]
Clinical laboratory parameters, ECG parameters, blood pressure (BP) and heart rate (HR)	X		X	Screening/Day 1

[1]Repeat Day 1 values are only used if a repeat visit was deemed necessary

Unless otherwise stated, if baseline data is missing, no derivation will be performed, and baseline will be set to missing. If a Repeat Day 1 visit is required, then this value will be used as the baseline measurement instead.

5.3. Multicentre Studies

Participants will be recruited from 3 centers and will be randomised stratifying by centre. Enrolment will be presented by investigative site.

5.4. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data
10.8	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 Screened/Enrolled/Safety population, unless otherwise specified. The study population analyses will include a total column, unless otherwise specified.

Study population analyses including analyses of subject'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 10 List of Data Displays.

6.2. Display Details

6.2.1. Study Disposition

Participant Status and Reason for Study Withdrawal

The number and percentage of subjects who completed the study as well as participants who withdrew from the study will be summarized by participant status and reason for withdrawal. Also, a summary of number of subjects by country and site id by treatment group and overall total.

A listing of reasons for study withdrawal will be provided for all participants who were withdrawn from the study.

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 rescreened 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).

6.2.2. Protocol Deviations

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.

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. Demographic and Baseline Characteristics

Demographic Characteristics

Demographic data will be summarized by treatment group and overall.

A 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 for each treatment group and overall total.

Race and Racial Combinations

A summary of race and racial combinations will be produced for each treatment group and overall total.

6.2.4. Medical Conditions, Prior and Concomitant Medications

Medical Conditions

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

A listing of all medications taken by participants, including any of which are pre, on and 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.

6.2.5. Exposure

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

7. SAFETY ANALYSES

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

Objectives	Endpoints
Safety	
• Assess safety and tolerability	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest • Reasons for discontinuation of randomized study treatment • Absolute values and changes from baseline in clinical laboratory parameters, ECG parameters, blood pressure (BP) and heart rate (HR)

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs) and Serious (SAEs) will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

Adverse Events

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

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: 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
	Reticulocyte count	MCH	Lymphocytes
	Hgb	MCHC	Monocytes
	Hematocrit	RDW	Eosinophils
	WBC count (Absolute)		Basophils
Clinical Chemistry[1]	Sodium (serum)	AST[1]	Carbon Dioxide (total)
	Potassium (serum)	ALT[1]	Albumin
	Creatinine (serum)	Chloride (serum)	Urea (serum)
	Glucose	Bilirubin (total and direct/indirect)	Alkaline Phosphatase
Other laboratory tests	Serum ferritin	TSAT	hs-CRP
	Total cholesterol	LDL-C (direct)	HDL-C
	Triglycerides	Serum/Urine hCG pregnancy test[2]	FSH[3]
	HbA1c	Folate	Vitamin B_{12}
	Serology (hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)		

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

8. PHARMACODYNAMIC ANALYSES

8.1. Primary Pharmacodynamic Analyses

8.1.1. Endpoint / Variables

The endpoint of interest is FBF ratio.

FBF ratio is calculated as the FBF of the subject's treatment arm divided by the subject's non-treatment arm. The treatment arm is given either saline or the challenge agent. The non-treatment arm is given nothing.

The FBF measurement is calculated from the average of 5 values as recorded on the LabChart file. The 5 values of FBF are recorded manually from a blinded central reader reviewing the subject's FBF LabChart file.

8.1.2. Summary Measure

The summary measure of interest is the change in FBF ratio from Day 1 to Day 42 in response to acetylcholine.

If FBF procedure is repeated for Day 1 and/or Day 42, this data will take the place of the original Day 1 and Day 42 data respectively. A quality control (QC) check will be performed on the FBF data before the final analyses. The QC check will be to assess negative and extreme values for FBF (FBF).

Descriptive statistics (n, arithmetic mean, standard deviation (SD), minimum, median, maximum) will be calculated by treatment group for change in FBF ratio endpoints.

8.1.3. Population of Interest

The primary pharmacodynamics analyses will be based on the PDPP population, unless otherwise specified.

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

Due to the design of the PDPP population, only subjects who have FBF measurements for both Day 1 and Day 42 are included, and it is not possible to have missing FBF data. Therefore, no FBF data will be imputed.

8.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1.1 will be summarised using descriptive statistics and listed.

8.2. Secondary Pharmacodynamic Analyses

8.2.1. Endpoint / Variables

- Principle secondary endpoint: change in the absolute FBF
- Secondary endpoints:
    - FBF ratio, absolute FBF of Sodium nitroprusside and L-NMMA
    - Augmentation index
    - PWV

Absolute FBF is defined as only including the FBF value from the subject's treatment arm which is infused with either saline or challenge agents.

8.2.2. Summary Measure

Principle secondary endpoint: Change in the absolute FBF from Day 1 to Day 42 in response to acetylcholine

Secondary endpoints: Change in FBF ratio from Day 1 to Day 42 in response to sodium nitroprusside and L-NMMA.

Change in absolute FBF from Day 1 to Day 42 in response to sodium nitroprusside and L-NMMA.

Change in Augmentation Index (AIX, an indicator of arterial stiffness) as estimated by radial arterial pulse contours from Day 1 to Day 42.

Change in pulse wave velocity (PWV) from Day 1 to Day 42.

For the PWV dataset, there are two recorded values for each variable per day, with the option to collect a third value if the first two values varied (Refer: SRM) too much from each other. The average of the two closest absolute values will be used for analysis purposes.

If for any of these measures mentioned above, the respective procedures are repeated for Day 1 and/or Day 42, the data from the repeat visit will take place of the original Day 1 and Day 42 data respectively. Like the FBF data, a QC check will be performed for the PWV data before the final analyses. The QC check will be to assess negative and extreme values for PWV (PWV).

Descriptive statistics (n, mean, standard deviation (SD), minimum, median, maximum) will be calculated by treatment group.

8.2.3. Population of Interest

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

8.2.4. Strategy for Intercurrent (Post-Randomization) Events

Augmentation index and PWV data is expected to have minimal missing data, therefore these data points will not be imputed if missing.

8.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10 List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.2.1 will be summarised using descriptive statistics and listed.

9. REFERENCES

- GlaxoSmithKline Document Number 2016N291495_02. A randomized, repeat dose, open label, parallel group, multi-center study to evaluate the effect of daprodustat compared to darbepoetin alfa on forearm blood flow in participants with anemia of chronic kidney disease that are not dialysis dependent; 07-Aug-2019.

- GUI_137354: Information for Authors – Reporting and Analysis Plan, Global; GSK.

- 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.

- Medicines and Healthcare Products Regulatory Agency. Recombinant human erythropoietins: New advice for prescribing. Drug Safety Update. 2007; 1:2.

- SOP_54838: Development, Review & Approval of Reporting & Analysis Plan, Global; GSK.

10. APPENDICES

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

10.1.1. Exclusions from Per Protocol Population

There is no important protocol deviation identified in the study, hence no exclusions for per protocol population.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Activities

Procedure	Screening[1]	Treatment Period[2]						Follow-up[3]
	Up to 30 Days	Day 1	Repeat Day 1[17]	Day 14	Day 28	Day 42	Repeat Day 42[17]	
Informed consent	X							
Eligibility Criteria	X	X[4]						
Physical examinations, Medical History, Demographics	X	X[5]						
HemoCue Hgb	X	X[6]	X	X	X	X	X	
eGFR	X							
Vital signs	X	X[6]	X	X	X	X	X	X
Clinical chemistry[7]	X					X		X
Hematology[7]	X	X		X	X	X		X
Serum pregnancy test (FRP only)	X							
Urine pregnancy test (FRP only)[8]		X	X	X	X	X	X	X
Folate & Vitamin B_{12}	X							
12 Lead ECG	X	X[6]				X		X
Ferritin & TSAT	X							
hs-CRP	X	X				X		
Females only: FSH[9]	X							
5Brachial artery palpation	X							
Randomization		X						
Daprodustat administration[10]		<==========						
Darbepoetin alfa administration[10]		X[10]		X	X	See footnote 18		

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Procedure	Screening[1]	Treatment Period[2]						Follow-up[3]
	Up to 30 Days	Day 1	Repeat Day 1[17]	Day 14	Day 28	Day 42	Repeat Day 42[17]	
Study treatment adjustment[11]					X			
Liver chemistry monitoring				X	X			
International Normalized Ratio (INR)[12]	X	X	X			X	X	
Hepatitis B and C screening[13]	X							
HbA1c, lipids[7]		X						
Forearm Blood Flow (FBF)[14]		X	X			X	X	
Pulse Wave Velocity (PWV)[14]		X	X			X	X	
AE and SAE Assessment	X[15]	X	X	X	X	X	X	X
Blood draw for storage biomarkers[16]		X				X		
Review concomitant medications	X	X	X	X	X	X	X	X

[1] All participants will undergo screening assessments within 30 days of enrolment.

[2] Allowable time window ± 2 days except for the forearm blood flow (FBF) & pulse wave velocity (PWV) as noted.

[3] Allowable time window ± 3 days. Follow up will occur 7-14 days ± 3 following completion of the last FBF procedure. See Section 8.2 for guidance regarding EW participants.

[4] Eligibility criteria to be assessed prior to performance of the FBF procedure include HemoCue hemoglobin (Hgb), vital signs & 12-lead electrocardiogram (ECG).

[5] Only a brief physical exam on Day 1.

[6] As detailed in Exclusion Criteria (Section 6.2).

[7] Clinical chemistry, hematology and other laboratory tests as listed in Appendix 2.

[8] Local urine pregnancy testing will be standard for protocol unless serum testing is required by local regulations or Institutional Review Board (IRB)/ Independent Ethics Committee (IEC).

[9] As detailed in Inclusion Criteria (Section 6.1).

[10] The initial dose of study treatment will be **after** the Day 1/Repeat Day 1 FBF & PWV procedures. Participants will receive **EITHER** daprodustat **OR** darbepoetin alfa. The final dose of daprodustat will be Day 41 (i.e., the day prior to the FBF & PWV procedures), while the final dose of darbepoetin alfa will be Day 28. If repeat procedures are needed the dosing will be extended (See Section 9.6.1.4).

[11] See Section 7.2 for details on study treatment adjustment

[12] Applies only to participants on anti-coagulant therapy; further details concerning measurement of the international normalised ratio (INR) and subsequent actions can be found in the study reference manual (SRM).

[13] If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required

[14] The FBF & PWV assessments are to be performed following confirmation of INR < 3.0 for participants on anticoagulant therapy. The Day 42 FBF & PWV assessments can be delayed up to 1 week (i.e., Day 49)., while randomization (Day 1) should be delayed until the participant's INR < 3.0 (Section 9.6.1.1).

[15] Only serious adverse events (SAEs) assessed as related to study participation are collected at this visit. See Appendix 4 for additional details.

[16] As described in Section 9.8

[17] Indicates the procedures to be performed on the repeat visits only if the visit is deemed necessary. See Section 9.6.1.4.

[18] Darbepoetin is only to be given on Day 42 if a Repeat Day 42 is needed.

10.3. Appendix 3: Assessment Windows

10.3.1. 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.

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

10.4.1. Study Phases

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

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date + 1 day
Post-Treatment	Date > Study Treatment Stop Date + 1 day

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

10.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date + 1 day • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 day.

NOTES:

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

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The SAS Version 9.4 or above will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: arenv/arprod/ GSK1278863/mid205767/final_01
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	

10.5.2. 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 and/or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	
Note	
• All displays (TFL) will use the term 'Subjects' (i.e. reflect GSK Display Standards and CDISC SDTM/ADaM standards)	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. 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 for time points other than the baseline within a time window (as per Section 10.3.1), 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.
Study Day

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

Screening and Washout visits
• Rescreened subject's data will only be counted once, the latest visit will only be summarized.

10.6.2. Study Population

Demographics
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]2
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: The study duration will be assigned based on exposure date and by default will assign as 1 day for each date (if there is any repetation in the date we will consider only one record). Since there is no exposure end date collected for the study, we will be assigning by default value as 1 day. However, we are checking duplication in the bakend. • 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: Sum of each record in incremental order on all previous records and current record value get added as cumulative. • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

10.6.3. Safety

Laboratory Parameters

• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of 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

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' 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 and MCHC: Divide the g/L value by 10 to get the g/dL value.
  • TSAT: If unit is not percentage then multiply with 100 to get the % 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 • Folate and Vitamin B9 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.
• Scheduled central laboratory HGB values and HemoCue HGB value will be used for report. Conversion values (g/L value g/dL) also will be reported.
PCI Criteria Categories
• 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.

10.6.4. Pharmacodynamic

Primary/Principle Secondary/Secondary/Exploratory Endpoints
FBF Ratio/Absolute FBF
• If either a Day 1 Repeat or Day 42 Repeat measurement is available for forearm blood flow, the repeat value will be used instead. • Forearm blood flow for a given challenge agent dose (infused arm), or for values from the non-infused arm, will be the mean of 5 continuous time point values. • Forearm blood flow ratio is defined as the ratio of a subject's treatment (infused) arm value divided by the non-treatment (non-infused) arm value   ○ First, the mean of both the infused and non-infused arm will be taken separately for the given five measurements before going into the ratio calculation. An example of this is shown in the table below:

Primary/Principle Secondary/Secondary/Exploratory Endpoints

	Infused	Non-Infused	
Measurement 1	1.2	1.01	
Measurement 2	1.1	1	
Measurement 3	1.4	1.2	
Measurement 4	1.5	1.1	
Measurement 5	1.6	1.3	FBF Ratio
Average	**1.36**	**1.122**	**1.212121212**

- Absolute forearm blood flow is defined as the infused arm value.

Secondary Endpoint

PWV Dataset

For the PWV dataset, there are two recorded values for each variable per day, with the option to collect a third value if the first two values varied (Refer: SRM) too much from each other. The average of the two closest absolute values will be used for analysis purposes.

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. 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 last visit or the last scheduled procedure • Withdrawn subjects were not replaced in the study. • 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.

10.7.2. 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 subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of 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. ○ Missing Start Month: 'January' will be used unless this makes the start date before the month of start of study treatment; in this case the month of study treatment start will be used. ○ Missing Stop Month: 'December' will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.

Element	Reporting Detail
	• 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: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Hematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hemoglobin	g/dL		< 8 g/dL	> 13 g/dL
Platelet Count	GI/L or $x10^9$/ L		< 80 GI/L	> 500 GI/L
WBC Count	GI/L or $x10^9$/ L		< LLRR	> 5x ULRR
Neutrophils	GI/L or $x10^9$/ L		< 0.5 GI/L	
Lymphocytes	GI/L or $x10^9$/ L		< 0.5x LLRR	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		< 30 g/L	> 55 g/L
AST (SGOT)	U/L			>= 3x ULRR
ALT (SGPT)	U/L			>= 3x ULRR
Total billirubin	Umol/L			>= 2x ULRR
Potassium	mmol/L		> 0.5 mmol/L below LLRR	> 1.0 mmol/L above ULRR
Sodium (serum)	mmol/L		< 130 mmol/L	> 150 mmol/L

Iron Parameters				
Test Analyte	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Serum ferritin	ug/l		< 100 ug/l	> 800 ug/l
TSAT	Percent		<15%	> 40%

10.8.2. 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
Heart Rate	bpm	<= 40 bpm	>= 110 bpm

Note:
At visits where BP and HR are assessed in triplicate, the average of the 3 values will be used to assess PCI criteria.

10.8.3. FBF

Agent	Units	Clinical Concern Range			
		FBF Infused Arm		FBF Non-Infused Arm	
		Lower	Upper	Lower	Upper
Saline	mL/min	0.01	15.0	0.01	15.0
ACH	µg/min	0.01	150.0	0.01	30.0
SNP	µg/min	0.01	150.0	0.01	30.0
LNMMA	µmol/min	0.01	15.0	0.01	15.0

10.8.4. PWV

PWV Parameter	Units	Clinical Concern Range	
		Lower	Upper
Average Systolic BP (Seated & Supine)	mmHg	<= 80 mmHg	>= 160 mmHg
Average Diastolic BP (Seated & Supine)	mmHg	<= 50 mmHg	>= 100 mmHg
Central Systolic Pressure	mmHg	<= 80 mmHg	>= 160 mmHg
Central Diastolic Pressure	mmHg	<= 50 mmHg	>= 100 mmHg
Mean Arterial Pressure	mmHg	<= 40 mmHg	>= 200 mmHg
Central Pulse Pressure	mmHg	<= 10 mmHg	>= 200 mmHg
Peripheral Pulse Pressure	mmHg	<= 10 mmHg	>= 200 mmHg
Central Augmentation Pressure	mmHg	<= -50 mmHg	>= 100 mmHg
Central Augmentation Index	%	-30	60
Heart Rate	bpm	<= 40 bpm	>= 110 bpm
Aortic Tr	msec	<=0 msec	>=1000 msec
Carotid to Femoral Distance	mm	<= 200 mm	>= 1500 mm
Pulse Wave Velocity	msec	<= 2 msec	>= 35 msec
Notch to Carotid Distance	mm	<= 10 mm	>= 200 mm
Notch to Femoral Distance	mm	<= 200 mm	>= 1500 mm

10.9. Appendix 9: Abbreviations & Trademarks

10.9.1. Abbreviations

Abbreviation	Description
ACH	Acetylcholine,
ADaM	Analysis Data Model
AE	Adverse Event
AIX	Augmentation Index
BP	Blood Pressure
CDISC	Clinical Data Interchange Standards Consortium
CKD	Chronic Kidney Disease
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FBF	Forearm Blood Flow
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FPD	Future Pipeline Discovery
GSK	GlaxoSmithKline
HR	Heart Rate
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
L-NMMA	L-N^G-monomethyl arginine citrate
PCI	Potential Clinical Importance
PCPS	Projects, Clinical Platforms, and Sciences
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PDPP	Pharmacodynamic Per Protocol
PP	Per Protocol
PWV	Pulse Wave Velocity
QC	Quality Control
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
rhEPO	Recombinant Human Erythropoietin
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SNP	Sodium Nitroprusside
SOP	Standard Operation Procedure
SRM	Study Reference Manual
TFL	Tables, Figures & Listings

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables
Study Population	1.1 to 1.6
Safety	2.1 to 2.9
Pharmacodynamic	3.1 to 3.10
Section	**Listings**
ICH Listings	1 to 16
Other Listings	17 to 20

10.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Table	Listing
Safety	SAFE1	-
Pharmacodynamic	PD_T1 to PD_T5	PD_L1 to PD_L2

NOTES:

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

10.10.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

10.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Summary of Subject Status and Subject Disposition for the Study Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.3.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
Demographic and Baseline Characteristics					
1.4.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.5.	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
1.6.	Safety	DM6	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC

10.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Chemistry					
2.1.	Safety	SAFE1	Summary of Chemistry lab values	ICH E3	SAC
2.2.	Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC
Laboratory: Hematology					
2.3.	Safety	SAFE1	Summary of Hematology Values	ICH E3	SAC
2.4.	Safety	LB1	Summary of Hematology Changes from Baseline	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Other Screening Tests					
2.5.	Safety	SAFE1	Summary of other screen test lab values	ICH E3	SAC
ECG					
2.6.	Safety	SAFE1	Summary of ECG Values	IDSL	SAC
2.7.	Safety	EG2	Summary of Change from Baseline in ECG Values	IDSL	SAC
Vital Signs					
2.8.	Safety	SAFE1	Summary of Vital Signs	ICH E3	SAC
2.9.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC

10.10.6. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Endpoint					
3.1.	PDPP	PD_T1	Summary of Forearm Blood Flow Ratio in Response to Acetylcholine		SAC
3.2.	PDPP	PD_T2	Summary of Change in Forearm Blood Flow Ratio (Day 1 to Day 42), Acetylcholine		SAC
Principle Secondary Endpoint					
3.3.	PDPP	PD_T3	Summary of Change in Absolute Forearm Blood Flow (Day 1 to Day 42), Acetylcholine		SAC

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Endpoints					
3.4.	PDPP	PD_T2	Summmary of Change in Forearm Blood Flow Ratio (Day 1 to Day 42), Sodium Nitroprusside		SAC
3.5.	PDPP	PD_T3	Summary of Change in Absolute Forearm Blood Flow (Day 1 to Day 42), Sodium Nitroprusside		SAC
3.6.	PDPP	PD_T2	Summary of Change in Forearm Blood Flow Ratio (Day 1 to Day 42), L-NMMA		SAC
3.7.	PDPP	PD_T3	Summary of Change in Absolute Forearm Blood Flow (Day 1 to Day 42), L-NMMA		SAC
3.8.	PDPP	PD_T4	Summary of Augmentation Index and Pulse Wave Velocity		SAC
3.9.	PDPP	PD_T5	Summary of Change in Augmentation Index (Day 1 to Day 42)		SAC
3.10.	PDPP	PD_T5	Summary of Change in Pulse Wave Velocity (Day 1 to Day 42)		SAC

10.10.7. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Protocol Deviations					
4.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
5.	Safety	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Demographic Characteristics					
6.	Safety	DM2	Listing of Demographic Characteristics	ICH E3	SAC
Prior and Concomitant Medications					
7.	Safety	CM10	Listing of Concomitant Medications	IDSL	SAC
8.	Safety	MH2	Listing of Medical Conditions	IDSL	SAC
Exposure					
9.	Safety	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
10.	Safety	AE8	Listing of All Adverse Events	ICH E3	SAC
Serious Adverse Events					
11.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
12.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
All Laboratory					
13.	Safety	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance/Outside Normal Range	ICH E3	SAC
14.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
15.	Safety	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
Vital Signs					
16.	Safety	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC

10.10.8. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Endpoint					
17.	PDPP	PD_L1	Listing of Forearm Blood Flow		SAC
18.	PDPP	PD_L2	Listing of All Forearm Blood Flow Data for Participants with Any Value of Potential Clinical Importance		SAC
Secondary Endpoint					
19.	PDPP	PD_L3	Listing of Pulse Wave Velocity and Augmentation Index		SAC
20.	PDPP	PD_L4	Listing of All Pulse Wave Velocity and Augmentation Index Data for Participants with Any Value of Potential Clinical Importance		SAC

10.11. Appendix 11: Example Mock Shells for Data Displays

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Example: SAFE1 Page 1 of n
Protocol: 205767
Population: Safety

Table 2.1
Summary of Lab Values

Parameter	Treatment	N	Visit	n	Mean	SD	Min	P25	Median	P75	Max
HGB (g/dL)	Dapro	xxxx	Screening [1]	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 1	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Repeat Day 1	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 14	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 28	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 42	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Repeat Day 42	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Follow-up	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
	rhEPO	xxxx	Screening [1]	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 1	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Repeat Day 1	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 14	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 28	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Day 42	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Repeat Day 42	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx
			Follow-up	Xxxx	xx.x	xx.xx	Xx	xx.x	xx.x	xx.x	Xx

[1] Screening is an average of all screening values.

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Example: PD_T1 Page 1 of n
Protocol: 205767
Population: PDPP

Table 3.1
Summary of Forearm Blood Flow Ratio in Response to Acetylcholine

Treatment: Daprodustat		FBF Control Arm		FBF Infused Arm		Ratio [1]
Challenge Agent		Day 1	Day 42	Day 1	Day 42	
Saline	n	3	3	3	3	3
	Mean	1.75	1.75	1.75	1.75	1.75
	SD	0.834	0.834	0.834	0.834	0.834
	Median	1.65	1.65	1.65	1.65	1.65
	Min.	1.0	1.0	1.0	1.0	1.0
	Max	1.4	1.4	1.4	1.4	1.4
7.5 ug	n	3	3	3	3	3
	Mean	1.75	1.75	1.75	1.75	1.75
	SD	0.834	0.834	0.834	0.834	0.834
	Median	1.65	1.65	1.65	1.65	1.65
	Min.	1.0	1.0	1.0	1.0	1.0
	Max	1.4	1.4	1.4	1.4	1.4
15 ug	n	3	3	3	3	3
	Mean	1.75	1.75	1.75	1.75	1.75
	SD	0.834	0.834	0.834	0.834	0.834
	Median	1.65	1.65	1.65	1.65	1.65
	Min.	1.0	1.0	1.0	1.0	1.0
	Max	1.4	1.4	1.4	1.4	1.4

[1] The Day 42 ratio is calculated by taking the subject's Day 42 treatment (infused) arm and dividing by the Day 42 non-treatment (control) arm value. The Day 1 ratio is calculated by taking the subject's Day 1 treatment (infused) arm and dividing by the Day 1 non-treatment (control) arm value. The overall ratio is determined by taking the subject's Day 42 ratio and dividing by the Day 1 ratio.

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Example: PD_T2 Page 1 of n
Protocol: 205767
Population: PDPP

Table 3.2
Summary of Change in Forearm Blood Flow (FBF) Ratio (Day 1 to Day 42), Acetylcholine

Challenge Agent		Daprodustat FBF Ratio [1]	rhEPO FBF Ratio [1]	Change in FBF Ratio [2]
Saline	n	3	3	3
	Mean	1.75	1.75	1.75
	SD	0.834	0.834	0.834
	Median	1.65	1.65	1.65
	Min.	1.0	1.0	1.0
	Max	1.4	1.4	1.4
7.5 ug	n	3	3	3
	Mean	1.75	1.75	1.75
	SD	0.834	0.834	0.834
	Median	1.65	1.65	1.65
	Min.	1.0	1.0	1.0
	Max	1.4	1.4	1.4
15 ug	n	3	3	3
	Mean	1.75	1.75	1.75
	SD	0.834	0.834	0.834
	Median	1.65	1.65	1.65
	Min.	1.0	1.0	1.0
	Max	1.4	1.4	1.4

[1] The Day 42 ratio is calculated by taking the subject's Day 42 treatment (infused) arm and dividing by the Day 42 non-treatment (control) arm value. The Day 1 ratio is calculated by taking the subject's Day 1 treatment (infused) arm and dividing by the Day 1 non-treatment (control) arm value. The overall ratio is determined by taking the subject's Day 42 ratio and dividing by the Day 1 ratio.

[2] The FBF ratio difference between Daprodustat and rhEPO.

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Example: PD_T3
Protocol: 205767
Population: PDPP

Table 3.3
Summary of Change in Absolute FBF (Day 1 to Day 42), Acetylcholine

Treatment	Challenge Agent	N	Visit	n	Mean	SD	Median	Min.	Max.
Dapro	Saline	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5
	7.5 ug	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5
	15 ug	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5
	30 ug	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5
rhEPO	Saline	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5
	7.5 ug	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5
	15 ug	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5
	30 ug	4	AVG. Day 1	4	1.06	6.695	1.50	0.7	1.7
			AVG. Day 42	4	-0.17	5.722	0.17	-0.6	0.5

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Example: PD_T4 Page 1 of n
Protocol: 205767
Population: PDPP

Table 3.8
Summary of Augmentation Index and Pulse Wave Velocity

Treatment			Day 1	Day 42
Dapro	Augmentation Index	n	3	3
		Mean	25.0	25.0
		SD	0.15	0.15
		Median	25.5	25.5
		Min.	20	20
		Max	30	30
	Pulse Wave Velocity	n	3	3
		Mean	7.75	7.75
		SD	0.834	0.834
		Median	6.65	6.65
		Min.	7.0	7.0
		Max	9.5	9.5
rhEPO	Augmentation Index	n	1	1
		Mean	25.0	25.0
		SD	0.15	0.15
		Median	25.5	25.5
		Min.	20	20
		Max	30	30

Example: PD_T5
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Population: PDPP

Table 3.9

Summary of Change in Augmentation Index and Pulse Wave Velocity (Day 1 to Day 42)

Treatment		N	Visit	n	Mean	SD	Median	Min.	Max.
Dapro	Augmentation Index	4	AVG. Day 1	3	24.0	6.69	24.5	20	30
			AVG. Day 42	3	-2.0	5.72	-2.5	-2	-3
	Pulse Wave Velocity	4	AVG. Day 1	3	7.75	6.695	7.50	6.0	9.5
			AVG. Day 42	3	-0.50	5.722	1.50	-0.5	0.5
rhEPO	Augmentation Index	4	AVG. Day 1	3	24.0	6.69	24.5	20	30
			AVG. Day 42	3	-2.0	5.72	-2.5	-2	-3
	Pulse Wave Velocity	4	AVG. Day 1	3	7.75	6.695	7.50	6.0	9.5
			AVG. Day 42	3	-0.50	5.722	1.50	-0.5	0.5

Example : PD_L1
Protocol : 205767
Population : PDPP

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Listing 17

Listing of Forearm Blood Flow

Treatment	Unique Subject Id./ Subject Id.	Age (YEARS)/ Sex/ Race Detail	Visit	Challenge Agent	Challenge Agent Dose	Infusion Drug Unit	Avg.Infused Arm	Avg.Non-infused Arm	FBF Ratio
Dapro	PPD	65/ F/ ASIAN - JAPANESE HERITAGE	Day1	1	1	mL/min	1.2	1.3	1.22
			POST DOSE	2	7.5	µg/min	1.4	1.01	1.33
rhEPO	PPD	65/ F/ MIXED RACE	PRE-DOSE	1	1	mL/min	1.2	1.3	1.22

Example : PD_L2
Protocol : 205767
Population : PDPP

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Listing 18

Listing of All Forearm Blood Flow Data for Participants with Any Value of Potential Clinical Importance

Treatment	Arm	Unique Subject Id./ Subject Id.	Age (YEARS)/ Sex/ Race Detail	Visit/ Date[Time]	Saline (mL/min)	Ach (µg/min)	SNP (µg/min)	LNMMA (µmol/min)
Dapro	FBF - infused arm	PPD	65/ F/ ASIAN - JAPANESE HERITAGE	PRE-DOSE/ 2002-01-01 T14:00	xx H	xx L	xx H	xx H
				POST DOSE/ 2002-01-01 T14:00	xx H	xx L	xx H	xx H
	FBF – non infused arm	PPD	65/ F/ ASIAN - JAPANESE HERITAGE	PRE-DOSE/ 2002-01-01 T14:00	xx H	xx L	xx H	xx H
rhEPO	FBF - infused arm	PPD	65/ F/ MIXED RACE	PRE-DOSE/ 2002-01-01 T14:00	xx H	xx L	xx H	xx H

Note:(PCI) Potential Clinical Importance Flag: L=Low, H=High

Example : PD_L3

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Protocol : 205767
Population : PDPP

Listing 19

Listing of Pulse Wave Velocity and Augmentation Index

Treatment	Unique Subject Id./ Subject Id.	Age (YEARS)/ Sex/ Race Detail	Visit/Planned Time/ ECG Date[Time]	Pulse wave velocity test (unit)	Pulse wave result
Dapro	PPD	65/ F/ ASIAN - JAPANESE HERITAGE	Day1/PRE-DOSE/ 2002-01-01 T14:00	Central Diastolic BP (mmHg)	xx
			POST DOSE/ 2002-01-01 T14:00	Central Diastolic BP (mmHg)	xx
rhEPO	PPD	65/ F/ MIXED RACE	PRE-DOSE/ 2002-01-01 T14:00	Central Diastolic BP (mmHg)	xx

Example : PD_L4

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Protocol : 205767
Population : PDPP

Listing 20

Listing of All Pulse Wave Velocity and Augmentation Index Data for Participants with Any Value of Potential Clinical Importance

Treatment	Unique Subject Id./ Subject Id.	Age (YEARS)/ Sex/ Race Detail	Visit/Planned relative Time/ Date[Time]	Central Diastolic BP (mmHg)	Central Systolic BP (mmHg)	Heart Rate (bpm)	Pulse Wave Velocity	....
Dapro								
	PPD	65/ F/ ASIAN - JAPANESE HERITAGE	Day1/PRE-DOSE/ 2002-01-01 T14:00	xx H	xx L	xx H	xx H	
			POST DOSE/ 2002-01-01 T14:00	xx H	xx L	xx H	xx H	
rhEPO								
	PPD	65/ F/ ASIAN - JAPANESE HERITAGE	PRE-DOSE/ 2002-01-01 T14:00	xx H	xx L	xx H	xx H	

Note:(PCI) Potential Clinical Importance Flag: L=Low, H=High

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Reason for signing: Approved	Name: PPD Role: Author Date of signature: 10-Nov-2020 13:46:45 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 10-Nov-2020 13:59:49 GMT+0000

Signature Page for TMF-2204610 v1.0