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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for A 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, study in recombinant human erythropoietin (rhEPO) naïve non-dialysis participants with anemia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo.
Compound Number	:	GSK1278863
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 205270.
- 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.

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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 2016N298481_00

Revision Chronology:		
Protocol number:	Date:	Version:
2016N298481_00	22/Aug/2017	Original Protocol
2016N298481_02	23/Aug/2019	Protocol Amendment 1
Amendment conducted to provide clarity regarding follow-up of participants with ADPKD and to incorporate new safety data provided in the Investigator's Brochure.		

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**
• Mean Change in individual items of the SF-36 Vitality Domain from baseline. • Mean Change in SF-36 Physical Function domain from baseline.	• **% of participants having an improvement in SF-36 Vitality Domain ≥ 6 from baseline at Week 28.** • Mean Change in individual items of the SF-36 Vitality Domain from baseline. • Mean Change in SF-36 Physical Function domain from baseline	• Additional endpoint to analyse the SF-36 scoring.
•	• **Mean Change in SF-36 Vitality domain between baseline and Week 28, utilizing TREAT historical control data**	• Principle secondary endpoint for SF-36 to be based on hypothetical strategy with imputation. Utilizing TREAT historical control data moved to secondary endpoint.
• Mean change from baseline by domain and overall symptom score on the Chronic Kidney Disease - Anemia Questionnaire	• Mean change from baseline by domain and **single items** on the Chronic Kidney Disease - Anemia	• Removed overall symptom and added singe item

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
(CKD-AQ) symptom questionnaire	Questionnaire (CKD-AQ) symptom questionnaire	
• Summary of frequency and dose of IV iron use	• Summary of frequency and dose of IV iron use, **rhEPO and transfusion use**	• Adding additional variables of interest
•	• New displays related to COVID-19 pandemic have been added	• Assessing the impact of the COVID-19 pandemic
• Only include randomized subjects who have both baseline and at least one Hgb assessment during the EP in the primary Hgb analysis	• All randomized subjects will be included in the primary Hgb analysis by imputing missing post-baseline Hgb data using pre-specified multiple imputation approach	• Addressing the feedback from FDA

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

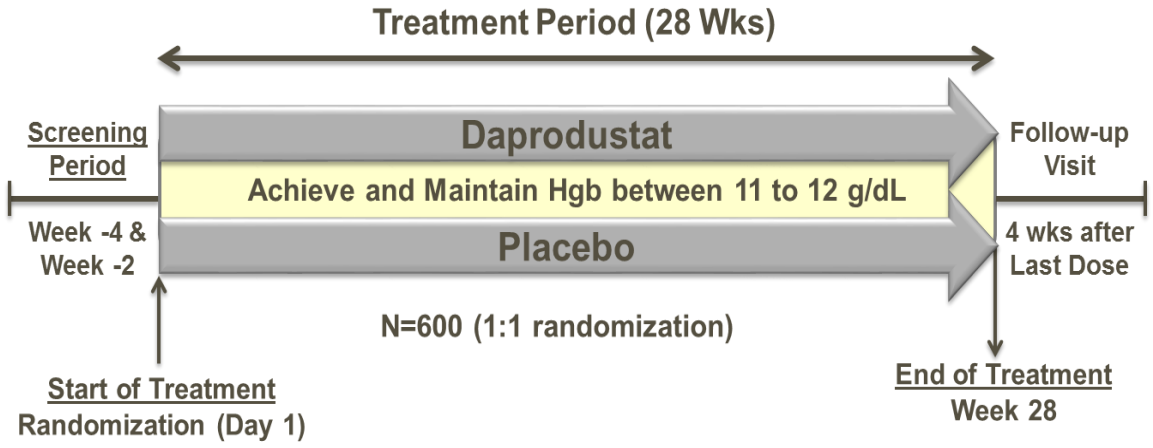
Objectives	Endpoints
Primary	
• To compare the efficacy of daprodustat to placebo on mean change in Hgb levels	• Mean change in Hgb between baseline and the Evaluation Period (EP, mean over week 24 to week 28 inclusive)
Principal Secondary	
• To compare the proportion of participants achieving increases in Hgb when treated with daprodustat versus placebo.	• % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP.
• To compare daprodustat to placebo for health related quality-of-life	• Mean Change in SF-36 Vitality domain between baseline and Week 28
Safety	
• To compare the safety and tolerability of daprodustat to placebo	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest and adjudicated MACE (composite of all-cause mortality, non-fatal MI and non-fatal stroke) • Reasons for discontinuation of study treatment • Absolute values and changes from baseline in laboratory parameters, Blood Pressure (BP) and heart rate (HR)
Secondary	
• To compare daprodustat to placebo on additional Hgb endpoints	• N (%) responders, defined as mean Hgb within range. • % time Hgb in range

Objectives	Endpoints
	• Mean change in Hgb from baseline.
• To compare daprodustat to placebo on the time to rescue	• Time to stopping study treatment due to meeting rescue criteria
• To compare daprodustat to placebo for improving symptoms of anemia of CKD	• Mean change from baseline by domain and single items on the Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ) symptom questionnaire
• To compare daprodustat to placebo on the severity and change in symptoms	• Change from baseline in PGI-S
• To compare daprodustat to placebo for improving health related quality-of-life	• % of participants having an improvement in SF-36 Vitality Domain ≥ 6 from baseline at Week 28. • Mean Change in individual items of the SF-36 Vitality Domain from baseline. • Mean Change in SF-36 Physical Function domain from baseline.
• To compare daprodustat to placebo on improving work productivity and regular daily activity impairment	• N (%) of patients currently employed on the WPAI-ANS-CPV • Change from baseline in percent and mean hours work time missed on the WPAI-ANS-CPV • Change from baseline in percent impaired (equivalent) on the WPAI-ANS-CPV • Change from baseline in overall percent work impairment (equivalent) on the WPAI-ANS-CPV • Change from baseline in percent activity impairment on the WPAI-ANS-CPV
• To compare daprodustat to placebo on improving health status	• Change in EQ-5D-5L utility score from baseline. • Change in EQ-VAS score from baseline.
• To compare daprodustat to placebo on BP	• Change from baseline in SBP, DBP, and MAP at week 28 • N (%) with at least one BP exacerbation event during the study
• To compare daprodustat to placebo for health related quality-of-life, utilizing	• Mean Change in SF-36 Vitality domain between baseline and Week 28, utilizing

Objectives	Endpoints
TREAT historical control data	TREAT historical control data
Exploratory	
• Further evaluations to compare daprodustat to placebo on Hgb variability	• % of time Hgb is above or below range. • Number (%) of participants with mean Hgb above and below range. • Number (%) of participants with a Hgb<7.5 g/dL • Number (%) of participants with a >2 g/dL increase in Hgb within any 4 week period up to EP and overall at week 28 • N (%) of participants with a Hgb value ≥ 13 g/dL during the treatment period • Number of times Hgb ≥ 13 g/dL during the treatment period • % of time Hgb ≥ 13 g/dL during the treatment period.
• Further evaluation to compare daprodustat to placebo on Hgb change.	• % of participants who achieved a Hgb increase of ≥1.0g/dL • % of time Hgb increase of ≥ 1.0 g/dL from baseline • % of participants having a Hgb increase of ≥ 1.0 g/dL at each post-baseline visit. • % of participants who achieved and maintained a Hgb increase of ≥1.0g/dL between baseline and EP.
• To compare daprodustat to placebo on measures of iron status and use	• Observed change from baseline in hepcidin, ferritin, transferrin saturation, serum iron, total iron binding capacity (TIBC) • Average monthly oral iron dose/participant (mg) to Week 28 • N (%) of participants who reduced oral iron supplementation from baseline • N (%) of participants requiring IV iron each month. • Average monthly IV iron dose/participant (mg) to Week 28 • Time to first IV iron, rhEPO and

Objectives	Endpoints
	Transfusion use • Summary of frequency and dose of IV iron use, rhEPO and transfusion use
• To compare daprodustat to placebo on renal function	• Estimated Glomerular Filtration Rate (eGFR) observed and change from baseline • Serum creatinine observed and change from baseline • N (%) transitioning to dialysis
• Evaluate the dose adjustment schemes	• Assigned dose by visit • Most recent dose prior to Week 24, Week 28 and End of Treatment • Maximum achieved dose • Number (%) of participants with 0, 1, 2 or >2 dose adjustment • Mean number of dose adjustments • Time dose held for Hgb≥13 g/dL
• To compare daprodustat to placebo on BP medication changes	• N (%) of subjects who had no change, an increase or a decrease in the number of BP medications from baseline to week 28 or final visit for non-completers
• To compare daprodustat to placebo on the severity and change in symptoms	• N(%) of participants within each PGI-C symptom change.
• To compare daprodustat to placebo for improving physical activity (actigraphy)	• Change in percent and mean number of hours of daily sedentary activity from baseline. • Change in percent sleep efficiency from baseline.

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This is a 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center Phase 3 study in participants with anemia associated with chronic kidney disease (CKD) who are not on dialysis. This study will enroll anemic participants who have a HemoCue Hgb 8.5 to 10.0 g/dL, inclusive. These participants will have a limited history of IV iron use and be rhEPO naïve prior to screening and randomization. • This study includes a 4-week screening period, a 28-week treatment period, and a 4-week follow-up period. • The total duration of study participation for each participant will be approximately 36 weeks.
Dosing	• Daprodustat and placebo doses for participants will be titrated based upon HemoCue Hgb. Dose modifications for these participants will follow a protocol-specified dose adjustment algorithm to achieve and maintain Hgb within the target range of 11.0 to 12.0 g/dL, inclusive. Dose changes will be made programmatically in a blinded fashion by the IRT system in order to ensure that GSK, investigators and participants stay blinded to the study treatment and the dose adjustments.
Schedule of Activities	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• The randomization schedule will be generated by PPD, and PPD's IRT system will be used for treatment allocation. • Participants will be stratified by region. Following stratification, participants will be randomized centrally in a 1:1 ratio to receive either daprodustat or matching placebo tablets.
Interim Analysis	• At the time of finalizing the RAP, no interim analysis is currently planned due to an adequate rate to recruitment.
Rescue	• A rescue algorithm will be provided to minimize the impact of participants having an inadequate response to the treatment for their anemia for an extended period of time and to enable rescue therapy to be provided to the

Overview of Study Design and Key Features	
	participants based on local clinical practice.

2.4. Statistical Hypotheses

The primary Hgb efficacy objective will assess the estimand defined as the comparative treatment effect in mean Hgb change between baseline and evaluation period (EP, i.e., week 24 to week 28 inclusive) regardless of adherence to treatment, the use of non-randomized ESA medication for any reason including rescue therapy, or the use of blood transfusions, in patients defined by the inclusion/exclusion criteria and assuming patients do not die before the end of the EP. The primary Hgb efficacy assessment is based on the central lab Hgb, Q^2. If central lab Hgb is missing then the data will be derived from Hemocue Hgb. The analysis will test whether daprodustat is superior to placebo according to the following statistical hypotheses:

- **Null:** The difference in mean change in Hgb between baseline and EP, between treatment arms (daprodustat-placebo), is less than or equal to 0 g/dL.
- **Alternative:** The difference in mean change in Hgb between baseline and EP between treatment arms (daprodustat-placebo), is greater than to 0 g/dL.

Statistical significance will be assessed at the one-sided 2.5% level. An analysis of covariance (ANCOVA) model including the randomization stratification factor, baseline hemoglobin and treatment will be used to obtain a point estimate and the two-sided 95% CI for the treatment difference (daprodustat-placebo) and generate the one-sided p-value for the superiority test. Superiority will be established if the one-sided p-value is less than 0.025.

3. PLANNED ANALYSES

3.1. Interim Analyses

Protocol states the below paragraph, but at the time of finalizing the RAP, no interim analysis is currently planned due to an adequate rate to recruitment.

An interim analysis to assess futility may be performed if the rate of the enrolment is considerably slower than expected. This analysis will only consist of the principal secondary endpoint of QoL SF-36 vitality sub-score, due to its considerably larger sample-size requirement for a powered analysis compared to the primary endpoint. The primary endpoint of mean change in Hgb between baseline and EP, and the principal secondary endpoint of % of participants having a Hgb increase of ≥1.0 g/dL from baseline at EP will not be included in this interim analysis. The potential outcomes of this analysis include the continuation of the study with no change and the stopping of the enrolment. It is planned that the interim analysis will only be performed once approximately 200 participants have completed 28 weeks of study in order to preserve power for the primary endpoint should the study be discontinued. If the observed difference for the QoL vitality endpoint between daprodustat and placebo is less than 2 points at the time of the interim analysis, study enrolment will be stopped. This decision guideline was determined to have favorable operating characteristics, such as an unconditional power of <30%, and an acceptably low probability of a false stop (<10%). Since the study will not be stopped for positive results, type I error will not be inflated. Inference on the aforementioned Hgb parameters will still be made as per Section 7.1 and Section 7.2, even if the study is stopped for futility based on QoL SF-36 vitality subscore.

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 and final study clinic visits have occurred.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by GSK Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to GSK and PPD procedures.

4. ANALYSIS POPULATIONS

Inclusion in any analysis population is contingent on a participant signing informed consent.

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All randomized participants. • Participants will be analyzed according to the treatment to which they were randomized. • Use of the enrolled population is required for some displays; for this study, the enrolled and ITT populations will be identical.	• Study Population
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. • Note: Participants who were not randomized but received at least one dose of study treatment should be listed. [1]	• Safety
Intent-to-Treat (ITT)	• Comprise all randomized participants regardless of whether they took study drug. • 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.	• Study Population • Efficacy

Refer to Appendix 10: 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. Otherwise, participants will be analyzed according to the treatment to which they were randomized. If participant received both treatments then analysis will be based on Daprodustat treatment.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be 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 [version 2 20180514].

- Data will be reviewed prior to unblinding and freezing of the database to ensure all important deviations, including those that 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			
PPD IWRS		Data Displays for Reporting	
Code	Description	Description	Order in TFL
2	Placebo	Placebo	1
1	Daprodustat	Dapro	2
--	--	Total	3

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 on or before the randomization date (except as noted below). This is generally expected to be the pre-dose value from the Day 1 visit, although such values may be missing.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screen Week -4	Screen Week -2	Day 1 (Pre-Dose)	
Efficacy				
Hgb[1]			X	Day 1
Iron Parameters			X	Day 1
Monthly Oral iron[1]			X	Day 1
Monthly IV iron[2]			X	Day 1
Estimated Glomerular Filtration Rate (eGFR)			X	Day 1
Serum Creatinine			X	Day 1
Safety				
SBP/DBP and HR			X	Day 1
Lipid Parameters, Clinical Chemistry, Hematology, Other Laboratory, and Hepatobiliary (liver) Tests			X	Day 1
PRO				
Actigraphy			X	Day 1
SF-36 Domain and			X	Day 1

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screen Week -4	Screen Week -2	Day 1 (Pre-Dose)	
Component Scores				
CKD-AQ			X	Day 1
WPAI-ANS-CPV			X	Day 1
EQ-5D-5L & VAS			X	Day 1
PGI-S			X	Day 1
PGI-C			X	Day 1

NOTES:

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

[1] Baseline monthly oral iron dose will be defined as total oral iron (mg) over the 4 weeks prior to randomization. See Section 10.6.3.

[2] Baseline IV monthly iron dose will be defined as total IV iron (mg) over the 8 weeks prior to screening, since participants may only receive up to one IV iron dose within the 8 weeks prior to screening and no IV iron use between screening visit and randomization. See Section 10.6.3.

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

Lipid parameters will be log-transformed and the percent change from baseline will be reported. Other endpoints may also be log-transformed if deemed appropriate. Hepcidin, Ferritin, and serum iron will also be log-transformed.

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 global study, enrolment will be presented by investigative site, country, and the regions.

Region	Countries[2]
1	Republic of Korea[1]
2	Poland, , Romania, , Russian Federation,
3	Australia[1], Canada[1], Italy, , France, [1], United Kingdom[1], Spain[1], [1]
4	Argentina, Brazil[1], Mexico
5	US[1]

NOTES:

[1]: Countries which will collect the EQ-5D-5L and EQ VAS.

[2] Countries that do not participate or do not randomize any participants will be removed from the regional grouping.

5.4. Examination of Covariates, Other Strata and Subgroups

- The following is a non-exhaustive list of covariates that may be used in summaries of demographics, descriptive summaries and statistical analyses.
- Additional covariates of clinical interest may also be considered.
- If the percentage of participants is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
    - If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup
- The primary and principal secondary endpoints will be evaluated for a set of prespecified subgroups. Subgroup analyses are aimed to assess for consistency with the overall result, and they may have low power if the subgroup is small. Statistical models (ANCOVA or CMH chi-squared test) will be adjusted for the covariates used in the original analysis, subgroup, treatment and treatment by subgroup interaction. Point estimates and two-sided 95% CIs will be estimated (presented on Forest Plots) and the subgroup by treatment interaction p-value calculated. Subgroup analyses will not be adjusted for multiplicity.

Subgroups (Based on status before randomization)	**Categories**
Age	<65 years, ≥65 years - <75 years, ≥75 years
Gender	Female, Male
Race Group	**Summary tables:** American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race **Analysis**: American Indian or Alaskan Native, Asian, Black, White (exclude Native Hawaiian or Other Pacific Islander and Mixed Race)
Ethnicity	Hispanic, non-Hispanic
Region	Per Section 5.3
Baseline BMI	<30kg/m^2, ≥30kg/m^2

Subgroups (Based on status before randomization)	**Categories**
Baseline Weight	<75kg, ≥75kg
Baseline Hgb	<8.5g/dL, 8.5-<9g/dL, 9-10g/dL, > 10g/dL <9g/dL, 9-<10g/dL, 10-11g/dL, >11g/dL
Serum Iron Levels at Baseline	TSATs≥15% and Ferritin≥50 ng/mL vs TSATs<15% or Ferritin<50 ng/mL
Iron Replete Participants	TSATs≥20% and Ferritin≥100 ng/mL vs TSATs<20% or Ferritin<100 ng/mL
hsCRP	Quartile Analysis
Diabetic	Yes, or No
History of Heart Failure	Yes, or No
eGFR	<15, >=15
ADPKD (Autosomal Dominant Polycystic Kidney Disease)	ADPKD, non-ADPKD *Note: Only used for analyses of eGFR*

5.5. Multiple Comparisons and Multiplicity

The primary endpoint will be tested first for superiority using a one-sided 2.5% significance level. Conditional on achieving statistical significance, the first principal secondary endpoint will be tested for superiority using a one-sided 2.5% significance level. Finally, conditional on achieving statistical significance of both the primary endpoint and the first principal secondary endpoint, the second principal secondary endpoint will be tested for superiority using a one-sided 2.5% significance level. This three-step hierarchical strategy will preserve the study-wise Type I error rate at a one-sided 2.5% level.

The additional secondary/exploratory endpoints as listed in Section 7.3 and Section 7.4 are of exploratory nature, and if tested, will not be adjusted for multiplicity. Summary statistics and nominal one-sided 2.5% significance levels will be used to describe the results of these treatment comparisons.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Statistical models outputting adjusted means will use the SAS option "OM" which allows the adjusted means to be based on a weighting scheme that considers the actual proportion of the coefficients in the model that are found in the data.

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 ITT population unless otherwise specified. Summaries will include a total column, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, population analyzed, demographic and baseline characteristics, medical conditions, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10 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 (ITT) participants who, as documented in the eCRF Study Conclusion form, have completed all study periods through the Week 28 visit.

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 subreasons for discontinuation, and related to study treatment.

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. (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 Participant by Country and Site ID

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

A listing of participants for whom the treatment blind was broken during the study will be provided.

A listing of planned and actual treatments will be provided. This listing will include country, site ID, investigator name, 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, and ITT populations 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.

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 include all subgroup variables listed in Section 5.4, and will be summarized by treatment group and overall for ITT and Safety populations.

A by-participant listing of demographic and baseline characteristics will also be produced. This listing will include treatment, site ID, unique subject ID, partial date 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 and race and racial combination details will be produced for each treatment group and overall.

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

A summary of smoking history will be provided by treatment group and overall.

6.2.5. Medical Conditions, Prior and Concomitant Medications

Medical Conditions

A summary of 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 10.4.1). 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 10.4.1 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 10.6.2) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group and overall.

Summary of treatment compliance will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group and overall. As well as by categories: under compliant < 80%, compliance >=80% and <=120%, and over compliant >120%.

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, and dosing frequency.

6.2.7. Other Displays

The following COVID-19 related displays will be provided.

- Summary of Subject Status and Subject Disposition by Relationship to COVID-19 Pandemic.
- Summary of Treatment Status and Reasons for Discontinuation of Study Treatment by Relationship to COVID-19 Pandemic
- Important Protocol Deviations by Relationship to COVID-19 Pandemic
- Proportion of Subject Visits Impacted by COVID-19 Pandemic
- Summary of Treatment Interruption Due to COVID-19 Pandemic

- Figure of Visits Impacted by COVID-19 Pandemic
- Listing of All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

The primary efficacy estimand is the effect of daprodustat treatment relative to placebo regardless of adherence to treatment, the use of non-randomized ESA medication for any reason including rescue therapy, or the use of blood transfusions, in patients defined by the inclusion/exclusion criteria and assuming patients do not die before the end of the EP.

The primary Hgb efficacy assessment is based on the central lab Hgb, Q^2. If central lab Hgb is missing then the data will be derived from Hemocue.

7.1.1. Endpoint / Variables

Mean change in Hgb between baseline and over the evaluation period (EP, mean over Week 24 and 28).

7.1.2. Summary Measure

Model-adjusted mean treatment difference (LS mean difference) in Hgb change between baseline and over the evaluation period.

7.1.3. Population of Interest

The target population is defined by the study's inclusion and exclusion criteria.

The analysis population included in the primary efficacy analyses will be based on the All Randomized (ITT) population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The following are the intercurrent events for the primary efficacy analyses:

- Death prior to the end of the EP (i.e. before Week 28 visit)
- Randomized treatment discontinuation prior to the end of the EP
- Use of non-randomized ESA medications for any reason including rescue prior to the end of the EP
- Receipt of blood transfusions prior to the end of the EP

Except for the intercurrent event of deaths prior to the end of the EP, a treatment policy strategy will be used in which all scheduled Hgb data recorded during the EP (Weeks 24-28) will be included in the primary efficacy analysis, regardless of discontinuation of study medication due to any reasons, and regardless of receipt of non-randomized ESA medications for any reason including rescue, or blood transfusions. For deaths, a hypothetical strategy will be used as described in Section 7.1.5.1.

The following are causes of missing Hgb data affecting the primary efficacy endpoint that are not due to intercurrent events:

- Study withdrawal prior to the end of the EP
- Permanent switching from clinic visits to remote visits prior to start to EP
- Intermittent missing Hgb values at one or more visits with the EP

Missing data will be imputed as described in Section 7.1.5.1.

7.1.5. 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 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables

- Mean change in Hgb between baseline and over the evaluation period (EP, mean over Weeks 24 to 28)

Model Specification

- The EP Hgb value will be defined as the mean of all available Hgb values (on and off-treatment) during the EP (Week 24 to Week 28 inclusive)
- The ANCOVA model used to quantify the difference in mean Hgb change will adjust for the following baseline values:
    - Treatment
    - Baseline Hgb (see Section 5.2)
    - Region (as randomized, see Section 5.3 & Section 5.4)

Multiple Imputation Analysis

- Multiple imputation analysis will be performed using all available Hgb values (on and off-treatment) and conducted under a set of assumptions about missing Hgb values (see Section 10.6.3).
    - For each of the missing dataset (out of the 200 imputed as indicated above), the missing scheduled Hgb values through Week 28 will be imputed based on the MNAR assumption and will be performed using PROC MI. The regression will have region, treatment, baseline Hgb, off treatment status, prior scheduled (possibly imputed) Hgb values as covariates (see Model Checking & Diagnostics, below). The seed for reproducibility is set to 205270.
    - Missing data will be considered MNAR and classified as either being on-treatment or off-treatment, with the former being imputed with only on-treatment data and the latter being imputed with only off-treatment data
        - Subsequent missing data will be classified as being on-treatment, if
            - Patients who die, use non-randomized ESA Medication, Receipt of Blood Transfusions while on treatment
            - Study Drug Interruption (e.g. temporarily stopped trt due to COVID, then restarted)
        - Subsequent missing data will be classified as being off-treatment, if
            - Treatment discontinuation
            - Patients who die, use non-randomized ESA Medication, Receipt of Blood Transfusions after treatment discontinuation

- The low and high cutoffs at Hgb values of 6 g/dL and 15 g/dL will be applied to all imputed Hgb values.
- EP Hgb values will be computed and compared across treatment groups using the co-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.

Model Checking & Diagnostics

- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
- Models will be examined for treatment interactions with baseline Hgb and stratification factor
- Missing data imputation:
  - When imputing for each of the missing dataset (out of the 200), if there are error and or warning messages related to the by statement and/or regression model (e.g. not enough observations with the statement), try impute with randomized treatment, baseline Hgb, treatment status, prior scheduled (possibly imputed) Hgb values and region as covariates.
  - If there are no observed off-treatment Hgb values at a visit, the missing Hgb values at that visit will be imputed based on only the observed on-treatment Hgb values.

Model Results Presentation

- All available observed Hgb values (on and off-treatment) will be summarized using mean, standard deviation, minimum, P25, median, P75 and maximum at each visit by treatment group. In addition to scheduled visits, the baseline value and mean EP will be included (see Section 10.6.3). The summaries described above will be produced using the analysis defined Hgb.
  - This display will be repeated for visits up to and including Week 28, using the data used for the primary Hgb analysis (i.e., including imputed values).
- All available observed Hgb change from baseline values (on and off-treatment) will also be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at each post-baseline visit, including the mean EP (see Section 10.6.3).
  - This display will be repeated for visits up to and including Week 28, using the data used for the primary Hgb analysis (i.e., including imputed values).
- The number and percentage of subjects with imputed data in the primary Hgb analysis will be provided by treatment group. The number and percentage of subjects by reason for data imputation will be provided. Reasons include: death before Week 24, death during Week 24 – 28, investigator site closed before Week 24, investigator site closed during Weeks 24-28, lost to follow-up before Week 24, lost to follow-up during Week 24 – 28, consent withdrawn before Week 24, consent withdrawn during Week 24 – 28, and other monotone missing Hgb values. Subjects will be further classified as either having observed both scheduled EP Hgb values, Having observed a partial schedule of EP Hgb values, having observed no scheduled EP Hgb values with at least one unscheduled EP Hgb value, or having observed no EP Hgb values, scheduled or unscheduled. For subjects with partial scheduled EP Hgb values, the amount of imputed data (1 scheduled Hgb values missing) will be summarized. For subjects with partial scheduled EP Hgb values and a monotone imputed data pattern, the reason for the monotone imputed scheduled EP Hgb values will be provided. Reasons include: death during Week 24-28, investigator site closed during Weeks 24-28, lost to follow-up during Week 24 – 28, consent withdrawn during Week 24 – 28, and other monotone imputed Hgb values. And for summaries of the amount of missing scheduled EP Hgb values, the presence or absence of additional unscheduled EP Hgb values will be summarized.

• The least square (LS) mean estimates and standard errors by treatment group, LS mean difference, two-sided 95% CI and one-sided superiority p-value for the difference in the primary Hgb endpoint between the daprodustat and placebo arms from the ANCOVA model will be presented. The number of subjects contributing to the analysis and the associated mean and standard deviation of the baseline and EP Hgb values will also be displayed with the results of the ANCOVA model. • All available mean Hgb values (on and off-treatment) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values and the 95% CI by time will include horizontal reference lines to depict the hemoglobin analysis range (11-12 g/dL), vertical reference lines to identify the EP (weeks 24-28), and the number of subjects by treatment group contributing to each mean value. • All available Hgb change from baseline values (on and off-treatment) will be displayed graphically for each scheduled study visit using a line plot. The line plot of mean values and the 95% CI by time will include vertical reference lines to identify the EP (Weeks 24-28), and the number of subjects by treatment group contributing to each mean value. • A listing of all hemoglobin values will be provided, including treatment, site ID, unique subject ID, subject ID, visit, assessment date, select demographic information and central laboratory and HemoCue Hgb values.
Model Results Interpretation
Superiority will be established if the one-sided p-value is less than 0.025.
Subgroup Analyses
• Subgroup analysis will be performed using all available Hgb values (on and off-treatment) and separately using evaluable Hgb values only (see Section 10.6.3). • Subgroup analysis details are discussed in Section 5.4. • The ANCOVA model used to quantify the difference in mean Hgb change will adjust for the following baseline values: ○ Treatment ○ Baseline Hgb (see Section 5.2) ○ Region (as randomized, see Section 5.3 & Section 5.4) ○ Subgroup ○ Subgroup * treatment interaction term
Supportive Analyses
• A supportive analysis using while alive and on treatment strategy (on-drug analysis) will be considered. In this analysis, the EP Hgb will be determined using evaluable Hgb values (Section 10.6.3). Hgb values collected after IP discontinuation, or within 8 weeks following a red blood cell transfusion, a whole blood transfusion, or a nonrandomized ESA treatment would be irrelevant to the analysis, since they are not of interest in this estimand.

7.2. Principal Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

Principal Secondary	
Objectives	**Endpoints**
• To compare the proportion of participants achieving increases in Hgb when treated with daprodustat versus placebo.	• % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP.
• To compare daprodustat to placebo for health related quality-of-life.	• Mean Change in SF-36 Vitality domain between baseline and Week 28.

7.2.2. Summary Measure

Principal Secondary	
Endpoints	**Summary Measure**
• % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP.	• Relative response rate (Dapro vs Placebo) of % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP.
• Mean Change in SF-36 Vitality domain between baseline and Week 28.	• Mean treatment difference (Dapro – Placebo) in the Change in SF-36 Vitality sub-score between baseline and Week 28.

7.2.3. Population of Interest

The target population is defined by the study's inclusion and exclusion criteria.

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

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

For the first principal secondary endpoint of % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP, a treatment policy strategy will be used in the analysis to include all on and off treatment Hgb values of the ITT populations, including values taken after rescue and IP discontinuation.

The following are the intercurrent events for the first principle secondary efficacy analysis:

- Death prior to the end of the EP (i.e. before Week 28 visit)
- Randomized treatment discontinuation prior to the end of the EP
- Use of non-randomized ESA medications for any reason including rescue prior to the end of the EP
- Receipt of blood transfusions prior to the end of the EP

Except for the intercurrent event of deaths prior to the end of the EP, a treatment policy strategy will be used in which all scheduled Hgb data recorded during the EP (Weeks 24-28) will be included in the primary efficacy analysis, regardless of discontinuation of study medication due to any reasons, and regardless of receipt of non-randomized ESA medications for any reason including rescue, or blood transfusions. For deaths, a hypothetical strategy will be used as described in Section 7.2.5.2

The following are causes of missing Hgb data affecting the first principle secondary efficacy endpoint that are not due to intercurrent events:

- Study withdrawal prior to the end of the EP
- Permanent switching from clinic visits to remote visits prior to start to EP
- Intermittent missing Hgb values at one or more visits with the EP

Missing data will be imputed as described in Section 7.2.5.2.

For the second principal secondary endpoint of mean change in SF-36 vitality sub-score between baseline and Week 28, a hypothetical strategy will be used assuming subjects had not had intercurrent events specified below. Data collected after IP discontinuation will not be included in the statistical analysis and will be treated as missing data. The missing SF-36 vitality sub-scores will be imputed as outlined in Section 7.2.5.2.

The following are the intercurrent events for the second principle secondary efficacy analysis:

- Death prior to the end of the EP (i.e. before Week 28 visit)
- Randomized treatment discontinuation prior to the end of the EP

7.2.5. 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 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

In addition, descriptive statistics for each individual item within the SF-36 vitality subscore will be generated (See Section 7.3.2.1). Of particular interest are the items assessing if participants have a lot of energy, feel tired, and feel worn out. These concepts have been found to be important and relevant in this population [Martin, 2011].

7.2.5.1. Interim Analysis

No interim analysis is planned to occur.

7.2.5.2. Statistical Methodology Specification

Endpoint / Variables
• % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP. • Mean Change in SF-36 Vitality domain between baseline and Week 28
Model Specification
• For the first principal secondary endpoint of % of participants having a Hgb increase of ≥1.0 g/dL from baseline to EP, the EP Hgb value will be defined as the mean of all available Hgb values (on and off-treatment) during the EP (Week 24 to Week 28 inclusive).A Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment, and region (see Section 5.3), will be used to make comparisons between the treatment groups. A treatment policy strategy will be used in the analysis to include all on and off treatment Hgb values of the ITT populations, including values taken after rescue and IP discontinuation. • For the second principal secondary endpoint of mean change in SF-36 vitality sub-score

between baseline and Week 28, a hypothetical strategy will be used which includes only on-treatment values and exclude the measures taken after IP disc/rescue medication. The SF-36 vitality sub-scores will be imputed if missing. An ANCOVA model will be used including factors for baseline score, treatment, and region.

Model Results Presentation

- For the first principal secondary endpoint, the number and % of participants having a Hgb (on and off-treatment) increase of ≥1.0 g/dL from baseline to EP by treatment group, relative response rate (daprodustat vs. placebo) and two-sided 95% CI will be provided along with the one-sided CMH p-value for the treatment group comparison.
- For the second principal secondary endpoint, each individual item within the SF-36 vitality subscore will be summarized using mean, standard deviation, minimum, P25, median, P75 and maximum at baseline, Week 8, Week 12, and Week 28 visit by treatment group. (See Section 7.3.2.1)
- For the second principal secondary endpoint, all available SF-36 vitality sub-score change from baseline values (on-treatment only) will also be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum at Week 8, Week 12, and Week 28 visit. (See Section 7.3.2.1)
- For the second principal secondary endpoint, the LS means estimated from treatment difference, will be presented along with one-sided p-value and 95% CI. The number of participants contributing to the analysis and the associated mean and standard deviation of the baseline and Week 28 SF-36 Vitality sub-score value will also be displayed with the results of the model.
- For the second principal secondary endpoint, all available SF-36 vitality sub-score values (on-treatment) will be displayed graphically for each scheduled study Week 8, Week 12, and Week 28 visit using a line plot.
- For the second principal secondary endpoint, all available SF-36 vitality sub-score change from baseline values (on-treatment) will be displayed graphically for each scheduled study Week 8, Week 12, and Week 28 visit using a line plot. The line plot of mean values ± standard errors by time will include horizontal reference line to identify zero change, and the number of participants by treatment group contributing to each mean value.
- SF-36 data will be summarized and analysed using both norm-based and traditional scoring, see Section 10.6.5 for details. The traditional scoring will be considered as the primary results and norm-based as supportive results.

Multiple Imputation HGB Increase ≥1.0 g/dL

- For the first secondary endpoint, the imputed data from the primary endpoint will be used for deriving the % of participants having a HGB increase of ≥1.0 g/dL from baseline to EP.

Multiple Imputation SF-36 Analysis

- For the SF-36 principle secondary endpoint, multiple imputation analysis will be performed using on treatment SF-36 values and conducted under a set of assumptions about missing sf-36 values (see Section 10.6.3).
    - Missing scheduled SF-36 data in both arms through Week 28 will be considered MAR and imputed using PROC MI procedure with NIMPUTE = 200 and FCS to generate 200 datasets. The seed for reproducibility is set to 205270. The imputations will be done by randomized treatment, include region as categorical covariate.
    - Week 28 SF-36 values will be computed and compared across treatment groups using the principle secondary 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.
    - Subjects with scheduled off-treatment SF-36 data will be imputed assuming they were on treatment.
    - The low and high cutoffs at SF-36 values of 0 and 100 for traditional scoring and 22.89 and 70.42 for norm-based scoring will be applied to all imputed SF-36 values.
- For the SF-36 principle secondary endpoint supportive analysis imputing subjects who have remote/over the phone SF-36 visits during Week 28 and those subjects who were treatment interrupted prior to their Week 28 visit will be performed using on treatment SF-36 values and conducted under a set of assumptions about missing sf-36 values (see Section 10.6.3). This is a similar imputation strategy as outlined above but will be based on on-treatment SF-36 values and consider those subjects who completed SF-36 remotely/over the phone or who were treatment interrupted prior to Week 28 as missing.

Supportive Analyses

- For the first principal secondary endpoint, a supportive analysis using while alive and on treatment strategy (on-drug analysis) will be performed using a Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment, and region (see Section 5.3), will be used to make comparisons between the treatment groups. No imputation will be performed for this analysis.
- For the second principal secondary endpoint, a treatment policy strategy (on and off treatment) analysis will be performed using an ANCOVA model including all participants with on and off treatment values, including factors for baseline score, treatment, and region. This will be done for both traditional and norm-based scoring. No imputation will be performed for this analysis.
- For the second principal secondary endpoint, a while alive and on treatment strategy (on treatment only) analysis will be performed using an ANCOVA model including all participants with on treatment values, excluding subjects who IP discontinue/rescue, including factors for baseline score, treatment, and region. This will be done for both traditional and norm-based scoring. No imputation will be performed for this analysis.
- For the second principal secondary endpoint, an analysis imputing subjects who have remote/over the phone SF-36 visits during Week 28 and those subjects who were treatment interrupted prior to their Week 28 visit will be performed using an ANCOVA model including factors for baseline score, treatment, and region. This analysis will be based on the hypothetical strategy outlined above. This will be done for both traditional and norm-based scoring. This analysis will only be performed if at least 10% of the ITT population is identified to have remote/over the phone SF-36 visits during Week 28 and those subjects who were treatment interrupted prior to their Week 28 visit have observed week 28 SF-36 data.

Subgroup Analyses

- For the first principal secondary endpoint, subgroup analysis will be performed using all available Hgb values (on and off-treatment). A Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment and subgroup, will be used to make comparisons between the treatment groups. A treatment policy strategy will be used in the analysis to include all on and off treatment Hgb values of the ITT populations, including values taken after rescue and IP discontinuation. The imputed data from the primary endpoint will be used for deriving the % of

participants having a HGB increase of ≥1.0 g/dL from baseline to EP.

- For the second principal secondary endpoint, subgroup analyses will be performed using an ANCOVA model, including factors for baseline score, treatment, region, subgroup and subgroup treatment interaction. A hypothetical strategy will be used as defined above. The SF-36 vitality sub-scores after IP discontinuation will be imputed based on the conservative assumption that there is no change in the sub-scores after the intercurrent event, so the last available on-treatment values (or baseline values if there is no on-treatment values) will be used in the imputation. This will be done for both traditional and norm-based scoring.

7.3. Additional Secondary Efficacy Analyses

7.3.1. Endpoint / Variables

Secondary	
Objectives	**Endpoints**
• To compare daprodustat to placebo on additional Hgb endpoints	• N (%) responders, defined as mean Hgb within range. • % time Hgb in range • Mean change in Hgb from baseline.
• To compare daprodustat to placebo on the time to rescue	• Time to stopping study treatment due to meeting rescue criteria
• To compare daprodustat to placebo for improving symptoms of anemia of CKD	• Mean change from baseline by domain and single items on the Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ) symptom questionnaire
• To compare daprodustat to placebo on the severity and change in symptoms	• Change from baseline in PGI-S
• To compare daprodustat to placebo for improving health related quality-of-life	• % of participants having an improvement in SF-36 Vitality Domain $\geq$ 6 from baseline at Week 28. • Mean Change in individual items of the SF-36 Vitality Domain from baseline. • Mean Change in SF-36 Physical Function domain from baseline.
• To compare daprodustat to placebo on improving work productivity and regular daily activity impairment	• N (%) of patients currently employed on the WPAI-ANS-CPV • Change from baseline in percent and mean hours work time missed on the WPAI-ANS-CPV • Change from baseline in percent impaired (equivalent) on the WPAI-ANS-CPV • Change from baseline in overall percent work impairment (equivalent) on the WPAI-ANS-CPV • Change from baseline in percent activity impairment on the WPAI-ANS-CPV

Secondary	
Objectives	**Endpoints**
• To compare daprodustat to placebo on improving health status	• Change in EQ-5D-5L utility score from baseline. • Change in EQ-VAS score from baseline.
• To compare daprodustat to placebo on BP	• Change from baseline in SBP, DBP, and MAP at week 28 • N (%) with at least one BP exacerbation event during the study
• To compare daprodustat to placebo for health related quality-of-life, utilizing TREAT historical control data	• Mean Change in SF-36 Vitality domain between baseline and Week 28, utilizing TREAT historical control data

7.3.2. 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 7.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.2.1. Statistical Methodology Specification

Hgb Variability

Secondary Efficacy Statistical Analyses: Hgb Variability
Endpoint / Variables
• N (%) responders, defined as mean Hgb within range (11-12 g/dL) during the EP (Week 24 to Week 28 inclusive). • % time Hgb in analysis range (11-12 g/dL), during the EP and during the treatment period (Day 1- Week 28) • Mean change in Hgb from baseline to Week 28.
Model Specification
• For the Hgb responder analysis, mean Hgb during the EP will be defined as in the on-drug supportive analysis (Section 10.6.3). Responders will be participants with a mean Hgb during the EP that falls within the Hgb analysis range of 11-12 g/dL. A Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment and the prognostic randomization stratification factor (region as randomized, see Section 5.3), will be used to compare the number and % of responders between the treatment groups. • For the analysis of % time in range, the method by Rosendaal [Rosendaal, 1993] will be used to calculate the percentage of time (days) a participant's Hgb is below, within and above the Hgb analysis range of 11 to 12 g/dL during the EP (Weeks 24-28) and during the treatment period (Day 1 – Week 28). A van Elteren test (stratified Wilcoxon rank sum test) will be used to compare the percentage of time in range between treatment arms, adjusting for treatment and

the prognostic randomization stratification factor (see Section 5.3). This analysis will be performed using evaluable Hgb values only. Hodges-Lehmann estimate of the treatment difference will be used to assess non-inferiority in % time in range • For the secondary analysis of Hgb change from baseline to Week 28, a mixed model repeated measures (MMRM) approach will be used with an unstructured covariance matrix to compare the difference in means between arms. The model will be fitted to Hgb data collected after baseline up to Week 28. The model will include factors for treatment, time, prognostic randomization stratification factor (region, see Section 5.3), baseline Hgb and the baseline Hgb by time and treatment by time interaction terms. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors. This analysis will be performed using all available Hgb values (on and off-treatment) and separately using evaluable Hgb values only (see Section 10.6.3). In the analysis using all available Hgb values, participants who withdraw from the study before Week 28 are considered to be missing at random and in the analysis using evaluable Hgb values, participants who permanently discontinue randomized treatment before Week 28 are assumed to be missing at random.
Model Results Presentation
• For the responder analysis, the number and percentage of participants with mean EP Hgb, and end of treatment Hgb above, within and below the Hgb analysis range will be summarized by treatment group. • For the responder analysis, the number and % of responders by treatment group, relative response rate (daprodustat vs. placebo) and two-sided 95% CI will be provided along with the one-sided CMH p-value for the treatment group comparison. • The % time Hgb is above, in and below the Hgb analysis range (11-12 g/dL) during the EP will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. • The percent time in range for each treatment group, the stratified Mann-Whitey estimate of the treatment difference (daprodustat – placebo) and associated two-sided 95% CI [Kawaguchi, 2011] will be presented in addition to the one-sided superiority p-value from the van Elteren test. Hodges-Lehmann estimate of the treatment difference (daprodustat-placebo) and associated two-sided 95% CI will be presented. • For the MMRM analysis of change from baseline in Hgb, an LSMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - placebo) at Week 28. The one-sided non-inferiority p-value for this test will be calculated.
Model Results Interpretation
• For the responder analysis, the one-sided CMH p-value will be compared to 0.025 to assess nominal significance. • For the percent time in range analysis, a nominal superiority will be achieved if the lower limit of the two-sided 95% CI is above 0 and the one-sided p-value is < 0.025 • For the MMRM analysis of change from baseline in Hgb, superiority will be achieved if the lower limit of the two-sided 95% CI is above 0 and the one-sided p-value is < 0.025

Time to Rescue

Secondary Efficacy Statistical Analyses: Time to Rescue
Endpoint / Variables
• Time to stopping study treatment due to meeting rescue criteria
Model Specification

• The Cox Proportional Hazards model will adjust for the following baseline categorical values:
  ○ Treatment
  ○ Region (as randomized, see Section 5.3)
• Confidence intervals for the rate per 100 person-years will also be reported. For within-group rates, the two-sided 95% CI will be obtained using an exact Poisson method. For difference in rates between treatments, the two-sided 95% CI will be constructed with a Normal approximation using Wald's method [Liu, 2006].
• Analysis will include only those efficacy endpoints occurring within the time period for treatment discontinuation. Calculation of time-to-event or censoring is described in further detail in Section 10.6.3.
• Time to stopping study medication due to meeting rescue criteria is defined as the time from Randomization until the date on which a participant permanently stops study medication due to meeting criteria for rescue.

Model Results Presentation

• Summaries will include the number and percentage of participants evaluated for rescue by reason in addition to the number and percentage of participants qualifying for each step in the rescue algorithm
• The analysis model results presentation:
  ○ Number (%) of participant permanently stopping randomized treatment due to meeting rescue criteria within each treatment arm
  ○ Number (%) of participant censored
  ○ Incidence rate per 100 person-year and the associated two-sided 95% confidence intervals for each treatment arm
  ○ Hazard ratio and the associated two-sided 95% confidence interval
  ○ One-sided p-value for the test of superiority of daprodustat vs placebo
  ○ Absolute rate difference per 100 person-year and the associated two-sided 95% confidence interval

Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance

Symptoms Severity and Change

Secondary Efficacy Statistical Analyses: Symptom Severity and Change
Endpoint / Variables
• Change from baseline in PGI-S at Week 28 • Mean change from baseline by domain and single items on the Chronic Kidney Disease - Anemia Questionnaire (CKD-AQ) symptom questionnaire
Model Specification
• Scoring for the PGI-S is outlined in Section 10.6.5. • The mean change from baseline in PGI-S score, and each CKD-AQ domain score and each single item score will be analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in means between arms. The models will be fitted to data collected after baseline up to Week 28, using on treatment values and exclude the measures taken after IP discontinuation. The models will include factors for treatment, time, region (See Section 5.3), treatment by time interaction, corresponding baseline score values (i.e. PGI-S, CKD-AQ domains, and CKD-AQ single items in the corresponding model) and the baseline score by time interaction. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.
Model Results Presentation
• PGI-S scores, CKD-AQ domain, and single item scores will be summarized using on treatment mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Change from baseline in PGI-S scores, CKD-AQ domain, and single item scores will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Bar charts displaying mean for the CKD-AQ domain scores will be provided by treatment group by visit. • For the MMRM analyses of change from baseline in PGI-S scores, and CKD-AQ domain scores, an LSMEANS statement will provide adjusted treatment group means and standard errors, a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - Placebo), and a one-sided superiority p-value for this test at Week 28. • Additionally, shift tables by treatment group will be generated that display the number and percentage of participants in each PGI-S category at baseline and the resulting PGI-S category at each scheduled on treatment visit. • Stacked bar charts will be produced by treatment group that display the percentage of participants with each PGI-S response at baseline and Week 28.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance. • Clinically meaningful effects for PRO assessments will be specified in a separate reimbursement RAP.

HRQoL and Utility Score

Secondary Efficacy Statistical Analyses: HRQoL and Utility Score
Endpoint / Variables
• % of participants having an improvement in SF-36 Vitality Domain ≥ 6 from baseline at Week 28 • Mean Change in individual items of the SF-36 Vitality Domain from baseline at Week 28. • Mean Change in SF-36 Physical Function domain from baseline at Week 28. • Change in EQ-5D-5L utility score from baseline at Week 28. • Change in EQ-VAS score from baseline at Week 28.
Model Specification
• For the % of participants having an improvement in SF-36 Vitality Domain ≥ 6 from baseline at Week 28, a Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment and region (see Section 5.3), will be used to make comparisons between the treatment groups. This will be based on the traditional scoring. As in the second principal secondary endpoint, on-treatment SF-36 vitality sub-scores will be used, and exclude the measures taken after IP discontinuation. Subjects with missing SF-36 data will be imputed based on treatment status as described in Section 7.2.5.2. • Scoring for the SF-36 parameters and EQ-5D parameters is outlined in Section 10.6.5. • The mean change from baseline in SF-36 HRQoL scores (individual items of the Vitality Domain, overall score of the Physical Function Domain), EQ-5D-5L score, and EQ-VAS score will be analyzed using an MMRM approach with an unstructured covariance matrix to compare the difference in means between arms. The models will be fitted to HRQoL data collected after baseline up to Week 28, using on treatment values and exclude the measures taken after IP discontinuation. The model will include factors for treatment, time, region (See Section 5.3), treatment by time interaction, corresponding baseline value (HRQoL parameter or utility scores) and the baseline value by time interaction term. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.
Model Results Presentation
• The number and % of participants having an improvement in SF-36 Vitality Domain ≥ 6 from baseline at Week 28, by treatment group, relative response rate (daprodustat vs. placebo) and two-sided 95% CI will be provided along with the one-sided CMH p-value for the treatment group comparison. • SF-36 HRQoL scores (individual items of the Vitality Domain, overall score of the Physical Function Domain), will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Change from baseline in SF-36 HRQoL scores (individual items of the Vitality Domain, overall score of the Physical Function Domain) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits. • Bar charts displaying mean value for the individual items of the Vitality Domain, overall score of the Physical Function Domain will be provided by treatment group and by visit. • EQ-5D-5L responses will be summarized by dimension at all scheduled visits, including the derived end of treatment visit. • EQ-5D-5L and EQ-VAS scores will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits, including the

derived end of treatment visit. • Change from baseline in EQ-5D-5L and EQ-VAS scores will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all scheduled visits, including the derived end of treatment visit. • Bar chart displaying mean scores for the EQ-5D-5L will be provided by treatment group and by visit. • For the MMRM analyses of change from baseline in HRQoL parameters and utility scores, an LSMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - placebo) and a one-sided superiority p-value for this test at Week 28 for the SF-36 HRQoL scores (individual items of the Vitality Domain, overall score of the Physical Function Domain), the EQ-5D-5L and EQ VAS.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance. • Clinically meaningful effects for PRO assessments focused on metrics that would be needed for a reimbursement agency or health technology assessment agency will be specified in a separate reimbursement RAP

Work Productivity and Regular Daily Activity Impairment

Secondary Efficacy Statistical Analyses: Work Productivity and Regular Daily Activity Impairment
Endpoint / Variables
• N (%) of patients currently employed on the WPAI-ANS-CPV • Change from baseline in percent and mean hours work time missed on the WPAI-ANS-CPV • Change from baseline in percent impaired (equivalent) on the WPAI-ANS-CPV • Change from baseline in overall percent work impairment (equivalent) on the WPAI-ANS-CPV • Change from baseline in percent activity impairment on the WPAI-ANS-CPV
Model Results Presentation
• The summary statistics (mean, standard deviation, minimum, P25, median, P75, and maximum) will be provided by treatment group for each of the responses to the WPAI-ANS-CPV at all scheduled on treatment visits. • For the continuous responses to the WPAI-ANS-CPV, the change from baseline will be summarized by treatment group using mean, standard deviation, minimum, P25, median, P75, and maximum at all scheduled visits.

Blood Pressure

Secondary Efficacy Statistical Analyses: Blood Pressure
Endpoint / Variables
• Change from baseline in SBP, DBP, and MAP at week 28 • N (%) with at least one BP exacerbation event during the study
Model Specification
• For the change from baseline in SBP, DBP, and MAP at week 28, a MMRM approach will be used with an unstructured covariance matrix to compare the difference in means between

arms. The models will be fitted to BP (SBP, DBP, and MAP) data collected after baseline up to Week 28. All available on-treatment BP (SBP, DBP, and MAP) data will be used in the model; a subject must have a baseline value and at least one on-treatment assessment to be included in the analysis. The models will include factors for treatment, time, region (see Section 5.3), baseline BP (SBP, DBP, and MAP) and the baseline BP (SBP, DBP, and MAP) by time and treatment by time interaction terms. Analyses will be done with the MIXED procedure in SAS, using the Kenward-Roger option to estimate denominator degrees of freedom and standard errors. • For the % of participants with at least one BP exacerbation event during the study, a Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment and region (see Section 5.3), will be used to make comparisons between the treatment groups. At least one BP exacerbation is defined in Section 10.6.3.
Model Results Presentation
• For the MMRM analyses of change from baseline in BP (SBP, DBP, and MAP) data, an LSMEANS statement will provide adjusted treatment group means and standard errors and a point estimate and two-sided 95% confidence interval for the adjusted mean treatment difference (daprodustat - placebo) and a one-sided superiority p-value for this test at Week 28 for the BP (SBP, DBP, and MAP) data. • The number and % of participants with at least one BP exacerbation event during the study, by treatment group, relative response rate (daprodustat vs. placebo) and two-sided 95% CI will be provided along with the one-sided CMH p-value for the treatment group comparison.
Model Results Interpretation
• One-sided p-values will be compared to 0.025 to assess nominal significance

HRQoL and Utility Score: Additional SF-36 Analyses

Secondary Efficacy Statistical Analyses: SF-36 Vitality
Endpoint / Variables
• Mean Change in SF-36 Vitality domain between baseline and Week 28, utilizing TREAT historical control data
Model Specification

• For the secondary endpoint of mean change in SF-36 vitality sub-score between baseline and Week 28, a hypothetical strategy will be used for the 205270 assuming subjects had not had intercurrent events specified below. Data collected after IP discontinuation will not be included in the statistical analysis and will be treated as missing data. The missing SF-36 vitality sub-scores will be imputed automatically assuming MAR in the dynamic borrowing method.
  ○ The following are the intercurrent events for the second principle secondary efficacy analysis:
  ▪ Death prior to the end of the EP (i.e. before Week 28 visit)
  ▪ Randomized treatment discontinuation prior to the end of the EP
• A hypothetical strategy will also be used for TREAT historical placebo data assuming subjects had not been discontinued from the placebo (i.e. had not been rescued). Data collected after subject's being rescued will not be included in the statistical analysis and will be treated as missing data. The missing SF-36 vitality sub-scores will be imputed automatically assuming MAR in the dynamic borrowing method.

- A covariate-adjusted borrowing method [Han, 2017] will be used to combine the data from this study and the TREAT historical placebo data. The analysis model will be set up as follows:

  $$y_i = y_0 + \beta_C \cdot I_i^C + \beta_h \cdot I_i^h + \alpha_1 \cdot x_1 + \alpha_2 \cdot x_2 + \alpha_3 \cdot x_3 + \alpha_4 \cdot x_4 + \alpha_5 \cdot x_5 + \varepsilon_i$$

  Where y_i is the change from baseline in SF-36 Vitality Sub-score at week 28 for participant i, y_0 is mean change from baseline in SF-36 for the treatment (Dapro) group, β_C and β_h are the regression coefficients for the mean change difference of the current and historical controls over the treatment (Dapro) group respectively. For participant $i, i = 1,2, \dots, N$, participant i belongs to the historical placebo (TREAT) group if $I_i^C = 0$ and $I_i^h = 1$, participant i belongs to current placebo group if $I_i^C = 1$ and $I_i^h = 0$, participant i belongs to the treatment (Dapro) group if $I_i^C = 0$ and $I_i^h = 0$. α_1 is the coefficient for covariate x_1 (baseline SF-36 Vitality Sub-score), and $\alpha_{2, \dots} \alpha_5$ are the coefficients for each region category (using Region 5: US as the reference).
- A Bayesian Hierarchical model will be defined using the above analysis model, where β_C is the parameter of interest. Both β_C and β_h are assumed to have $N(\mu, \tau^2)$, where τ^2 is the variance for the between-trial heterogeneity, which plays a key role in controlling the level of borrowing. As suggested in [Han, 2017], one appropriate form of prior for τ^2 is $\tau^{-2} \sim \Gamma(1, \epsilon)$. $\epsilon = 0.8$ will be used to allow the fair amount of variability between the historical control and the current control while preserving type I error. Details of the simulation settings and results are in a separate document.
- Other priors defined in the model are: $y_0 \sim N(\mu_0, \sigma_0^2)$, $y_i \sim N(\mu_i, \sigma_1^2)$, $\alpha_1, \alpha_2, \dots, \alpha_5, \mu_0, \mu_1 \sim N(0,100)$, $\sigma_0^{-2}, \sigma_1^{-2} \sim \Gamma(0.01, 0.01)$, $x_1 \sim N(\mu_1, \sigma_{x1}^2)$ where $\mu_1 \sim N(0,100)$ and $\sigma_{x1}^{-2} \sim \Gamma(0.01,0.01)$ for baseline SF-36 Vitality Sub-score.
- 10,000 burn in and 20,000 Bayesian iterations will be used.

Model Results Presentation

- For the SF-36 secondary endpoint, the Bayesian empirical mean and standard deviation of the change from baseline will be presented for each treatment arm (i.e. Placebo, Historical Placebo, and Dapro), the Bayesian empirical mean for β_C, will be presented along with one-sided p-value and 95% credible interval. The number of participants contributing to the analysis and the associated mean and standard deviation of the baseline and Week 28 SF-36 Vitality sub-score value will also be displayed with the results of the Bayesian model.
- SF-36 data will be summarized and analysed using both norm-based and traditional scoring, see Section 10.6.5 for details.

Model Results Interpretation

- One-sided p-values will be compared to 0.025 to assess nominal significance

7.4. Exploratory Efficacy Analyses

No statistical testing is planned for exploratory endpoints.

7.4.1. Endpoint / Variables

Exploratory	
Objectives	**Endpoints**
• Further evaluations to compare daprodustat to placebo on Hgb variability	• % of time Hgb is above or below range. • Number (%) of participants with mean Hgb above and below range. • Number (%) of participants with a Hgb<7.5 g/dL • Number (%) of participants with a >2 g/dL increase in Hgb within any 4 week period up to EP • N (%) of participants with a Hgb value ≥ 13 g/dL during the treatment period • Number of times Hgb ≥ 13 g/dL during the treatment period • % of time Hgb ≥ 13 g/dL during the treatment period.
• Further evaluation to compare daprodustat to placebo on Hgb change.	• % of participants who achieved a Hgb increase of ≥1.0g/dL • % of time Hgb increase of ≥ 1.0 g/dL from baseline • % of participant having a Hgb increase of ≥ 1.0 g/dL at each post-baseline visit. • % of participants who achieved and maintained a Hgb increase of ≥1.0g/dL between baseline and EP.
• To compare daprodustat to placebo on measures of iron status and use	• Observed change from baseline in hepcidin, ferritin, transferrin saturation, serum iron, total iron binding capacity (TIBC) • Average monthly oral iron dose/participant (mg) to Week 28 • N (%) of participants who reduced oral iron supplementation from baseline • N (%) of participants requiring IV iron each month. • Average monthly IV iron dose/participant (mg) to Week 28 • Time to first IV iron use, rhEPO and transfusion use

Exploratory	
Objectives	**Endpoints**
	• Summary of frequency and dose of IV iron use, rhEPO and transfusion use
• To compare daprodustat to placebo on renal function	• Estimated Glomerular Filtration Rate (eGFR) observed and change from baseline • Serum creatinine observed and change from baseline • N (%) transitioning to dialysis
• Evaluate the dose adjustment schemes	• Assigned dose by visit • Most recent dose prior to Week 24, Week 28 and End of Treatment • Maximum achieved dose • Number (%) of participants with 0, 1, 2 or >2 dose adjustment • Mean number of dose adjustments • Time dose held for Hgb≥13 g/dL
• To compare daprodustat to placebo on BP medication changes	• N (%) of subjects who had no change, an increase or a decrease in the number of BP medications from baseline to week 28 or final visit for non-completers
• To compare daprodustat to placebo on the severity and change in symptoms	• N(%) of participants within each PGI-C symptom change.
• To compare daprodustat to placebo for improving physical activity (actigraphy)	• Change in percent and mean number of hours of daily activity from baseline. • Change in percent sleep efficiency from baseline.

7.4.2. Planned Exploratory Efficacy Display Details

Hgb Variability

All exploratory Hgb endpoints include those participants on treatment only.

Endpoint/Variables
• % of time Hgb is above or below the target range of 11 to 12 g/dL during the EP and during the treatment period • Number (%) of participants with mean Hgb above, within, and below the Hgb target range during the EP and during the treatment period • Number (%) of participants with a Hgb <7.5 g/dL during the EP and during the treatment period • Number (%) of participants with a >2 g/dL increase in Hgb within any 4-week period up to and including the EP • N (%) of participants with a Hgb value ≥ 13g/dL during the treatment period

- Number of times Hgb ≥ 13 g/dL during the treatment period
- % of time Hgb ≥ 13 g/dL during the treatment period
- N (%) of participants who achieved a Hgb increase of ≥1.0g/dL during the EP
- % of time Hgb increase of ≥ 1.0 g/dL from baseline during the treatment period
- N (%) of participant having a Hgb increase of ≥ 1.0 g/dL at each post-baseline visit.
- N (%) of participants who achieved and maintained a Hgb increase of ≥1.0g/dL between baseline and EP

Planned Exploratory Displays

- The % time Hgb is above or below the Hgb target range (11-12 g/dL) during the EP and during the treatment period will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).
- Number (%) of participants with mean Hgb above, within and below the Hgb target range during the EP and during the treatment period will be summarized by treatment group. This summary will be presented using evaluable Hgb values only (see Section 10.6.3)
- The number and percentage of participants with a Hgb value < 7.5g/dL during the EP and during the treatment period will be summarized by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).
- The number and percentage of participants with a >2 g/dL increase in Hgb within any 4-week period up to and including the EP will be summarized by visit up to Week 28 and overall at Week 28 by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).
- The number and percentage of participants with a Hgb value ≥ 13 g/dL and the number of times a Hgb value ≥ 13 g/dL occurs during the treatment period will be summarized by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).
- The percentage of time Hgb is ≥ 13 g/dL during the treatment period will be calculated using the Rosendaal method [Rosendaal, 1993]. The percentage of time Hgb is ≥ 13 g/dL during the treatment period will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).
- The number and percentage of participants who achieved a Hgb increase of ≥1.0g/dL during the EP will be summarized by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).
- The percentage of time Hgb increase of ≥ 1.0 g/dL from baseline during the treatment period will be calculated using the Rosendaal method [Rosendaal, 1993]. The percentage of time Hgb increase of ≥ 1.0 g/dL from baseline during the treatment period will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).
- The number and percentage of participants who have a Hgb increase of ≥ 1.0 g/dL at each post-baseline visit will be summarized by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).

• The number and percentage of participants who achieved and maintained a Hgb increase of ≥1.0g/dL between baseline and EP will be summarized by treatment group using central laboratory Hgb values and separately using HemoCue Hgb values. To be considered as maintaining Hgb increase ≥1.0g/dL, must have both Week 24 and Week 28 CFB ≥1.0g/dL. This summary will be presented using evaluable Hgb values only (see Section 10.6.3).

Iron Parameters

Endpoint / Variables
• Observed change from baseline in hepcidin, ferritin, transferrin saturation (TSAT), serum iron, total iron binding capacity (TIBC) across all visits • Average monthly oral iron dose/participant (mg) to Week 28 • N (%) of participants who reduced oral iron supplementation relative to baseline [defined as total oral iron (mg) over 4 weeks prior to randomization] during EP [defined as average monthly oral iron dose (mg) over Weeks 24 to 28] and during the treatment period • N (%) of participants requiring IV iron each month. • Average monthly IV iron dose/participant (mg) to Week 28 • Time to first IV iron use, rhEPO and transfusion use • Summary of frequency and dose of IV iron use, rhEPO and transfusion use
Planned Exploratory Displays
• Hepcidin, ferritin, and serum iron on-treatment values will be log-transformed (see Section 5.2.2) and summarized using geometric mean, coefficient of variation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided. • TSAT and TIBC on-treatment values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided. • Percent change from baseline in log-transformed (see Section 5.2.2) hepcidin, ferritin, and serum iron on-treatment values will be summarized using geometric mean, coefficient of variation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided. • Change from baseline in TSAT and TIBC on-treatment values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided. • Average monthly oral or IV iron dose (mg)/participant to Week 28 will be determined by calculating the total elemental oral or IV iron dose per participant from Day 1 to Week 28 while the participant was on randomized treatment and dividing by (the number of days the participant was on randomized treatment/30.4375 days). (see Section 10.6.3) • Average monthly oral iron dose/participant and average monthly IV iron dose/participant at baseline, and while on treatment to Week 28 will be summarized by treatment group (see Section 10.6.3). Summaries will include mean, standard deviation, minimum, P25, median,

P75, and maximum by treatment group.

- The number and percentage of participants that reduced oral iron supplementation relative to baseline during the EP and during the treatment period while on treatment will be summarized by treatment group (see Section 10.6.3).
- The number and percentage of participants who required IV iron during study treatment (day 1 to week 28) will be summarized by treatment group.
- Time to first IV iron use, rhEPO and transfusion use is defined as the time from Randomization until the date on which a participant received IV iron, rhEPO, or transfusion use for the first time after Randomization. Time to first IV iron use will use on-treatment values only, while time to first rhEPO and transfusion use will use both on-treatment and on/off-treatment values post-randomization. First rhEPO use differs from rescue, there may be instances of rhEPO being given but participants not rescued. The Number (%) of participant received IV iron, rhEPO and transfusion use within each treatment arm will be summarised with mean, standard deviation, minimum, P25, median, P75, and maximum of the time to first IV, rhEPO and transfusion use by treatment group.
- The frequency and dose of IV iron use, rhEPO and transfusion use will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group.
- A listing of all IV iron use, rhEPO and transfusion use during the study will be provided. This listing will include treatment, site ID, unique subject ID, select demographic information, frequency and dose of IV iron use, frequency and dose of rhEPO use, and frequency of transfusions.

Renal Function

Endpoint / Variables

- Estimated Glomerular Filtration Rate (eGFR) observed and change from baseline
- Serum creatinine observed and change from baseline
- N (%) transitioning to dialysis

Planned Exploratory Displays

- eGFR and serum creatinine on-treatment values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group. Graphical summaries will be provided.
- Change from baseline in eGFR and serum creatinine on-treatment values will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum for each scheduled visit by treatment group and by subgroup ADPKD. Graphical summaries will be provided.
- Number (%) of participants transitioning to dialysis will be summarized by treatment group.

Dose Adjustment Scheme

Endpoint / Variables
• Assigned dose by visit • Most recent dose prior to Week 24, Week 28 and end of study treatment • Maximum achieved dose • Number (%) of participants with 0, 1, 2, or >2 dose adjustments during the treatment period • Mean and median number of dose adjustments during the treatment period • Time dose held for Hgb ≥13 g/dL during the treatment period
Planned Exploratory Displays
• The assigned dose by visit will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. • The most recent dose prior to Week 28 and end of treatment will be summarized by the number and percentage of participants at each dose level. • The maximum achieved dose will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. • The number and percentage of participants with 0, 1, 2, or >2 dose adjustments will be summarized by treatment group during the treatment period. This summary will be produced twice – the first time counting all dose adjustments, including adjustments related to periods of dose holds (i.e., no study treatment is given), the second time excluding dose adjustments related to periods of dose hold. • The time (in days) that study treatment was withheld for Hgb values ≥ 13 g/dL per participant will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum during the treatment period.

Blood Pressure

Endpoint / Variables
• N (%) of subjects who had no change, an increase or a decrease in the number of BP medications from baseline to week 28 or final visit for non-completers
Planned Exploratory Displays
• Summary table listing the N (%) of subjects in each treatment group who have no change, an increase or a decrease in the number of BP medications from baseline to week 28 or final visit for non-completers. Summary to include: o For subjects who have no change in the number and class of blood pressure medications taken between baseline and Week 28. o For subjects who have the same number of blood pressure medications taken at baseline and Week 28, but a change in the class o For subjects who have an increase in the number of blood pressure medications taken between baseline and Week 28 o For subjects who have a decrease in the number of blood pressure medications taken

between baseline and Week 28 ▪ If a subject has an increase and then a decrease (or vice versa) in the number of blood pressure medications taken, for reporting purposes that subject will be categorized as having an increase in the number of medications and they will appear in the increase table above.

Severity and Change in Symptoms

Endpoint / Variables
• N(%) of participants within each PGI-C symptom change.
Planned Exploratory Displays
• Scoring for the PGI-S is outlined in Section 10.6.5. The number and percentage of participants in each PGI-C category at each scheduled on treatment visit will be summarized.

Physical Activity (Actigraphy)

Endpoint / Variables
• Change in percent and mean number of hours of daily activity from baseline. • Change in percent sleep efficiency from baseline. • Wear time of actigraphy device
Planned Exploratory Displays
• The on treatment percentage of daily light, moderate, vigorous, very vigorous, and moderate to vigorous physical activity (MVPA) activity at each Actigraphy collection period will be defined as the average percentage of daily light, moderate, vigorous, very vigorous, and MVPA activity during the collection period. • The on treatment mean number of hours of daily light, moderate, vigorous, very vigorous, and MVPA activity at each Actigraphy collection period will be calculated as the average number of hours of daily light, moderate, vigorous, very vigorous, and MVPA activity during the collection period. • The on treatment percentage and mean number of daily light, moderate, vigorous, very vigorous, and MVPA activity, the percent sleep efficiency, and wear time will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all Actigraphy collection periods. • Change from baseline in the on treatment percentage and mean number of daily light, moderate, vigorous, very vigorous, and MVPA activity, the percent sleep efficiency, and wear time will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum by treatment group at all Actigraphy collection periods.

7.5. Pharmacogenetics Analyses

Blood samples will be collected as outline in the Schedule of Activities Table in Section 10.2.1 for potential future pharmacogenetics (PGx) analysis of the response to daprodustat (GSK1278863). If PGx analysis is pursued, details will be included in a separate RAP.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified. The details of the planned displays are provided in Appendix 10: List of Data Displays.

Objectives	Endpoints
Safety	
• To compare the safety and tolerability of daprodustat to placebo	• Incidence and severity of AEs and serious adverse events (SAEs) including AEs of special interest and adjudicated MACE (composite of all-cause mortality, non-fatal MI and non-fatal stroke) • Reasons for discontinuation of study treatment • Absolute values and changes from baseline in laboratory parameters, Blood Pressure (BP) and heart rate (HR)

8.1. Adjudicated MACE

Adjudicated MACE comprises of all-cause mortality, non-fatal MI and non-fatal stroke.

A summary of the number and percentage of participants having first-occurrence MACE will be provided by treatment group. The number and percentage of the types of events that make up the first occurrence of MACE will also be provided by treatment group.

A summary of all MACE including the number and percentage of participants and number of events (including first and subsequent MACE) by type of event will be provided by treatment group.

Summaries will be produced for all adjudicated MACE and separate summaries for a category of all Adjudicated MACE or Thromboembolic Events or Hospitalization for HF

A listing of all MACE events occurring during the study will be provided and will include treatment, site ID, unique subject ID, select demographic information, event type, event date, and study day.

8.2. 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. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. See Section 10.4.2 for AE treatment state definitions.

The analyses of the CEC-adjudicated MACE have been described in Section 8.1. However, AE summaries will also include the AEs and SAEs associated with the adjudicated events listed below:

- All-cause mortality (CV and non-CV mortality)
- Non-fatal MI
- Non-fatal stroke

For the purpose of AE summaries, the investigator-reported AE details will be used, regardless of the adjudication outcome of the event, unless otherwise specified.

AESIs

Adverse events of special interest and exposure-adjusted AE incidence rate calculation are described in Section 10.6.4.

Summaries of AESIs will include the number, percentage, and exposure-adjusted AE incidence rate per 100 person-years of subjects having at least one occurrence, the number of events, the number of subjects by number of occurrences, the characteristics of the AE (serious, drug-related, etc.), outcome, maximum intensity, time to first onset/worsening, and action taken summarized by treatment group. For each count, a subject 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

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.

Adverse Events

The number, percentage, and exposure-adjusted AE incidence rate per 100 person-years 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. Similarly, the number and percentage of participants reporting at least one follow-up AE will be summarized by treatment group, primary system organ class, and preferred term.

In addition, all treatment emergent AEs will be summarized by treatment group, primary system organ class, higher level term and preferred term. In addition to generating number and percentage of subjects with treatment emergent SAEs, relative risk and 95% Wald confidence intervals will be presented for each HLT and PT as described in Section 10.6.4.

Summaries of all treatment emergent AEs will be produced for the following subgroups - age group, gender, race group, and weight quartile- by treatment group, primary system organ class, and preferred term.

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 ≥ 5% of participants in any treatment group) will be summarized by preferred term and treatment group.

The number and percentage of participants reporting treatment emergent AEs assessed by the investigator to be related to the study drug (termed as drug-related hereafter) will be summarized by treatment group, primary system organ class, and preferred term.

The number and percentage of participants reporting treatment emergent AEs by maximum intensity will be summarized by treatment group, primary system organ class, and preferred term.

The number and percentage of participants reporting treatment emergent drug-related AEs by maximum intensity will be summarized by treatment group, primary system organ class, and preferred term.

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.

The number and percentage of participants and the number of occurrences of common non-serious treatment emergent adverse events (those occurring in ≥ 5% of participants in any treatment group) will be summarized by primary system organ class, preferred term, and treatment group.

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

Serious and Other Significant Adverse Events

The number and percentage of participants and the number of occurrences of treatment emergent SAEs will be provided for each treatment group. These events will be summarized by treatment group, primary system organ class, and preferred term. Follow-up SAEs will be summarized similarly.

Additionally, a tabular display of exposure-adjusted AE incidence rate per 100 person-years of participants reporting at least one SAE will be produced by treatment group, primary system organ class, and preferred term.

All treatment emergent SAEs will also be summarized by treatment group, primary system organ class, higher level term and preferred term. In addition to generating number and percentage of subjects with TE SAEs, relative risk and 95% Wald confidence intervals will be presented for each HLT and PT as described in Section 10.6.4.

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

The number and percentage of participants with treatment emergent drug-related SAEs will be summarized by treatment group, primary system organ class and preferred term.

The number, percentage, and exposure-adjusted AE incidence rate per 100 person-years of participants with fatal AEs will be provided for each treatment group. These events will be summarized by treatment group, primary system organ class, and preferred term.

Additionally, the number and percentage of participants with treatment emergent serious, fatal and non-fatal, drug-related AEs will be summarized by treatment group and overall frequency.

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

The number, percentage, and exposure adjusted AE incidence rate per 100 person-years 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.

A listing of other significant adverse events will be produced. Other significant adverse events are events that are not reported as fatal or serious but represent ICH-defined 'Other significant adverse events' (i.e., marked haematological and other laboratory abnormalities or led to an intervention, dose reduction, or significant additional concomitant therapy). For this study, other significant AEs will be defined as non-fatal non-serious AEs resulting in an action taken with study treatment of either 'dose interrupted/delayed' or 'dose reduced'.

8.3. Clinical Laboratory Analyses

Clinical chemistry, hematology and other laboratory tests are assessed in this study according to the schedule outlined in the Schedule of Activities (see Section 10.2.1) 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
			Basophils
Clinical Chemistry [1]	Sodium (serum)	Aspartate aminotransferase (AST)	Carbon Dioxide (total)
	Potassium (serum)	Alanine aminotransferase (ALT)	Albumin
	Calcium (total and albumin-adjusted)	Inorganic phosphate	Urea (serum)
	Creatinine (serum)	Bilirubin (total and direct/indirect)	Chloride (serum)
	eGFR		
Iron parameters	Iron (serum)	Ferritin	UIBC
	Hepcidin	TIBC	TSAT
Lipid parameters	Total cholesterol	LDL-C (direct)	HDL-C
Other laboratory tests	Urine/serum hCG pregnancy test [2,3]	FSH [4]	Estradiol [4]
	HemoCue Hgb	hsCRP	

WBC, white blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width, AST, aspartate transaminase; LDL-C, low density lipoprotein-C; HDL-C, high density lipoprotein-C; TIBC, total iron binding capacity; hCG, human chorionic gonadotropin; FSH, follicle-stimulating hormone.

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 6 the protocol.
2. For women of childbearing potential only.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC, and for participants who transition to dialysis during the study.
4. Screening only. As needed for postmenopausal women when their menopausal status is in doubt. See Inclusion Criteria Section 6.1 of the protocol.

Summaries of central laboratory Hgb values, HemoCue Hgb values, iron parameter values (serum iron, ferritin, hepcidin, TIBC, TSAT) are included in earlier efficacy sections and will not be included with clinical laboratory displays. However, these parameters may be included in PCI summaries.

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 10.2.1), 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 10.5.2 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 10.8.1.

All of the tabular summaries described below will include summaries in SI units; conventional units will also be provided for the following laboratory tests: hemoglobin, MCHC, total calcium, albumin-adjusted calcium, inorganic phosphate, albumin, urea, total cholesterol, LDL-C, HDL-C, and eGFR. Conversions from SI units to conventional units are included in Section 10.6.4.

eGFR equation is outlined in Section 10.6.4.

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 10: List of Data Displays.

8.4. Other Safety Analyses

Electrocardiograms (ECGs) will be read locally and ECG data will not be included in summary tables or individual participant listings.

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 10: List of Data Displays.

Vital signs are assessed in this study according to the schedule outlined in the Time and Events table (see Section 10.2.1) and include the following assessments:

- SBP
- DBP
- HR

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

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. Graphical summaries may be provided.

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

A listing of all vital signs data for participants with on-treatment vital signs values outside of PCI criteria will be provided.

Reasons for stopping randomized treatment and for early study withdrawal will also be summarized by treatment group and time to stopping treatment or study will be presented graphically and assessed.

The following COVID-19 related displays will be provided.

A summary of the number and percentage of subjects for the following assessments will be produced: Case Diagnosis, COVID-19 Test performed, and Results of the COVID-19 test.

Summaries of characteristics of COVID-19 AEs will include the number, percentage of subjects having at least one occurrence, the outcome, maximum intensity, and the duration of the AE summarized by treatment group. For each count, a subject will be summarized as follows:

- Outcome: The subject 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 subject will be counted in the ‘severe’ category if there is at least one specific AE with severe intensity. A subject 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.
- Duration of the occurrence (days): AE resolution date – AE onset date/AE worsening date + 1 for the occurrence
- A summary of exposure adjusted incidence rates over time (see Section 10.6.4) will be produced for Any AE, Any SAE, and Any Severe AE. The summary will be produced overall, by Country, Region, Sex, and by Age at randomization (Grouping 2). A summary of exposure adjusted incidence rates will also be produced for Common (>5%) AEs by time blocks.

9. REFERENCES

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10. APPENDICES

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

No per protocol population is defined in this RAP.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

Table 2 Schedule of Activities

Protocol activity (visits ±1 week) (Note: All visit timings are relative to Day 1)	Screening Week -4[1]	Screening Week -2	Treatment Period: Day 1 through Week 28						Follow-up Visit (4 weeks post treatment)
			Day 1	Week 2	Full study visit Week 4, 16	Abbreviated study visit Week 8, 12, 20, 24	Week 28	Unscheduled	
Informed Consent	X								
Assess eligibility	X		X						
IRT system call	X	X	X	X	X	X	X	X	X
Birth Year (demography)	X								
History: medical, hospitalization, height, weight		X	X[2]						
SBP/DBP and HR [3]		X	X (triplicate)	X	X		X(triplicate)	X	X
ECG		X[4]					X		
Ultrasound of kidney and adrenal glands (if able to be visualized)		X[5]					X[15]		
Anemia therapy[6]	X		X		X	X	X	X	X
Rescue medication [7]					X	X	X	X	
Review concomitant medications		X	X	X	X	X	X	X	X
Females only: estradiol and FSH (if required and only for women whose menopausal status is unclear)		X							
FRP only: urine pregnancy test[8]		X	X		X	X[16]	X		X
HemoCue Hgb	X		X (Duplicate)[9]	X	X	X	X	X	
Hematology [10]	X		X		X	Hgb only	X	X	X
Clinical chemistry [10]	X		X		X		X	X	X
Iron Panel [10]	X		X		X[11]		X	X	X
Hepcidin			X		X		X		
Lipids (non-fasting)			X				X		
hsCRP			X				X		
Distribution of participant reminder tool[12]			X						
Adverse Event Assessment	X[13]	X[13]	X	X	X	X	X	X	X

Protocol activity (visits ±1 week) (Note: All visit timings are relative to Day 1)	Screening Week -4[1]	Screening Week -2	Treatment Period: Day 1 through Week 28						Follow-up Visit (4 weeks post treatment)
			Day 1	Week 2	Full study visit Week 4, 16	Abbreviated study visit Week 8, 12, 20, 24	Week 28	Unscheduled	
Genetic Sample [14]			X						

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ECG, electrocardiogram; FSH, follicle stimulating hormone; FRP, Females of Reproductive Potential; WOCBP, woman of childbearing potential; hCG, human chorionic gonadotropin; UIBC, unsaturated iron binding capacity; hsCRP, high sensitivity C-reactive protein, serious adverse events (SAEs).

1. If participants does not meet eligibility criteria during/after Week -4, then Week -2 visit should not be conducted.
2. Only history related to medical and hospitalization will be re-checked on Day 1 to confirm eligibility prior to randomization.
3. SBP/DBP, HR (single readings unless otherwise indicated)
4. ECG can be conducted at Week -2 visit or at Day 1 prior to randomization.
5. Ultrasound of the kidneys and adrenal glands must be performed prior to randomization. The screening period may be extended up to 2 weeks if needed. A documented ultrasound of the kidneys within the 6 months prior to screening may be used to assess entry criteria provided the size and cyst category has been reported. If a more sensitive imaging study [e.g., magnetic resonance imaging (MRI), computed tomography (CT)] has been performed within this timeframe and a report is available, this may be used in place of the ultrasound. See Section 9.5.4 of protocol.
6. Record historical and current anemia therapy in eCRF, if applicable.
7. See details on rescue in Section 7.7.2 of protocol.
8. Repeat pregnancy test prior to study treatment re-administration if it is interrupted for >7 days and there was also a lapse in contraceptive use, regardless of the reason for the interruption. If a participant becomes post-menopausal (as defined in Section 12.4 of protocol) during the study, pregnancy tests are no longer required.
9. Participant are eligible for randomization if the initial HemoCue Hgb assessment is from 8.5 to 10.0 g/dL. Repeat a HemoCue Hgb assessment and use the average of the two values for randomization only if the initial assessment is from 10.1 to 10.3 g/dL, or if the initial assessment is from 8.2 to 8.4 g/dL. All HemoCue Hgb assessments, starting after Day 1 to end of treatment visit, should be conducted at the end of the study visit, only prior to study medication or rescue medication dispensation.
10. See details on hematology, clinical chemistry and other laboratory assessments in Section 9.5.5 of protocol.
11. Ferritin, total iron and UIBC will be assessed at Week 16, but not at Week 4.
12. Participants will be given a reminder tool (at Day 1) and instructed to promptly inform site staff of any health changes. Health changes include new symptoms or medical problems (e.g., pregnancy, hospitalizations) and changes in medication.
13. Only SAEs assessed as related to study participation or a GSK product are collected at this visit. See Section 9.3.1 of protocol for additional details
14. Informed consent for optional Genetic research should be obtained before collecting a sample. To minimize potential study bias, the genetic sample should be collected on Day 1.
15. France sites only (to be performed after the End of Study visit and prior to the Follow-up visit).
16. For Argentinian sites **only** and only in WOCB

Table 3 Schedule of Activities for Participant Reported Outcomes and Actigraphy

Protocol Activity (visits ±1 week) (Note: All visit timings are relative to Day 1)	**Screening Week -4**	**Week -2**	**Treatment Period: Day 1 through Week 28**								**Follow-up Visit**
			Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	
Dispense Actigraphy Device		X		X	X				X		
Actigraphy (wearable)[1,5,6]			X		X	X				X	
Participant Global Impression of Severity (PGI-S)[2,3]		X	X		X	X				X	
Participant Global Impression of Change (PGI-C)[2,3]					X	X				X	
Symptoms of aCKD questionnaire2		X	X		X	X				X	
Short Form 36 (SF-36)[2,3]			X		X	X				X	
EuroQol 5 Dimension 5 Level Health Utility Score (EQ-5D-5L) and EuroQol Visual Analogue Scale (EQ-VAS) [2,3,4]			X		X	X				X	
Work Productivity and Activity Impairment Questionnaire (WPAI-ANS-CPV) [2,3]			X		X	X				X	

1. Actigraphy device should be worn for 7 days prior to the study visits indicated in Table 3 and as described in Section 9.7 of protocol. Data will be downloaded from device during the study visits indicated in Table 3.
2. Participant reported outcomes questionnaire should be completed as the first assessment, prior to conducting any other visit assessments (e.g. Adverse event assessment, HemoCue Hgb, etc.)
3. Participants who are unable to or require assistance to read must not complete the questionnaires
4. Only in selected countries. See Section 12.8 (Appendix 8) of protocol.
5. Sites can contact participants to wear the actigraphy device 7 days prior to study visit.
6. All efforts should be made to encourage participation in this activity monitoring assessment. If a participant is unable to take part, the reason should be documented, and they may continue in the study.

Table 4 Schedule of Activities for Participants Permanently Discontinuing Study Treatment

Protocol Activity (Note: All visit timings are relative to Day 1)	Early Treatment Discontinuation Visit (within 2 weeks of discontinuing study treatment)	Day 1 through Week 28		
		Week 4, 16, 28 ± 2 weeks	Week 24	Unscheduled
IRT system call	X	X	X	X
SBP/DBP, HR	X (Triplicate)			X
ECG	X			
Rescue medication [1, 2]	X	X	X	
Urine (serum if transitioned to dialysis) pregnancy test (WOCBP only)	X [7]			
HemoCue Hgb	X	X	X	X
Hematology[3]	X	X	Hgb Only	
Clinical chemistry[3]	X	X		
Iron Panel	X			
Hospitalization[1] , transition to dialysis[1]	X	X	X	X
hsCRP	X			
Adverse event assessment	X	X	X	X
Review concomitant medications	X	X	X	X
Actigraphy [4]	X[9]	X		
CKD-AQ [8]	X	X		
PGI-S, PGI-C [8]	X	X		
SF-36 [8]	X	X		
EQ-5D-5L& EQ-VAS [6, 8]	X	X		
WPAI-ANS-CPV [5, 8]	X	X		

1. Record in eCRF, if applicable.
2. See details on rescue in Section 7.7.2 of protocol.
3. See details on hematology and clinical chemistry in Section 9.5.5 of protocol.
4. Actigraphy device should be worn for 7 days prior to the study visit indicated in Table 4 and as described in Section 9.7 of protocol. Data will be downloaded at the Discontinuation Visit.
5. If local dialect or language is available.
6. Only in selected countries. See Section 12.8 (Appendix 8) of protocol.
7. Additional pregnancy test required at subsequent visit. Must be at least 4 weeks after the end of randomized treatment.
8. Participants who are unable to or require assistance to read must not complete the questionnaires.
9. If actigraphy device is available, participants should be instructed to wear actigraphy device for up to 7 days prior to early treatment discontinuation visit.

10.3. Appendix 3: Assessment Windows

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 time of occurrence relative to the treatment start and stop dates and last non-zero dose date (see Section 10.6.1).

10.4.1.1. Treatment States for Hgb, Iron Parameters, Transfusion and PRO Data

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

10.4.1.2. Treatment States for BP, Lipid Parameters, Clinical Chemistry, Hematology, Other Laboratory Tests, Hepatobiliary (Liver) and Vital Signs Data

Treatment State	Definition
Pre-Treatment	Date ≤ Treatment Start Date
On-Treatment	Treatment Start Date < Date ≤ Last Non-Zero Dose Date + 1 day
Post-Treatment	Date > Last Non-Zero Dose 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

10.4.1.3. 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———						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

10.4.2. 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 until the follow-up visit at the time points specified in the SoA from Appendix 10. 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 participants 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.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

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 3.6.1 may be used for analysis and the production of graphics.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: gsk1278863/mid205270
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

Reporting Standards
General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant 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. • 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 randomization will be used in figures, summaries, statistical analyses and

Reporting Standards
calculation of any derived parameters, unless otherwise stated. • All scheduled visits, regardless of deviation from the planned assessment times and/or scheduled visit days will be used in tables, figures and formal statistical analyses unless otherwise stated. • The derived end of treatment value (see Section 10.6.1) will also be included in displays of data by visit. • 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 participant's listings. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables, with the following exceptions: • If the table includes a row for all post-baseline assessments, unscheduled visits will be included in this row. • Some Hgb endpoints will include unscheduled Hgb values (See Section 10.6.3) • Unscheduled visits will not be included in figures, with similar exceptions: • If the figure includes a data value for all post-baseline assessments, unscheduled visits will be included in this value. • Some Hgb endpoints will include unscheduled Hgb values (See Section 10.6.3) • 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.
Adjusted Means
SAS option OBSMARGINS will be used to generate all adjusted mean values, e.g. LSMEANS statement in relevant SAS procedures will include the OBSMARGINS option (or OM as an abbreviation), to weight least square means coefficients of the categorical variables in the model to be proportional to those found in the input dataset.

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

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.   ○ Triplicate BP and HR measurements, duplicate HemoCue Hgb are expected at certain time points (See Section 10.2.1) • 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.
Randomization Date
• Date participant 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

Treatment Start Date
• First randomized treatment dose start date
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.

General
Treatment Stop Date
• Calculated as the latest randomized treatment dose stop date. • The eCRF does not allow for the possibility of missing or partial dates to be recorded for the dose stop date on the study treatment form
End of Treatment Value
• Only defined for participants with a non-missing treatment start date • Hgb, iron parameters, oral iron, PRO and Actigraphy: the latest value on or before the treatment stop date + 1 day. Blood pressure, central laboratory, and vital signs parameters: the latest value on or before the last non-zero dose date + 1 day, or if the last non-zero dose date is missing, the study completion date for participants who have a non-missing treatment start date.
Study Completion/Withdrawal Date
• Date of withdrawal for participants withdrawing (i.e., participants who actively withdraw or are deemed lost to follow-up) from study or date of completion of study for participants who complete the study. • Note: Participants who die while on study are considered as having completed the study
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

First Study Contact Date
• First study contact with the participant while on the study
Last Study Contact Date
• Last study contact with participant (clinic, telephone or other contact with participant) with the participant while on the study
Time Definitions (per GSK standard principles)
• 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days
Production of Two-Sided p-values
• The majority of the efficacy and safety analyses in this study will use one-sided 2.5% p-values assess statistical significance. Should two-sided p-values be required for publication purposes after the study is complete, the corresponding two-sided p-values will be produced at that time.

10.6.2. Study Population

Demographics
Age
• Only year of birth will be collected in this study for privacy protection reasons. The day and month of the DOB will not be collected for any site. • GSK standard IDSL algorithms will be used for calculating age where birth month and date will be set to "30th June." • Birth date will be presented in listings as 'YYYY'.

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 participants who have more than one Asian category selected, but no other categories. White – Mixed Race includes participants who have more than one White category selected, but no other categories.

Randomized Treatment Discontinuation, Study Withdrawal, and Possible Follow-up Time
Randomized Treatment Discontinuation
• Randomized Treatment Discontinuation Censored Time (days) = Treatment stop date – Randomization date +1 Note: In the case where a participant on randomized treatment is lost to follow-up, a final treatment stop date is presumed, though unobserved. In this case, the last point of contact of the participant is used for both the treatment stop date and withdrawal date. In the case where a participant on randomized treatment dies and has a missing treatment stop date, the date of death or imputed date of death (see Section 10.7.2.1) will be used for the treatment stop date.
• Time to Randomized Treatment Discontinuation (days) = Treatment stop date – Randomization date +1
• Randomized Treatment Person Years = (Cumulative total of time to randomized treatment discontinuation for participants who discontinued randomized treatment + Cumulative total of randomized treatment discontinuation censoring time for participants who did not discontinue randomized treatment) / 365.25
• Randomized Treatment Discontinuation Incidence Rate (per 100 person years) = 100* Number of participants who discontinued randomized treatment / randomized treatment person years
Study Withdrawal
• Study Censored Time (days) = Study completion date – Randomization date +1
• Time to Study Withdrawal (days) = Study withdrawal date – Randomization date +1
• Study Person Years = (Cumulative total time to study withdrawal for participants withdrawing from the study + Cumulative total of study censoring time for participants who did not withdraw from study) / 365.25
• Study Withdrawal Incidence Rate (per 100 person years) = (100 * Number of participants who have withdrawn from study) / 365.25

Treatment Compliance

- Compliance will be calculated based on data recorded in the Study Treatment Details eCRF pages and will only be calculated for participants with a non-missing treatment start date, and will not be calculated after a participant's treatment stop date, or study conclusion date for participants who have a non-missing treatment start date and a missing treatment stop date.
- A compliance % will be calculated to each randomized treatment exposure record according to the following formula.
    - Daprodustat/Placebo Doses

      Compliance for each participant is calculated as the average of the compliance per bottle. The compliance per bottle is calculated as 100% * [# dispensed – (# returned + # lost)] / (dose stop date – dose start date +1)
- Exposure records corresponding to periods of dose hold/zero-dose as assigned by the IRT will be assigned as 100% compliance, and any gaps between exposure records will be assigned as 0% compliance.
- Under compliance is defined as < 80%
- Compliant is defined as >= 80% and <= 120%
- Over compliant is defined as > 120%

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)
    - For example, if for a given visit a subject is given three bottles with doses of 4mg, 8mg, and 0mg, this subjects dose for that visit is = 4+8+0=12mg

ADPKD Subgroup

- The ADPKD subgroup consists of participants who have Autosomal Dominant Polycystic Kidney Disease, as recorded in the Medical History page of the eCRF
- The non-ADPKD subgroup consists of the participants who are not in the ADPKD subgroup.

10.6.3. Efficacy

Hemoglobin Values

Central Laboratory and HemoCue Hgb Values

- When source of Hgb measurement is not specified:
    - For reporting purposes, central laboratory Hgb values will be used, unless otherwise specified. However, if a central laboratory Hgb value is missing, a corresponding non-missing HemoCue Hgb value will be used.
- Multiple HemoCue Hgb values at a single visit:
    - The dose adjustment algorithm will require sites to obtain two HemoCue Hgb values at some visits. In the case where two HemoCue Hgb values are obtained at a visit, the average of the two measurements, which will be rounded to the nearest 10th decimal place, should be used as the HemoCue Hgb value for that visit.

Hemoglobin Values
Evaluable Hemoglobin Values
• Evaluable Hgb values are on-treatment Hgb values (see Section 10.4.1) that are not taken within the 8 weeks following a red blood cell transfusion, a whole blood transfusion, or a nonrandomized ESA treatment which occurs on or after the randomization date.
Evaluation Period (EP) Hemoglobin Value for Primary Hgb Analysis
• For each participant, the mean of all available (on and off treatment) Hgb values for Week 24 through Week 28, inclusive, including any unscheduled Hgb values that were taken during this time period.
Evaluation Period (EP) Hemoglobin Value for On-drug Hgb Supportive Analysis
• For each participant, the mean of all evaluable Hgb values for Week 24 through Week 28, inclusive, including any unscheduled Hgb values that were taken during this time period.
Imputed Hemoglobin Values
• For each missing value between baseline to Week 28 (inclusive), 200 imputed values will be generated using the multiple imputation method (see Section 7.1.2). The average of these 200 imputed values will be used as the value for this missing value in the summary tables and figures. • For the primary efficacy Hgb analysis and the corresponding subgroup analyses using all available observed and imputed Hgb values (on and off-treatment), Rubin's rules [Rubin, 1987] will be used to combine results of the imputed datasets using SAS PROC MIANALYZE procedure.

Time In Range
Time in Range During the EP
• Number of days that a participant's Hgb is within the analysis range of 11-12 g/dL, or >=13 g/dL, or increase of ≥ 1.0 g/dL from baseline inclusive for Week 24 through Week 28 inclusive, including any unscheduled evaluable Hgb values. • If Hgb is missing, linear interpolation is used to estimate Hgb between visits, accounting for any intermittent missing values (Rosendaal, 1993).
Percent Time in Range During the EP
• Time in Range During the EP / [Earlier of (Treatment Stop Date, Week 28 visit date) – Week 24 visit date + 1] • Note: Percent time in/below/above range during the EP is only defined for subjects with a Treatment Stop Date that is on or after their Week 24 visit date, and have at least two evaluable Hgb values on different days, where at least one evaluable Hgb value is contained within the EP and another evaluable Hgb value occurs within the range of the Week 12 visit through Week 28 visit, inclusive.
Time in Range During the Treatment Period
• Number of days that a participant's Hgb is within the analysis range of 11-12 g/dL, or >=13 g/dL, or increase of ≥ 1.0 g/dL from baseline inclusive for Day 1 through Week 28 inclusive, including any unscheduled evaluable Hgb values. • If Hgb is missing, linear interpolation is used to estimate Hgb between visits, accounting for any intermittent missing values (Rosendaal, 1993).
Percent Time in Range During the Treatment Period
• Time in Range During the Treatment Period / [Earlier of (Treatment Stop Date, Week 28 visit date) – Day 1 visit date + 1]

Time to Stopping Randomized Treatment Due to Meeting Rescue Criteria
Event Date
• Treatment stop date when the primary reason and subreason for randomized treatment stop are: ○ Primary reason: Participant reached protocol-defined stopping criteria

Time to Stopping Randomized Treatment Due to Meeting Rescue Criteria
○ Subreason: Rescue
General Definitions
• Time to event (days) = date of event – randomization date +1 • Censored time (days) = censoring date – randomization date + 1
• Rescue person years = (cumulative total time to stopping randomized treatment for participants who stopped randomized treatment due to meeting rescue criteria + cumulative total of censoring time for participants who did not stop randomized treatment due to meeting rescue criteria) / 365.25 • Rescue incidence rate (per 100 person years) = (100 * number of participants who stopped randomized treatment due to meeting rescue criteria) / rescue person years • Rescue absolute rate difference (per 100 person years) = daprodustat rescue incidence rate (per 100 person years) – placebo rescue incidence rate (per 100 person years)
Time Period for Treatment Discontinuation
The period for treatment discontinuation begins at randomization. The end of this time period is defined as follows: • For participants who did not take randomized treatment, use the date of randomization • For participants whose treatment stop date is missing and who took randomized treatment, use study conclusion date • For participants either continuing on study past treatment stop date or completing/withdrawing on the same day as treatment stop date, use treatment stop date Any events that occurred before the start of this time period are considered to be prior to the time period for treatment discontinuation, and any endpoints that occurred after the end of this time period are considered to be post the time period for treatment discontinuation.

Iron Endpoints
TIBC
• TIBC will be calculated automatically by the central laboratory using: ○ TIBC = UIBC + total iron
TSAT
• TSAT will be calculated automatically by the central laboratory using: ○ TSAT = 100 * (Serum Iron/TIBC)
Oral Iron
• Elemental oral iron dose will be derived based on CMTERM and dose
Baseline Average Monthly Oral Iron
• Baseline monthly oral iron dose will be defined as total oral iron (mg) over the 4 weeks prior to randomization.
Average Monthly Oral Iron from Randomization to Week 28
• The calculation of the average monthly oral iron from Randomization to Week 28 will follow the calculation of the average monthly IV iron from Randomization to Week 28 in Section 10.6.3 below.
Average Monthly Oral Iron from Week 24 to Week 28
• The calculation of the average monthly oral iron from Week 24 to Week 28 will follow the calculation of the average monthly IV iron from randomization to Week 28 in Section 10.6.3 below, except randomization date will be replaced with Week 24 date.
Reduction in Oral Iron Supplementation
• A reduction in Oral iron supplementation relative to baseline occurs when Baseline average monthly oral

Iron Endpoints

iron > EP average monthly oral iron, when both baseline oral iron and EP average monthly oral iron are non-missing.

Baseline Average Monthly IV Iron

- Participants may receive up to one IV iron dose within the 8 weeks prior to screening and no IV iron use between screening visit and randomization (Day 1)
- If no IV iron was used within the 8 weeks prior to screening, the baseline monthly IV iron dose is 0; otherwise the recorded one IV iron dose is the baseline monthly IV iron dose.

Average monthly IV iron from Randomization to Week 28

- In order to calculate the average monthly IV iron dose from Randomization to Week 28, the dose of IV iron will be standardized to obtain a continuous single unit IV iron dose in terms of mg/month for the period from the Randomization date to the Week 28 visit date while the subject is on treatment.
    - Note: Participants who are randomized but never treated will not have a value for average monthly IV iron from Randomization to Week 28.
    - The time period starts with treatment start date, instead of randomization date. [missing treatment start date are excluded]
    - If the treatment end date [non-zero dose] is prior to the Week 28 date, then that is used instead. The last non-zero dose date is used for Dapro, treatment end date used for Placebo.
- IV iron therapy concomitant medication records that occur or are ongoing during the period from the participant's Day 1 visit date to the Week 28 visit date will be selected and ordered by start date and end date.
- The standardization will be carried out with the following formula:
    - Standardized IV iron dose (mg/week) = IV iron drug dose (mg) * frequency

Note: Frequency and Gap Factors defined as follows:

Frequency (from eCRF)	Frequency (for standardization formula)	Gap Factor
2 times per week	2	2.5 days
3 times per week	3	1.33 days
4 times per week	4	0.75 day
5 times per week	5	0.4 day
BID	14	0 days
Once daily	7	0 days
One time dose	see below	n/a
Every 12 Hours	14	0 days
Every 2 weeks	0.5	13 days
Every 4 weeks	0.25	27 days
Once a month	0.23	29 days
Once a week	1	6 days
TID	21	0 days

- If the frequency of the record is not 'one time dose', then duration is calculated as follows:
    - If the concomitant medication record start date ≥ Randomization date, the duration of the record is 0.
    - If the concomitant medication record end date + gap factor < (Randomization date), the

Iron Endpoints

duration of the record is 0.

- If the concomitant medication record end date + gap factor ≥ (Randomization date) or the record is ongoing, the duration of the record will be calculated as Stop Date – Start Date +1 day where:
  - Start date will be the latest of (concomitant medication record start date and the Randomization date).
  - Stop date will be the earliest of (concomitant medication record stop date + gap factor and the day before randomization).

- If the frequency of the record is 'one time dose', then:
  - If concomitant medication record start date < Randomization date, or if Randomization date ≤ concomitant medication record start date, then duration of the record is 0.
  - If Randomization date ≤ concomitant medication record start date < Randomization date, then:
    - Frequency (for standardization formula) = 1
    - Duration = 7 days
- The total dose for each IV iron record will be: Standardized dose*duration/7 days
- A weighted mean will then be used to obtain the baseline monthly IV iron dose:

  Mean baseline monthly IV iron dose = [(IV iron total dose$_{\text{Record 1}}$) + ... + (IV iron total dose$_{\text{Record n}}$)]/[(16* 7)/30.4375 days].

Blood Pressure Endpoints

BP Exacerbation

- BP exacerbations will be defined as (≥ 25 mmHg increase from baseline or SBP ≥ 180 mmHg or DBP ≥ 15 mmHg increase from baseline or DBP ≥ 110 mmHg) and grouped by type as follows:
  - BP exacerbations
    - SBP exacerbations
      - ≥ 25 mmHg increase from baseline or
      - SBP ≥ 180 mmHg
        - SBP ≥ 180 mmHg and baseline SBP < 180 mmHg (including subjects with a missing baseline SBP)
        - SBP ≥ 180 mmHg and baseline SBP >= 180 mmHg
    - DBP exacerbations
      - ≥ 15 mmHg increase from baseline or
      - DBP ≥ 110 mmHg
        - DBP ≥ 110 mmHg and baseline DBP < 110 mmHg (including subjects with a missing baseline DBP)

Blood Pressure Endpoints

- DBP ≥ 110 mmHg and baseline DBP >= 110 mmHg

Notes:

- BP values used to assess BP exacerbations must be on-treatment (see Section 10.4.1), unless otherwise specified.
- BP values used to assess BP exacerbations can be scheduled or unscheduled.
- For visits where BP is measured in triplicate, the average of the 3 BP values will be used to assess BP exacerbations.
- For subjects who start in-clinic dialysis during the study, BP exacerbations identified using post-dialysis BP values will be used in summaries and analyses of BP exacerbations, unless otherwise specified.
- Subjects with multiple exacerbation events on the same calendar date for each type defined above are considered to have one exacerbation event for event counts by type. For example, a subject with a SBP and a DBP exacerbation on the same date would count in each of the SBP and DBP types, but would only count as one BP exacerbation event in in the total BP exacerbation type.

MAP

- MAP = [(2*DBP)+SBP]/3

Imputation

HGB

- Generate missing rows for subjects who are missing any scheduled visits
  - Baseline does not need to be generated since a subject must have a baseline HGB to be randomized
- Populate variable “DTYPE” with "IMPUTED" for subjects with these newly created missing rows
- For date “ADT”, anchor on the baseline visit date, then add the subsequent weeks needed
  - For example of week 2 is missing then ADT = baseline ADT + 2 weeks
- For “APHASE”, deciding if the missing row should be marked as “On-Treatment” or “Post-Treatment”, the generated ADT should be compared to treatment end date “TRTEDT”. If TRTEDT + 1 >=ADT then “On-Treatment” or if TRTEDT + 1 <ADT then “Post-Treatment”.

SF-36

- Generate missing rows for subjects who are missing baseline, week 8, week 12, and week 28 sf-36 vitality scores (norm and traditional)
- Populate variable “DTYPE” with "IMPUTED" for subjects with these newly created missing rows
- For date “ADT”, anchor on the baseline visit date, then add the subsequent weeks needed
  - If the baseline (Day 1) is missing then baseline ADT will be the RANDDT (Randomization date).
  - For example of week 2 is missing then ADT = baseline ADT + 2 weeks
- For “APHASE”, deciding if the missing row should be marked as “On-Treatment” or “Post-Treatment”, the generated ADT should be compared to treatment end date “TRTEDT”. If TRTEDT + 1 >=ADT then “On-Treatment” or if TRTEDT + 1 <ADT then “Post-Treatment”.

10.6.4. 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
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 • 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
• Post-Randomization last contact date for censoring (participants not having AE) will be defined as the study completion date.

- Treatment emergent last contact date for censoring (participants not having AE) will be defined as follows:
  - 1 day after the last non-zero dose date (last non-zero dose date + 1) for participants not having treatment emergent AE and continuing on study past (last non-zero dose date + 1)
  - Last non-zero dose date for all other participants

- AE Participant Years: (Cumulative total of time to AE for participants who have the AE + Cumulative total of censoring time for participants without the AE) / 365.25
  - For treatment emergent AEs, the start date of the participant years value for each participant should be the treatment start date.
  - For post-randomization AEs, the start date of the participant years value for each participant should be the randomization date.
  - For follow-up AEs, the start date of the participant years value for each participant should be 28 days after the last non-zero dose date (last non-zero dose date + 28).
  - If the AE onset/worsening date is completely missing, then the randomization date will be used for calculations of participant years.

- Incidence Rate (per 100 participant years): (100 * Number of participants with at least 1 AE) / AE person years

- 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.

- Post-randomization values include on and off treatment values. This will map early withdrawal visits to their respective week visits.

- The exposure-adjusted incidence rate will be calculated as 100*(number of subjects with AE/sum of exposure duration across all subjects), where exposure duration = (treatment stop date – treatment start date + 1)/365.25, for subjects who DO NOT experience the AE of interest, and exposure duration = (start date of first AE of interest - treatment start date + 1)/365.25 for subjects who DO experience the AE of interest.
- Note that an AE is only counted once within a subject

- Relative risk and 95% confidence interval will be calculated as follows:
  Relative Risk (RR) = pd / pc
  Lower limit of 95% CI = RR * exp[-z * (v)1/2]
  Upper limit of 95% CI = RR*exp[z * (v)1/2], where

v = Variance[ln(RR)] = [(1-pc) / nc1] + [(1-pd) / nd1]
nc : number of subjects in placebo group
nd : number of subjects in daprodustat group
nc1 : number of subjects with AE in placebo group
nd1 : number of subjects with AE in daprodustat group
pc : proportion of subjects with AE in placebo group = nc1/ nc
pd : proportion of subjects with AE in daprodustat group = nd1/ nd
- z : 97.5th percentile of the standard normal distribution

Order of CV Safety Endpoint Events

- If multiple events occur on the same day or have imputed dates that place them on the same day, but it is not clear which event occurred first, then the following order will be applied:
  1. MI
  2. Stroke
  3. Hospitalization for Heart Failure

Order of CV Safety Endpoint Events
4. Thromboembolic Event: DVT 5. Thromboembolic Event: VAT 6. Thromboembolic Event: PE 7. Death

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 [Iverson, 2007]: • Hemoglobin, MCHC and Albumin: Divide the g/L value by 10 to get the g/dL value. • Total calcium and Albumin-adjusted calcium: Divide the mmol/L value by 0.25 to get the mg/dL value. • Inorganic phosphate: Divide the mmol/L value by 0.323 to get the mg/dL value. • Urea: Divide the mmol/L value by 0.357 to get the mg/dL value. • Total cholesterol, LDL-C and HDL-C: Divide the mmol/L value by 0.0259 to get the mg/dL value unit
• Estimated glomerular filtration rate (eGFR) will be calculated automatically by the central laboratory using the CKD Epidemiology Collaboration (CKD- EPI) for all subjects [Levey, 2009]. • The equation is as follows: CKD – EPI: GFR = 141 x min(S_{cr} / k,1)$^{\alpha}$ x max(S_{cr} / k,1)$^{-1.209}$ x 0.993^{Age} x 1.1018 [if female] x 1.159 [if black] Where: S_{cr}=Serum Creatinine (mg/dl), k=0.7 for females and 0.9 for males, a=-0.329 for females and -0.411 for males, min indicates the minimum of S_{cr} / k or 1, and max indicates the maximum of S_{cr} / k or 1. Creatinine umol/88.4=mg/dl. The demographic information used by the central laboratory for the calculation of eGFR (i.e., gender and race) will be reconciled with the demographic information contained in the eCRF to ensure consistency. The units for eGFR for displays will be mL/min/1.73m^2
• The following will be used to convert laboratory values from SI units to conventional units [Iverson,

Laboratory Parameters

2007]:

- Hemoglobin, MCHC and Albumin: Divide the g/L value by 10 to get the g/dL value.
- Total calcium and Albumin-adjusted calcium: Divide the mmol/L value by 0.25 to get the mg/dL value.
- Inorganic phosphate: Divide the mmol/L value by 0.323 to get the mg/dL value.
- Urea: Divide the mmol/L value by 0.357 to get the mg/dL value.
- Total cholesterol, LDL-C and HDL-C: Divide the mmol/L value by 0.0259 to get the mg/dL value.

SI units for eGFR are mL/sec/1.73m2 and the conventional units of mL/min/1.73m2

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
- Participants 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.
    - If a participant has both a decrease 'To Low' and an increase 'To High', then the participant is counted in both the 'To Low' and 'To High' categories.
    - If a participant was High at baseline and decreases to Low during the time interval, then the participant is counted in the 'To Low' category. Likewise, if a participant was low at baseline and increases to high during the time interval, then the participant is counted in the 'To High' category.
    - Participants 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

COVID-19

Exposure Duration

- For subjects who DO NOT experience the event, the exposure duration is calculated as: (treatment stop date or end date of time block, whichever occurs sooner – treatment start date or start date of time block, whichever occurs later + 1)/365.25
- For subjects who DO experience the event, the exposure duration is calculated as: (start date of AE – treatment start date or start date of time block, whichever occurs later + 1)/365.25

Exposure Adjusted Incidence Rate

- Exposure adjusted incidence rate (rate/100 PY) = (number of subjects with the adverse event during the time block / total exposure duration across all subjects) * 100

Time Periods
• Pre COVID-19 pandemic period: the date of interest is prior to the country specific start date of COVID-19 pandemic measures. For example, for recruitment and demographic summaries, pre COVID-19 period is defined as the randomization date of the subject is prior to the country specific start date of COVID-19 pandemic measures. • During COVID-19 period: the date of interest is after the country specific start date of COVID-19 pandemic measures. For example, for recruitment and demographic summaries, during COVID-19 period is defined as the randomization date of the subject is after the country specific start date of COVID-19 pandemic measures. • There is currently no post COVID-19 period.

10.6.5. Participant Reported Outcomes

CKD-AQ
General Information & Scoring
• The CKD-AQ is a newly-developed 21-item PRO measure assessing symptoms and symptom impact in patients with anemia associated with CKD. An interim cut of blinded observations from approximately 400 participants, approximately 350 from study 200808 [GlaxoSmithKline Document Number 2015N230102_03, 12OCT2016] and approximately 50 from study 201410 [GlaxoSmithKline Document Number 2015N234534_01, 06OCT2017], who had completed the baseline (Day 1) CKD-AQ was taken to establish the scoring algorithm and any potential domains of the instrument. Further details of the scoring can be found in the psychometric report [GlaxoSmithKline Document Number Atlas IS 16443, 03OCT2018]. • Exploratory factor analysis of the CKD-AQ identified three domains (multi-item scales): (1) a Tired/Low Energy/Weak scale consisting of ten items – Items CCI [redacted] CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. [redacted]; (2) a Chest Pain/Shortness of Breath scale consisting of four items – Items CCI [redacted] CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. [redacted]; and (3) a Cognitive scale consisting of three item – Items CCI [redacted]. In addition to these three domains, four additional CKD-AQ single items – Items CCI [redacted], were retained based upon their CKD-relevant content. The CKD-AQ domains and single-item measures were recoded based on a 0-100 scoring with 0 representing CCI [redacted] and 100 CCI [redacted]. • Scoring instruction: ○ Step 1: For items 1-8, 17-23, recode from 5-pt scale CCI [redacted] to 0-100 (CCI [redacted]) scale by using (5-raw score)*25; for items 9-16, recode from 11-pt scale (CCI [redacted]) to 0-100 scale (CCI [redacted]) by using (10-raw score)*10. ○ Step 2: calculate the domain and single item scores as follows: (items 16 and 18 were

CKD-AQ
General Information & Scoring
NOT used currently) ▪ Tired/Low Energy/Weak domain: average items CCI [redacted] (0-100 scale) ▪ Chest Pain/Shortness of Breath domain: average items CCI [redacted] (0-100 scale) ▪ Cognitive domain: average items CCI [redacted] (0-100 scale) ▪ CCI [redacted] (0-100 scale) ▪ CCI [redacted] (0-100 scale) ▪ CCI [redacted] (0-100 scale) ▪ CCI [redacted] (0-100 scale)

PGI-S
General Information & Scoring
• The PGI-S is a 1-item questionnaire designed to assess a participant's impression of disease severity on a 5-point disease severity scale (absent, mild, moderate, severe, or very severe). • Scores range from CCI [redacted] as follows: ○ CCI [redacted] ○ ○ ○ ○

SF-36
General Information & Scoring
• The SF-36 acute version 2 is a 36-item generic quality of life instrument designed to measure a participant's level of performance in the following eight health domains: Physical Functioning, Role-Physical (role limitations caused by physical problems), Social Functioning, Bodily Pain, Mental Health, Role-Emotional (role limitations caused by emotional problems), Vitality, and General Perception of Health. • Scoring of the questionnaire data will be performed using Optum PRO CoRE scoring software version 1.4 using a traditional scoring and norm-based scoring approach using 2009 norms and the maximum data recovery mode to handle missing data. • The 8 domain scores and scores for the physical and mental component summary measures will be provided by the Optum PRO CoRE software. • For SF-36 question CCI [redacted], full of life, and question CCI [redacted], a lot of energy, will be transformed so the higher the score the better the health. The following formula will be used: ○ (5 - aval) + 1 = transformed aval, where aval is raw score. ○ For example if a subject's answer is 4, a little of time, this will be transformed to a value of 2.

WPAI-ANS-CPV
General Information & Scoring
• The WPAI-ANS-CPV is an anemia-specific questionnaire designed as a self-reported quantitative assessment of social functioning related to work and regular daily activities within two concepts: Work productivity impairments via absenteeism (time missed from work) and

WPAI-ANS-CPV
General Information & Scoring

presenteeism (impairment at work) and regular daily activity impairment.
• Scoring of the WPAI-ANS-CPV will be as follows:
• All scores will be multiplied by 100 to express results in percentages
• Domains/Concept Scoring:
  ○ Percent of participants currently employed: Question 1
  ○ Percent work time missed due to problem: Question 2 / (Question 2 + Question 4)
  ○ Percent impairment while working due to problem: Question 5 /10
  ○ Percent overall work impairment due to problem: Question 2 / (Question 2 + Question 4) +[(1-(Question 2 / (Question 2 + Question 4)))x(Question 5 / 10)]
• Percent activity impairment due to problem: Question 6 / 10

EQ-5D-5L
General Information & Scoring
• The EQ-5D-5L is a self-assessment questionnaire, consisting of five items covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a five-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). • The responses for the five dimension together form a five-figure description of a health state (i.e., the score of 11112 describes the health state of no problems with mobility, self-care, usual activities or pain/discomfort, but slight problems with anxiety/depression). Each of these five-figure health states has an attached valuation (utility score), expressed as a single index on a scale from 0-1, where 1 is CCI CCI and 0 is CCI . • EQ-5D-5L health states are converted to a single summary index score by applying a country-specific value set formula that essentially attaches weights to each of the levels in each dimension. Use United Kingdom (UK) value set.

EQ-VAS
General Information & Scoring
• The EQ-VAS is a self-assessment visual analogue scale, ranging from 0=CCI – 100=CCI . • The EQ-VAS will only be assessed in the countries listed in Section 5.3.

PGI-C
General Information & Scoring

• The PGI-C is a 1-item questionnaire designed to assess a participant's impression of change in their anemia of CKD on a 7-point Likert-type response scale (very much improved, moderately improved, minimally improved, no change, minimally worse, moderately worse, or very much worse).
• Scores range from CCI to CCI as follows:
  ○ CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
  ○
  ○
  ○
  ○
  ○
  ○

10.6.6. Actigraphy

Actigraphy
Derivations

• The protocol defined scheduled visits for actigraphy are Day 1, Week 8, Week 12, and Week 28
  ○ The scheduled visits will be defined as any actigraphy data collected from the visit date minus 7 days
  ○ Any actigraphy data collected outside this window will be labelled as unscheduled
  ○ Only scheduled, on treatment visits will be summarized
• Mean Hour of Daily Activity = sum of category / # of days actigraphy recorded, by scheduled visit
  ○ Sum of category = Sum by xztest and by scheduled visit
  ▪ Where xztest are the following five variables:
  • Light, moderate, vigorous, very vigorous, and moderate to vigorous physical activity (MVPA) activity
• Wear time = sum of wear time / # of days actigraphy recorded, by scheduled visit
• Percent of daily activity = sum of category / sum of wear time, by scheduled visit
  ○ Sum of category = Sum by xztest and by scheduled visit
  ▪ Where xztest are the following five variables:
  • Light, moderate, vigorous, very vigorous, and moderate to vigorous physical activity (MVPA) activity
• Percent sleep efficiency = average percent sleep efficiency, by scheduled visit
  ○ Average by number of records for sleep efficiency
  ▪ For example, a subject has 7 days of data collection but has 8 records, sum the sleep efficiency percent's and divide by 8.

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 has completed all phases of the study including the Follow-up visit, which takes place 4 weeks after the end of study treatment. • Withdrawn participants will not be 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.

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: o 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. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
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.
Other Missing or Partial Dates	Missing or Partial dates for AE/SAE, Clinical Events, EOSI, Study treatment dates are not allowed.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Clinical Chemistry			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
Albumin (serum)	g/L	< 30 g/L	> 55 g/L
Aspartate Aminotransferase	IU/L		≥ 3x ULRR
Alanine Aminotransferase	IU/L		≥ 3x ULRR
Bilirubin (total)	μmol/L		≥ 2x ULRR
Calcium (albumin-adjusted)	mmol/L	< 1.87 mmol/L	> 2.56 mmol/L
Inorganic phosphate	mmol/L	< 0.81 mmol/L	> 1.77 mmol/L
Potassium (serum)	mmol/L	> 0.5 mmol/L below LLRR	> 1.0 mmol/L above ULRR

Hematology			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
Platelet Count	GI/L	< 80 GI/L	> 500 GI/L
WBC Count with Differential	GI/L	< LLRR	> 5x ULRR
Neutrophils	GI/L	< 0.5x LLRR	
Lymphocytes	GI/L	< 0.5x LLRR	

Iron Parameters			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
Ferritin	ng/mL	< 100 ng/mL	> 800 ng/mL
TSAT	%	<15%	> 40%

Other PCI Values			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag	**High Flag**
iPTH	ng/L		> 9x ULRR

10.8.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	≤ 85 mmHg	≥ 180 mmHg
Diastolic Blood Pressure	mmHg	≤ 45 mmHg	≥ 110 mmHg
Heart 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.

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse Event
AESI	Adverse event of special interest
AIC	Akaike's Information Criteria
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
A&R	Analysis and Reporting
BP	Blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CKD	Chronic kidney disease
CKD-AQ	Chronic Kidney Disease - Anemia Questionnaire
CKD-EPI	Chronic kidney disease Epidemiology Collaboration
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV	Cardiovascular
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
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EP	Evaluation period
EPO	Erythropoietin
EQ-5D-5L	EuroQol 5 Dimension 5 Level Health Utility Index
EQ-VAS	EuroQol Visual Analogue Scale
ESA	Erythropoietin-stimulating agent
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
hCG	Human chorionic gonadotrophin
HD	Hemodialysis
HDL-c	High density lipoprotein-C

Abbreviation	Description
HDPE	High density polyethylene
Hgb	Hemoglobin
HIF	Hypoxia-inducible factor
HR	Heart rate
HR-QoL	Health Related Quality of Life
HRT	Hormone replacement therapy
hsCRP	High sensitivity C-reactive protein
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
IV	Intravenous
LDH	Lactate dehydrogenase
LDL-C (direct)	Directly measured Low density lipoprotein-C
MACE	Major adverse cardiovascular event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	MCV Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed Model Repeated Measures
MRI	Magnetic resonance imaging
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHI	Prolyl hydroxylase inhibitor
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
RBC	Red blood cell
RDW	Red blood cell distribution width
rhEPO	Recombinant human erythropoietin
SAE	Serious adverse event

Abbreviation	Description
SAC	Statistical Analysis Complete
SBP	Systolic blood pressure
SD	Standard deviation
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SF-36	Short form - 36
SOP	Standard Operation Procedure
sPAP	Systolic pulmonary artery pressure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TIBC	Total iron binding capacity
TSAT	Transferrin saturation
UIBC	Unsaturated iron binding capacity
U	Units
ULN	Upper limit of normal
WBC	White blood cells
WPAI-ANS-CPV	Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms Clinical Practice Version

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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ActiGraph GT9X Link
HemoCue
Optum PRO CoRE
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	Figures
Study Population	1.1 to 1.26	1.1
Efficacy	2.1 to 2.135	2.1 to 2.25
Safety	3.1 to 3.55	3.1 to 3.4
Section	**Listings**	
ICH Listings	1 to 29	
Other Listings	31 to 34	

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	Figure	Table	Listing
Study Population	-	Shell 1 - 30	-
Efficacy	EFF_F1- EFF_F4	EFF_T1- EFF_T50	-
Safety	Shell 3.4-3.7	Shell 1-50	Shell 1-12

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
DR	Dry-run
SAC	Final Statistical Analysis Complete

10.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	ITT	Shell 5	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, GSK CTR, FDAAA, EudraCT	DR, SAC
1.2.	ITT	Shell 6	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	DR, SAC
1.3.	Screened	Shell 2	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	DR, SAC
1.4.	Enrolled	Shell 8	Summary of Number of Subject by Country and Site ID	EudraCT/Clinical Operations	DR, SAC
Protocol Deviation					
1.5.	ITT	Shell 15	Summary of Important Protocol Deviations	ICH E3	DR, SAC
1.6.	ITT	Shell 30	Summary of Inclusion/Exclusion Criteria Deviations	ICH E3	DR, SAC
Population Analysed					
1.7.	Screened	Shell 1	Summary of Study Populations	IDSL	DR, SAC
1.8.	ITT	Shell 4	Summary of Exclusions from the Safety Population	IDSL	DR, SAC
Demographic and Baseline Characteristics					
1.9.	ITT	Shell 16	Summary of Demographic Characteristics – ITT, included in primary HGB analysis	Only include those subjects that were part of the primary HGB analysis	DR, SAC
1.10.	ITT	Shell 16	Summary of Demographic Characteristics - ITT	ICH E3, GSK CTR, FDAAA, EudraCT	DR, SAC
1.11.	Safety	Shell 16	Summary of Demographic Characteristics - Safety	ICH E3, GSK CTR, FDAAA, EudraCT	DR, SAC
1.12.	Enrolled	Shell 17	Summary of Age Ranges	EudraCT	DR, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.13.	ITT	Shell 18	Summary of Race and Racial Combinations	ICH E3, FDA, GSK CTR, FDAAA, EudraCT	DR, SAC
Prior and Concomitant Medications					
1.14.	ITT	Shell 20	Summary of Medical Conditions	ICH E3	DR, SAC
1.15.	ITT	CM1	Summary of Pre-treatment Medications by ATC Level and Ingredient	ICH E3	DR, SAC
1.16.	ITT	CM1	Summary of On-treatment Medications by ATC Level and Ingredient	ICH E3	DR, SAC
1.17.	ITT	CM1	Summary of Post-treatment Medications by ATC Level and Ingredient	ICH E3	DR, SAC
Exposure and Treatment Compliance					
1.18.	ITT	Shell 26	Summary of Exposure to Study Treatment	ICH E3	DR, SAC
1.19.	ITT	Shell 28	Summary of Randomized Treatment Compliance		DR, SAC
1.20.	ITT	Shell 27	Summary of Randomized Treatment Compliance Categories		DR, SAC
Additional Study Population Tables					
1.21.	ITT	ES1	Summary of Subject Status and Subject Disposition by Relationship to COVID-19 Pandemic	Page by Related, Not-related	SAC
1.22.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment by Relationship to COVID-19 Pandemic	Page by Related, Not-related	SAC
1.23.	ITT	DV1	Important Protocol Deviations by Relationship to COVID-19 Pandemic	Page by Related, Not-related	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.24.	ITT	PAN4	Proportion of Subject Visits Impacted by COVID-19 Pandemic		SAC
1.25.	ITT	Shell 31	Summary of Treatment Interruption Due to COVID-19 Pandemic		SAC
1.26.	ITT	Shell 19	Summary of Smoking History		SAC

10.10.5. Study Population Figures

Study Population: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population Figures					
1.1	ITT	PAN8	Visits Impacted by COVID-19 Pandemic		SAC

10.10.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Primary Efficacy Analyses: Model based Mean Change in Hgb between Baseline and Evaluation Period					
2.1.	ITT	EFF_T1	Summary of Post-Randomization Hemoglobin (g/dL) by Visit	On and off-treatment Analysis HGB only	DR, SAC
2.2.	ITT	EFF_T2	Summary of Post-Randomization Change from Baseline in Hemoglobin (g/dL) by Visit	On and off-treatment	DR, SAC
2.3.	ITT	EFF_T1	Summary of Post-Randomization Observed and Imputed Hemoglobin (g/dL) Data by Visit	On and off-treatment	DR, SAC
2.4.	ITT	EFF_T2	Summary of Post-randomization Observed and Imputed Hemoglobin (g/dL) Change from Baseline Data by Visit	On and off-treatment	DR, SAC
2.5.	ITT	EFF_T3	Summary of Imputed Data in the Primary Hemoglobin Analysis	On and off-treatment	DR, SAC
2.6.	ITT	EFF_T4	Summary of Primary Analysis of Post-Randomization Hemoglobin Change from Baseline to the Evaluation Period	On and off-treatment	DR, SAC
Primary Efficacy Subgroup Analyses					
2.7.	ITT	EFF_T2	Summary of Post-Randomization Change from Baseline in Hemoglobin (g/dL) by Visit by Subgroup	On and off-treatment	DR, SAC
2.8.	ITT	EFF_T2	Summary of Post-Randomization and Imputed Change from Baseline in Hemoglobin (g/dL) by Visit by Subgroup	On and off-treatment	DR, SAC
2.9.	ITT	EFF_T5	Summary of Subgroup Analysis of Post-Randomization Hemoglobin Change from Baseline to the Evaluation Period	On and off-treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.10.	ITT	EFF_T5	Summary of Subgroup Analysis of Hemoglobin Change from Baseline to the Evaluation Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
Primary Efficacy Supportive Analyses					
2.11.	ITT	EFF_T4	Supportive Analysis: Summary of Analysis of Hemoglobin Change from Baseline to the Evaluation Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
Principal Secondary Efficacy Analyses					
2.12.	ITT	EFF_T24	Summary of Analysis of Subjects with Post-Randomization Hemoglobin increase of≥1.0 g/dL from baseline to EP	On and off-treatment	DR, SAC
2.13.	ITT	EFF_T25	Summary of Imputed Data for SF-36 Vitality Analyses		DR, SAC
2.14.	ITT	EFF_T17	Summary of On-Treatment SF-36 Vitality Data by Visit, Traditional Scoring	Traditional scoring On-treatment	DR, SAC
2.15.	ITT	EFF_T18	Summary of On-Treatment Change from Baseline in SF-36 Vitality Data by Visit, Traditional Scoring	Traditional scoring On-treatment	DR, SAC
2.16.	ITT	EFF_T17	Summary of On-Treatment Observed and Imputed SF-36 Vitality Data by Visit, Traditional Scoring	Traditional scoring Include all on treatment values plus hypothetical imputation strategy	DR, SAC
2.17.	ITT	EFF_T18	Summary of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline Data by Visit, Traditional Scoring	Traditional scoring Include all on treatment values plus hypothetical imputation strategy	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.18.	ITT	EFF_T42	Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28, Traditional Scoring	Traditional scoring Include all on treatment values plus hypothetical imputation strategy	DR, SAC
Principal Secondary Efficacy Supportive Analyses					
2.19.	ITT	EFF_ T24	Supportive Analysis: Summary of Analysis of Subjects with Hemoglobin increase of≥1.0 g/dL from baseline to EP While on Treatment	On-treatment	DR, SAC
2.20.	ITT	EFF_T17	Summary of On-Treatment SF-36 Vitality Data by Visit, Norm-based Scoring	Norm-based scoring On-treatment	DR, SAC
2.21.	ITT	EFF_T18	Summary of On-Treatment Change from Baseline in SF-36 Vitality Data by Visit, Norm-based Scoring	Norm-based scoring On-treatment	DR, SAC
2.22.	ITT	EFF_T17	Summary of On-Treatment Observed and Imputed SF-36 Vitality Data by Visit, Norm-based Scoring	Norm-based scoring Include all on treatment values plus hypothetical imputation strategy	DR, SAC
2.23.	ITT	EFF_T18	Summary of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline Data by Visit, Norm-based Scoring	Norm-based scoring Include all on treatment values plus hypothetical imputation strategy	DR, SAC
2.24.	ITT	EFF_T42	Supportive Analysis: Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28, Norm-based Scoring	Norm-based scoring Include all on treatment values plus hypothetical imputation strategy	DR, SAC
2.25.	ITT	EFF_T42	Supportive Analysis: Summary of Analysis of SF-36 Vitality Change from Baseline at Week 28 While On Treatment, Traditional Scoring	Traditional scoring Include all on treatment values	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.26.	ITT	EFF_T42	Supportive Analysis: Summary of Analysis of SF-36 Vitality Change from Baseline at Week 28 While On Treatment, Norm-based Scoring	Norm-based scoring Include all on treatment values	DR, SAC
2.27.	ITT	EFF_T42	Supportive Analysis: Summary of Analysis of Post-Randomization SF-36 Vitality Change from Baseline at Week 28, Traditional Scoring	Traditional scoring Include all on and off treatment values	DR, SAC
2.28.	ITT	EFF_T42	Supportive Analysis: Summary of Analysis of Post-Randomization SF-36 Vitality Change from Baseline at Week 28 , Norm-based Scoring	Norm-based scoring Include all on and off treatment values	DR, SAC
2.29.	ITT	EFF_T42	Supportive Analysis: Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28, Excluding remote SF-36 and Treatment Interrupted, Traditional Scoring	Traditional scoring Include all on treatment values plus imputation Only perform if 10% of ITT have remote/trt interrupted week 28 sf-36 data	SAC
2.30.	ITT	EFF_T42	Supportive Analysis: Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28, Excluding remote SF-36 and Treatment Interrupted, Norm-based Scoring	Norm-based scoring Include all on treatment values plus imputation Only perform if 10% of ITT have remote/trt interrupted week 28 sf-36 data	SAC
Principal Secondary Efficacy Subgroup Analyses					
2.31.	ITT	EFF_T27	Summary of Analysis of Subjects with Post-Randomization Hemoglobin increase of≥1.0 g/dL from baseline to EP by Subgroup	On and off-treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.32.	ITT	EFF_T28	Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28 by Subgroup, Traditional Scoring	Traditional scoring Include all on treatment values plus imputation	DR, SAC
2.33.	ITT	EFF_T28	Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28 by Subgroup, Norm-based Scoring	Norm-based scoring Include all on treatment values plus imputation	DR, SAC
Secondary Efficacy Statistical Analyses: Hgb Variability					
2.34.	ITT	EFF_T7	Summary of Analysis of Hemoglobin Responders During the Evaluation Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.35.	ITT	EFF_T8	Summary of Percentage of Time Hemoglobin Within the Target Range During the Evaluation Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.36.	ITT	EFF_T9	Summary of Analysis of Percentage of Time Hemoglobin Within the Target Range During the Evaluation Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.37.	ITT	EFF_T8	Summary of Percentage of Time Hemoglobin Within the Target Range During the Treatment Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.38.	ITT	EFF_T9	Summary of Analysis of Percentage of Time Hemoglobin Within the Target Range During the Treatment period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.39.	ITT	EFF_T10	Summary of Analysis of Post-Randomization Hemoglobin Change from Baseline at Week 28	On and off-treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.40.	ITT	EFF_T10	Summary of Analysis of Hemoglobin Change from Baseline at Week 28 using Evaluable Hemoglobin Values	On-treatment	DR, SAC
Secondary Efficacy Statistical Analyses: Time to Rescue					
2.41.	ITT	EFF_T11	Summary of Subjects Meeting Rescue Evaluation Criteria and Subjects Rescued		DR, SAC
2.42.	ITT	EFF_T12	Summary of Analysis of Time to Permanently Stopping Randomized Treatment Due to Meeting Rescue Criteria		DR, SAC
Secondary Efficacy Statistical Analyses: Symptom Severity and Change					
2.43.	ITT	EFF_T13	Summary Statistics for On-Treatment PGI-S Scores	On-treatment Page by domain/single item Row by visit, column by treatment	DR, SAC
2.44.	ITT	EFF_T13	Summary Statistics for On-Treatment CKD-AQ Domain and Single Item Scores	On-treatment Page by domain/single item Row by visit, column by treatment	DR, SAC
2.45.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment PGI-S Scores	On-treatment Page by domain/single item Row by visit, column by treatment	DR, SAC
2.46.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment CKD-AQ Domain and Single Item Scores	On-treatment Page by domain/single item Row by visit, column by treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.47.	ITT	EFF_T15	Summary of Analysis of the Change from Baseline in On-Treatment PGI-S Scores	On-treatment Page by domain/single item Row by visit, column by treatment	DR, SAC
2.48.	ITT	EFF_T15	Summary of Analysis of the Change from Baseline in On-Treatment CKD-AQ Domain and Single Item Scores	On-treatment Page by domain/single item Row by visit, column by treatment	DR, SAC
2.49.	ITT	EFF_T16	Summary of Shifts from Baseline in On-Treatment PGI-S Scores	On-treatment Page by domain/single item Row by visit, column by treatment	DR, SAC
Secondary Efficacy Statistical Analyses: HRQoL and Utility score					
2.50.	ITT	EFF_T38	Summary of Analysis of Subjects with % of participants having an improvement in On-Treatment Observed and Imputed SF-36 Vitality Domain ≥ 6 from baseline at Week 28	Traditional scoring Include all on treatment values plus imputation	DR, SAC
2.51.	ITT	EFF_T17	Summary Statistics for On-Treatment SF-36 Individual Vitality Scores and 8 Domain Scores	On-treatment, both norm and traditional scoring needed for 8 domains and following individual vitality scores with PARAMCD=”BP”,”BP_NBS”,”GH”,”GH_NBS”,”MH”,”MH_NBS”,”PF”,”PF_NBS”,”RE”,”RE_NBS”,”RP”,”RP_NBS”,”SF”,”SF_NBS”,”VT”,”VT_NBS”,"SF36423A","SF36427A","SF36429","SF36431"	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.52.	ITT	EFF_T18	Summary Statistics for the Change from Baseline in On-Treatment SF-36 Individual Vitality Scores and 8 Domain Scores	On-treatment, both norm and traditional scoring needed for 8 domains and following individual vitality scores with PARAMCD=”BP”,”BP_NBS”,”GH”,”GH_NBS”,”MH”,”MH_NBS”,”PF”,”PF_NBS”,”RE”,”RE_NBS”,”RP”,”RP_NBS”,”SF”,”SF_NBS”,”VT”,”VT_NBS”,"SF36423A","SF36427A","SF36429","SF36431"	DR, SAC
2.53.	ITT	EFF_T19	Summary of On-Treatment EQ-5D-5L Responses by Dimension and Visit	On-treatment	DR, SAC
2.54.	ITT	EFF_T13	Summary Statistics for On-Treatment EQ-5D-5L Scores	On-treatment	DR, SAC
2.55.	ITT	EFF_T13	Summary Statistics for On-Treatment EQ-VAS Scores	On-treatment	DR, SAC
2.56.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment EQ-5D-5L Scores	On-treatment	DR, SAC
2.57.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment EQ-VAS Scores	On-treatment	DR, SAC
2.58.	ITT	EFF_T20	Summary of Analysis of the Change from Baseline in On-Treatment SF-36 Individual Vitality Scores and Physical Function Domain Scores	On-treatment	DR, SAC
2.59.	ITT	EFF_T15	Summary of Analysis of the Change from Baseline in On-Treatment EQ-5D-5L Scores	On-treatment	DR, SAC
2.60.	ITT	EFF_T15	Summary of Analysis of the Change from Baseline in On-Treatment EQ-VAS Scores	On-treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Secondary Efficacy Statistical Analyses: Work Productivity and Regular Daily Activity Impairment					
2.61.	ITT	EFF_T19	Summary of On-Treatment Subject Employment	On-treatment	DR, SAC
2.62.	ITT	EFF_T21	Summary of On-Treatment Mean Hours Missed from Work in the Past 7 Days	On-treatment, question 2 from WPAI form	DR, SAC
2.63.	ITT	EFF_T22	Summary of Change from Baseline in On-Treatment Mean Hours Missed from Work in the Past 7 Days	On-treatment, question 2 from WPAI form	DR, SAC
2.64.	ITT	EFF_T21	Summary of On-Treatment Percent Time Missed from Work	On-treatment	DR, SAC
2.65.	ITT	EFF_T22	Summary of Change from Baseline in On-Treatment Percent Time Missed from Work	On-treatment	DR, SAC
2.66.	ITT	EFF_T21	Summary of On-Treatment Percent Impairment at Work	On-treatment	DR, SAC
2.67.	ITT	EFF_T22	Summary of Change from Baseline in On-Treatment Percent Impairment at Work	On-treatment	DR, SAC
2.68.	ITT	EFF_T21	Summary of On-Treatment Percent Overall Work Impairment	On-treatment	DR, SAC
2.69.	ITT	EFF_T22	Summary of Change from Baseline in On-Treatment Percent Overall Work Impairment	On-treatment	DR, SAC
2.70.	ITT	EFF_T21	Summary of On-Treatment Percent Regular Daily Activity Impairment	On-treatment	DR, SAC
2.71.	ITT	EFF_T22	Summary of Change from Baseline in On-Treatment Percent Regular Daily Activity Impairment	On-treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Secondary Efficacy Statistical Analyses: Blood Pressure					
2.72.	ITT	EFF_T40	Summary of Analysis of Change from Baseline in On-Treatment Systolic Blood Pressure at Week 28	On-treatment	DR, SAC
2.73.	ITT	EFF_T40	Summary of Analysis of Change from Baseline in On-Treatment Diastolic Blood Pressure at Week 28	On-treatment	DR, SAC
2.74.	ITT	EFF_T40	Summary of Analysis of Change from Baseline in On-Treatment Mean Arterial Pressure at Week 28	On-treatment	DR, SAC
2.75.	ITT	EFF_T41	Summary of Analysis of On-treatment Blood Pressure Exacerbation Events	On-treatment	DR, SAC
Secondary Efficacy Statistical Analyses: SF-36					
2.76.	ITT	EFF_T26	Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28, including external historical placebo dataset, Traditional Scoring	Traditional scoring On-Treatment Observed and Imputed	DR, SAC
2.77.	ITT	EFF_T26	Summary of Analysis of On-Treatment Observed and Imputed SF-36 Vitality Change from Baseline at Week 28, including external historical placebo dataset, Norm-based Scoring	Norm scoring On-Treatment Observed and Imputed	DR, SAC
Exploratory Efficacy Statistical Analyses: Hgb Variability					
2.78.	ITT	EFF_T8	Summary of Percentage of Time Hemoglobin is above or below the target range of 11 to 12 g/dL during the EP using Evaluable Hemoglobin Values	On-treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.79.	ITT	EFF_T8	Summary of Percentage of Time Hemoglobin is above or below the target range of 11 to 12 g/dL during the Treatment Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.80.	ITT	EFF_T6	Summary of Number of Subjects with mean Hemoglobin above, within, or below the Hemoglobin target range during the EP using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.81.	ITT	EFF_T6	Summary of Number of Subjects with mean Hemoglobin above, within, or below the Hemoglobin target range during the Treatment Period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.82.	ITT	EFF_T6	Summary of Number of Subjects with a Hemoglobin <7.5 g/dL during the EP using Evaluable Hemoglobin Values	On-treatment Repeat for HemoCue Hgb and Central Laboratory Hgb	DR, SAC
2.83.	ITT	EFF_T6	Summary of Number of Subjects with a Hemoglobin <7.5 g/dL during the Treatment Period using Evaluable Hemoglobin Values	On-treatment Repeat for HemoCue Hgb and Central Laboratory Hgb	DR, SAC
2.84.	ITT	EFF_T51	Summary of Hemoglobin Increases Using Evaluable Hemoglobin Values	On-treatment Include overall at week 28 Repeat for HemoCue Hgb and Central Laboratory Hgb Similar to 204837 table 2.042	DR, SAC
2.85.	ITT	EFF_T6	Summary of Number of Subjects with a Hemoglobin value ≥13g/dL during the treatment period using Evaluable Hemoglobin Values	On-treatment Repeat for HemoCue Hgb and Central Laboratory Hgb	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.86.	ITT	EFF_T8	Summary of Number of Times Hemoglobin ≥13 g/dL during the treatment period using Evaluable Hemoglobin Values	On-treatment Repeat for HemoCue Hgb and Central Laboratory Hgb	DR, SAC
2.87.	ITT	EFF_T8	Summary of Percentage of Time Hemoglobin ≥13 g/dL during the treatment period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.88.	ITT	EFF_T6	Summary of Number of Subjects who achieved a Hemoglobin increase of ≥1.0g/dL during the EP using Evaluable Hemoglobin Values	On-treatment Repeat for HemoCue Hgb and Central Laboratory Hgb	DR, SAC
2.89.	ITT	EFF_T8	Summary of Percentage of Time Hemoglobin increase of ≥ 1.0 g/dL from baseline during the treatment period using Evaluable Hemoglobin Values	On-treatment	DR, SAC
2.90.	ITT	EFF_T6	Summary of Number of Subjects having a Change from Baseline Hemoglobin of ≥ 1.0 g/dL at each post-baseline visit using Evaluable Hemoglobin Values	On-treatment Repeat for HemoCue Hgb and Central Laboratory Hgb	DR, SAC
2.91.	ITT	EFF_T6	Summary of Number of Subjects who achieved and maintained a Hemoglobin increase of ≥1.0g/dL during EP using Evaluable Hemoglobin Values	On-treatment Repeat for HemoCue Hgb and Central Laboratory Hgb	DR, SAC
Exploratory Efficacy Statistical Analyses: Iron Parameters					
2.92.	ITT	EFF_T17	Summary of On-Treatment Hepcidin (nmol/L) by Visit	On-Treatment For min, max, median, p25 and p75, you do not need to summarize with log transformed data since aval=exp(log(aval))	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.93.	ITT	Safety, Shell 27	Summary of On-Treatment Hepcidin (nmol/L) Percent Change from Baseline by Visit	On-Treatment	DR, SAC
2.94.	ITT	EFF_T17	Summary of On-Treatment Transferrin Saturation (%) by Visit	On-Treatment	DR, SAC
2.95.	ITT	EFF_T18	Summary of On-Treatment Transferrin Saturation (%) Change from Baseline by Visit	On-Treatment	DR, SAC
2.96.	ITT	EFF_T17	Summary of On-Treatment Ferritin (ug/L) by Visit	On-Treatment For min, max, median, p25 and p75, you do not need to summarize with log transformed data since aval=exp(log(aval))	DR, SAC
2.97.	ITT	Safety, Shell 27	Summary of On-Treatment Ferritin (ug/L) Percent Change from Baseline by Visit	On-Treatment	DR, SAC
2.98.	ITT	EFF_T17	Summary of On-Treatment Serum Iron (umol/L) by Visit	On-Treatment For min, max, median, p25 and p75, you do not need to summarize with log transformed data since aval=exp(log(aval))	DR, SAC
2.99.	ITT	Safety, Shell 27	Summary of On-Treatment Serum Iron (umol/L) Percent Change from Baseline by Visit	On-Treatment	DR, SAC
2.100.	ITT	EFF_T17	Summary of On-Treatment Total Iron Binding Capacity (umol/L) by Visit	On-Treatment	DR, SAC
2.101.	ITT	EFF_T18	Summary of On-Treatment Total Iron Binding Capacity (umol/L) Change from Baseline by Visit	On-Treatment	DR, SAC
2.102.	ITT	EFF_T32	Summary of On-Treatment Average Monthly Oral Elemental Iron Dose (mg) to Week 28	On-Treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.103.	ITT	EFF_T33	Summary of On-Treatment Number of Subjects who reduced oral elemental iron supplementation relative to baseline during EP	On-Treatment	DR, SAC
2.104.	ITT	EFF_T33	Summary of On-Treatment Number of Subjects who reduced oral elemental iron supplementation relative to baseline during treatment period	On-Treatment	DR, SAC
2.105.	ITT	EFF_T32	Summary of On-Treatment Average monthly IV iron dose/subject (mg) to Week 28	On-Treatment	DR, SAC
2.106.	ITT	EFF_T29	Summary of Time to First IV Iron Use While On-Treatment	On treatment only	DR, SAC
2.107.	ITT	EFF_T29	Summary of Time to First rhEPO Use	Page by on/off trt & on trt	DR, SAC
2.108.	ITT	EFF_T29	Summary of Time to First Transfusion Use	Page by on/off trt & on trt	DR, SAC
2.109.	ITT	EFF_T44	Summary of frequency and dose of IV iron use While On-Treatment	By treatment and by baseline iron usage	DR, SAC
2.110.	ITT	EFF_T44	Summary of frequency and dose of rhEPO use Post-Randomization	By treatment and by baseline iron usage	DR, SAC
2.111.	ITT	EFF_T44	Summary of frequency and dose of transfusion use Post-Randomization	By treatment and by baseline iron usage	DR, SAC
Exploratory Efficacy Statistical Analyses: Renal Function					
2.112.	ITT	EFF_T17	Summary of On-Treatment eGFR by Visit	On-Treatment	DR, SAC
2.113.	ITT	EFF_T18	Summary of On-Treatment eGFR Change from Baseline by Visit	On-Treatment	DR, SAC
2.114.	ITT	EFF_T17	Summary of On-Treatment eGFR by Visit, sub-group ADPKD	On-Treatment By ADPKD and treatment	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.115.	ITT	EFF_T18	Summary of On-Treatment eGFR Change from Baseline by Visit, sub-group ADPKD	On-Treatment By ADPKD and treatment	DR, SAC
2.116.	ITT	EFF_T17	Summary of On-Treatment Serum creatinine by Visit	On-Treatment	DR, SAC
2.117.	ITT	EFF_T18	Summary of On-Treatment Serum creatinine Change from Baseline by Visit	On-Treatment	DR, SAC
2.118.	ITT	EFF_T39	Summary of Number transitioning to dialysis		DR, SAC
Exploratory Efficacy Statistical Analyses: Dose Adjustment Scheme					
2.119.	ITT	EFF_T45	Summary of Assigned Dose (mg) by Visit		DR, SAC
2.120.	ITT	EFF_T50	Summary of Categories of Assigned Dose by Visit for Daprodustat		DR, SAC
2.121.	ITT	EFF_T46	Summary of Most recent dose prior to Week 24, Week 28 and end of study treatment		DR, SAC
2.122.	ITT	EFF_T39	Summary of Maximum achieved dose		DR, SAC
2.123.	ITT	EFF_T47	Summary of Number of Subjects with 0, 1, 2, or >2 dose adjustments during the treatment period		DR, SAC
2.124.	ITT	EFF_T48	Summary of Mean and median number of dose adjustments during the treatment period		DR, SAC
2.125.	ITT	EFF_T49	Summary of Time dose held for Hemoglobin ≥13 g/dL during the treatment period		DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exploratory Efficacy Statistical Analyses: Blood Pressure					
2.126.	ITT	EFF_T43	Summary of Changes in Blood Pressure Medications Relative to Baseline During the Study		DR, SAC
Exploratory Efficacy Statistical Analyses: Severity and Change in Symptoms					
2.127.	ITT	EFF_T23	Summary of On-Treatment PGI-C Categories	On-treatment	DR, SAC
Exploratory Efficacy Statistical Analyses: Physical Activity (Actigraphy)					
2.128.	ITT	EFF_T13	Summary Statistics for On-Treatment Percentage of Daily Activity	On-treatment, includes light, moderate, vigorous, very vigorous, and MVPA Row by scheduled visit: Day 1, Week 8, Week 12, and Week 28	DR, SAC
2.129.	ITT	EFF_T13	Summary Statistics for On-Treatment Mean Hour of Daily Activity	On-treatment, includes light, moderate, vigorous, very vigorous, and MVPA Row by scheduled visit: Day 1, Week 8, Week 12, and Week 28	DR, SAC
2.130.	ITT	EFF_T13	Summary Statistics for On-Treatment Percent (%) Sleep Efficiency	On-treatment Row by scheduled visit: Day 1, Week 8, Week 12, and Week 28	DR, SAC
2.131.	ITT	EFF_T13	Summary Statistics for On-Treatment Actigraphy Wear Time (Hours)	On-treatment Row by scheduled visit: Day 1, Week 8, Week 12, and Week 28	DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.132.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment Percentage of Daily Activity	On-treatment, includes light, moderate, vigorous, very vigorous, and MVPA Row by scheduled visit: Week 8 CFB, Week 12 CFB, and Week 28 CFB	DR, SAC
2.133.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment Mean Hour of Daily Activity	On-treatment, includes light, moderate, vigorous, very vigorous, and MVPA Row by scheduled visit: Week 8 CFB, Week 12 CFB, and Week 28 CFB	DR, SAC
2.134.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment Percent Sleep Efficiency	On-treatment Row by scheduled visit: Week 8 CFB, Week 12 CFB, and Week 28 CFB	DR, SAC
2.135.	ITT	EFF_T14	Summary Statistics for the Change from Baseline in On-Treatment Actigraphy Wear Time	On-treatment Row by scheduled visit: Week 8 CFB, Week 12 CFB, and Week 28 CFB	DR, SAC

10.10.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Primary Efficacy Analyses: Model based Mean Change in Hgb between Baseline and Evaluation Period					
2.1.	ITT	EFF_F1	Line Plot of Post-randomization Observed and Imputed Hemoglobin Data by Visit		DR, SAC
2.2.	ITT	EFF_F1	Line Plot of Post-randomization Observed and Imputed Hemoglobin Change from Baseline		DR, SAC
Principal Secondary Efficacy Analyses					
2.3.	ITT	EFF_F1	Line Plot of On-Treatment Observed and Imputed SF-36 vitality sub-score values by Visit, Traditional Scoring		DR, SAC
2.4.	ITT	EFF_F1	Line Plot of On-Treatment Observed and Imputed SF-36 vitality sub-score values Change from Baseline		DR, SAC
Secondary Efficacy Statistical Analyses: Symptom Severity and Change					
2.5.	ITT	EFF_F3	Bar Chart of On-treatment Baseline and CKD-AQ Domain and Single Item Scores by Visit	Page by domain and single item scores	DR, SAC
2.6.	ITT	EFF_F4	Stacked Bar Chart of On-treatment Baseline and Week 28 Scores for PGI-S Response		DR, SAC
Secondary Efficacy Statistical Analyses: HRQoL and Utility score					
2.7.	ITT	EFF_F3	Bar Chart of On-treatment SF-36 individual items of the Vitality Domain Scores Change from Baseline	Page by individual items	DR, SAC
2.8.	ITT	EFF_F3	Line Plot of On-treatment SF-36 Physical Function Domain Scores Change from Baseline		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.9.	ITT	EFF_F3	Bar Chart of On-treatment EQ-5D-5L Scores by Visit		DR, SAC
Exploratory Efficacy Statistical Analyses: Iron Parameters					
2.10.	ITT	EFF_F1	Line Plot of On-treatment Hepcidin Data by Visit		DR, SAC
2.11.	ITT	EFF_F1	Line Plot of On-treatment Hepcidin Percent Change from Baseline		DR, SAC
2.12.	ITT	EFF_F1	Line Plot of On-treatment TSAT Data by Visit		DR, SAC
2.13.	ITT	EFF_F1	Line Plot of On-treatment TSAT Change from Baseline		DR, SAC
2.14.	ITT	EFF_F1	Line Plot of On-treatment Ferritin Data by Visit		DR, SAC
2.15.	ITT	EFF_F1	Line Plot of On-treatment Ferritin Percent Change from Baseline		DR, SAC
2.16.	ITT	EFF_F1	Line Plot of On-treatment Serum Iron Data by Visit		DR, SAC
2.17.	ITT	EFF_F1	Line Plot of On-treatment Serum Iron Percent Change from Baseline		DR, SAC
2.18.	ITT	EFF_F1	Line Plot of On-treatment TIBC Data by Visit		DR, SAC
2.19.	ITT	EFF_F1	Line Plot of On-treatment TIBC Change from Baseline		DR, SAC
Exploratory Efficacy Statistical Analyses: Renal					
2.20.	ITT	EFF_F1	Line Plot of On-treatment eGFR Data by Visit		DR, SAC
2.21.	ITT	EFF_F1	Line Plot of On-treatment eGFR Change from Baseline		DR, SAC
2.22.	ITT	EFF_F1	Line Plot of On-treatment Serum Creatinine Data by Visit		DR, SAC
2.23.	ITT	EFF_F1	Line Plot of On-treatment Serum Creatinine Change from Baseline		DR, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exploratory Efficacy Statistical Analyses: Dose Adjustment Scheme					
2.24.	ITT	EFF_F5	Stacked Bar Chart of Assigned Daprodustat Dose by Visit		SAC
Additional Efficacy Figures					
2.25.	ITT	EFF_F4	Stacked Bar Chart of On-treatment Baseline and Week 28 Scores for PGI-C Response		SAC

10.10.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	Safety	Shell 32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term	ICH E3 Add exposure-adjusted AE incidence for both treatments	DR, SAC
3.2.	Safety	Shell 32	Summary of All Treatment Emergent Adverse Events by System Organ Class, Higher Level Term, and Preferred Term	ICH E3	DR, SAC
3.3.	Safety	Shell 32	Summary of All Follow-Up Adverse Events by System Organ Class and Preferred Term	ICH E3	DR, SAC
3.4.	Safety	Shell 33	Summary of Common (>=5%) Treatment Emergent Adverse Events by Overall Frequency	ICH E3	DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.5.	Safety	Shell 32.1	Summary of All Treatment Emergent Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3	DR, SAC
3.6.	Safety	Shell 32	Summary of All Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	ICH E3	DR, SAC
3.7.	Safety	Shell 32	Summary of All Serious Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term		DR, SAC
3.8.	Safety	AE20	Summary of Treatment Emergent Serious Fatal and Non-Fatal Drug-Related Adverse Events by Overall Frequency	Page by fatal vs non-fatal	DR, SAC
3.9.	Safety	Shell 32	Summary of All Non-Serious Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term		DR, SAC
3.10.	Safety	Shell 33	Summary of All Non-Serious Drug-Related Treatment Emergent Adverse Events by Overall Frequency		DR, SAC
3.11.	Safety	Shell 34	Summary of Common (>=5%) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	DR, SAC
3.12.	Safety	Shell 32.1	Summary of All Treatment Emergent Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	ICH E3	DR, SAC
3.13.	Safety	Shell 32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Race		DR, SAC
3.14.	Safety	Shell 32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Age		DR, SAC
3.15.	Safety	Shell 32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Gender		DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.16.	Safety	Shell 49	Summary of Treatment Emergent Adverse Events of Special Interest by Preferred Term	Add exposure-adjusted AE incidence for both treatments	DR, SAC
3.17.	ITT	Shell 1	Summary of First-Occurrence of Adjudicated MACE		DR, SAC
3.18.	ITT	Shell 3	Summary of All Adjudicated MACE		DR, SAC
3.19.	ITT	Shell 1	Summary of First Occurrence of Adjudicated MACE or Thromboembolic Events or Hospitalization for Heart Failure		DR, SAC
3.20.	ITT	Shell 3	Summary of All Adjudicated MACE or Thromboembolic Events or Hospitalization for Heart Failure		DR, SAC
Serious and Other Significant Adverse Events					
3.21.	Safety	Shell 34	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	DR, SAC
3.22.	Safety	Shell 32	Summary of Serious Treatment Emergent Adverse Events by System Organ Class, Higher Level Term, and Preferred Term	ICH E3	DR, SAC
3.23.	Safety	Shell 34	Summary of Serious Follow-Up Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	DR, SAC
3.24.	Safety	Shell 32	Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	IDSL Add exposure-adjusted AE incidence for both treatments	DR, SAC
Laboratory: Chemistry					
3.25.	Safety	Shell 16	Summary of Post-randomization Chemistry Change from Baseline	ICH E3	DR, SAC
3.26.	Safety	Shell 36	Summary of Worst Case On-treatment Chemistry Results PCI Criteria Post-Baseline Relative to Baseline	ICH E3	DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.27.	Safety	Shell 35	Summary of Worst Case On-treatment Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	DR, SAC
Laboratory: Hematology					
3.28.	Safety	Shell 16	Summary of Post-randomization Hematology Change from Baseline	ICH E3	DR, SAC
3.29.	Safety	Shell 36	Summary of Worst Case On-treatment Hematology Results by PCI Criteria Post-Baseline Relative to Baseline	ICH E3	DR, SAC
3.30.	Safety	Shell 35	Summary of Worst Case On-treatment Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	DR, SAC
Laboratory: Hepatobiliary (Liver)					
3.31.	Safety	Shell 37	Summary of Post-randomization Liver Monitoring/Stopping Event Reporting	IDSL	DR, SAC
3.32.	Safety	Shell 38	Summary of Post-randomization Hepatobiliary Laboratory Abnormalities	IDSL	DR, SAC
Vital Signs					
3.33.	Safety	Shell 15	Summary of Post-randomization Vital Signs by Visit	ICH E3	DR, SAC
3.34.	Safety	Shell 16	Summary of Post-randomization Change from Baseline in Vital Signs by Visit	ICH E3	DR, SAC
3.35.	Safety	Shell 36	Summary of Worst Case On-treatment Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	IDSL	DR, SAC
Other Safety Tables					
3.36.	Safety	PAN1	Summary of COVID-19 Assessment	No events column	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.37.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time	- Timeblock 1= pre-pandemic - Timeblock 2= during-pandemic	SAC
3.38.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time by Region	- Timeblock 1= pre-pandemic - Timeblock 2= during-pandemic	SAC
3.39.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time by Age	- Timeblock 1= pre-pandemic - Timeblock 2= during-pandemic	SAC
3.40.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates Over Time by Gender	- Timeblock 1= pre-pandemic - Timeblock 2= during-pandemic	SAC
3.41.	Safety	PAN11	Summary of Exposure Adjusted Incidence Rate for Common (>=5%) Adverse Events	- Timeblock 1= pre-pandemic - Timeblock 2= during-pandemic	SAC
3.42.	Safety	Shell 15	Summary of Post-randomization Chemistry by Visit		SAC
3.43.	Safety	Shell 15	Summary of Post-randomization Hematology by Visit		SAC
3.44.	Safety	Shell 32	Summary of All Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	ICH E3 Add exposure-adjusted AE incidence for both treatments	SAC
3.45.	Safety	Shell 32	Summary of Treatment Emergent Fatal Adverse Events by System Organ Class and Preferred Term	Add exposure-adjusted AE incidence for both treatments	SAC
3.46.	Safety	Shell 32	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Weight Quartile		SAC
3.47.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Death, Myocardial Infarction, Stroke, Heart Failure, Thromboembolic Events, and Thrombosis of Vascular Access		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.48.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis		SAC
3.49.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Cardiomyopathy		SAC
3.50.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Pulmonary Artery Hypertension		SAC
3.51.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Cancer-related Mortality and Tumor Progression and Recurrence		SAC
3.52.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Esophageal and Gastric Erosions		SAC
3.53.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Proliferative Retinopathy, Macular Edema, Choroidal Neovascularization		SAC
3.54.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Exacerbation of Rheumatoid Arthritis		SAC
3.55.	Safety	Shell 50	Summary of Characteristics of Treatment Emergent Adverse Event of Special Interest of Worsening of Hypertension		SAC

10.10.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
3.1.	Safety	AE10	Plot of Common (>=5%) Adverse Events	IDSL	DR, SAC
Laboratory					
3.2.	Safety	Shell 3.6	Scatter Plot of Maximum On Treatment ALT vs. Baseline for ALT	IDSL	DR, SAC
3.3.	Safety	Shell 3.7	Scatter Plot of On Treatment Maximum ALT vs. Maximum Total Bilirubin	IDSL	DR, SAC
Additional Safety Figures					
3.4.	Safety	Shell 3.4	Dot Plot of Treatment Emergent Adverse Events by Higher Level Term		SAC

10.10.10. 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.	ITT	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	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	DR, SAC
5.	Safety	TA1	Listing of Planned and Actual Treatments	IDSL	DR, SAC
Protocol Deviations					
6.	ITT	DV2	Listing of Important Protocol Deviations	ICH E3	DR, SAC
7.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	DR, SAC
Populations Analysed					
8.	Enrolled	SP3	Listing of Subjects Excluded from Any Population	ICH E3	DR, SAC
Demographic and Baseline Characteristics					
9.	ITT	DM2	Listing of Demographic Characteristics	ICH E3	DR, SAC
10.	ITT	DM9	Listing of Race	ICH E3	DR, SAC
Prior and Concomitant Medications					
11.	ITT	CM10	Listing of Concomitant Medications	IDSL	DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
12.	Safety	CM6	Relationship between ATC Level 1, 2, 3, Ingredient and Verbatim Text	IDSL	DR, SAC
Exposure and Treatment Compliance					
13.	ITT	EX3	Listing of Exposure Data and Treatment Compliance Data	ICH E3, include % treatment compliance for each subject	DR, SAC
Adverse Events					
14.	Safety	Safety Listing Shell 3	Listing of All Adverse Events	ICH E3	DR, SAC
15.	Safety	Safety Listing Shell 4	Listing of Subject Numbers for Individual Adverse Events	ICH E3	DR, SAC
16.	Safety	Safety Listing Shell 5	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	Safety Listing Shell 3	Listing of Treatment Emergent Fatal Serious Adverse Events	ICH E3	DR, SAC
18.	Safety	Safety Listing Shell 3	Listing of Treatment Emergent Non-Fatal Serious Adverse Events	ICH E3	DR, SAC
19.	Safety	Safety Listing Shell 6	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	DR, SAC
20.	Safety	Safety Listing Shell 3	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment	ICH E3	DR, SAC
21.	Safety	Safety Listing Shell 3	Listing of Other Significant Adverse Events	ICH E3	DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Hepatobiliary (Liver)					
22.	Safety	Safety Listing Shell 7	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	DR, SAC
23.	Safety	Safety Listing Shell 8	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	DR, SAC
All Laboratory					
24.	Safety	Safety Listing Shell 9	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance/Outside Normal Range	ICH E3	DR, SAC
25.	Safety	LB5	Listing of Laboratory Values of Potential Clinical Importance/Outside Normal Range		DR, SAC
26.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	DR, SAC
Vital Signs					
27.	Safety	Safety Listing Shell 10	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	IDSL	DR, SAC
28.	Safety	Safety Listing Shell 10	Listing of Vital Signs of Potential Clinical Importance	IDSL	DR, SAC

10.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
29.	ITT	MH2	Listing of Medical Conditions		DR, SAC
30.	ITT	Safety Listing Shell 12	Listing of all IV Iron use, rescue, rhEPO use, and blood transfusion		DR, SAC
31.	ITT	Safety Listing Shell 1	Listing of all adjudicated MACE		DR, SAC
32.	ITT	Safety Listing Shell 2	listing of adjudicated all-cause mortality		DR, SAC
33.	ITT	PAN7	Listing of All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic		SAC
34.	ITT	Efficacy Listing Shell 1	Listing of Hemoglobin Data		SAC

10.11. Appendix 11: Example Mock Shells for Data Displays

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

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Reason for signing: Approved	Name: PPD Role: Author Date of signature: 10-Nov-2020 23:49:39 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 11-Nov-2020 12:47:44 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 11-Nov-2020 17:13:56 GMT+0000

Reason for signing: Approved	Name: PPD Role: Author Date of signature: 12-Nov-2020 01:25:06 GMT+0000

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