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

Title	:	Reporting and Analysis Plan for 204716 A 24-week, Phase III, open-label, non-comparative, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese hemodialysis subjects with anemia associated with chronic kidney disease who are not taking erythropoiesis stimulating agents.
Compound Number	:	GSK1278863
Effective Date	:	29-Nov-2017

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204716.
- This RAP is intended to describe the 204716 analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Biostatistics Group 2, Biomedical Data Sciences Japan	29-Nov-2017

Approved by:

PPD Manager, Biostatistics Group 2, Biomedical Data Sciences Japan	29-Nov-2017
PPD Manager, Statistical Programming & Reporting Group, Biomedical Data Sciences Japan	29-Nov-2017

Revision History (Appendix 16):

Version	Date
Reporting and Analysis Plan_204716_Final_V1.0	19-Jun-2017
Reporting and Analysis Plan_204716_Amendment_Final_V1.1	11-Oct-2017
Reporting and Analysis Plan_204716_Amendment_Final_V1.2	29-Nov-2017

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP describes the planned analyses and outputs required for the final Clinical Study Report (CSR) for study 204716.
Protocol	• This RAP is based on the protocol amendment v04 (Dated: 19/Jul/2017) of study 204716 (GSK Document No.2015N266250_04].
Primary Objective	• To characterize the appropriateness of the starting dose of GSK1278863 in HD patients not using ESAs
Primary Endpoint	• Change from baseline in Hgb at Week 4 • Number (%) of subjects by Hgb change from baseline category at Week 4
Study Design	• This is a 24-week, Phase III, open-label, non-comparative, multi-center study to evaluate efficacy and safety of GSK1278863 in approximately 22 Japanese hemodialysis subjects with anemia associated with chronic kidney disease who are not taking erythropoiesis stimulating agents.
Planned Analyses	• No interim analysis is planned. • Final analyses will be performed according to the steps described in Section 3.2. • All decisions regarding final analyses, as defined in this RAP document, will be made prior to Database Freeze of the study data.
Analysis Populations	• All Screening Population will consist of all subjects who are given subject number and are collected data at screening. • Enrolled Population will consist of subjects in 'All Screening' except for screen failures (who never passed screening even if rescreened). • Assigned Population will consist of all randomized subjects regardless of study treatment actually received or not • All Treated Subjects Population will consist of all subjects who receive at least one dose of GSK1278863. • Pharmacokinetic (PK) Population will consist of all subjects who received GSK1278863 with the PK samples collected and analysed.
Hypothesis	• This single arm study is a study with an aim of an estimation. The primary objective of this study is to evaluate the initial anemia correction of GSK1278863 in HD patients not using ESAs. There will be no hypothesis testing performed in this study.
Primary Analyses	• For the change from baseline in Hgb at Week 4, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. • The change in Hgb at Week 4 will be classified into different categories (i.e., ≤-

Overview	Key Elements of the RAP
	2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, and >2 g/dL), and the number (%) of subjects in each category will be summarized.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

No changes from the originally planned statistical analysis specified in the protocol amendment v04 (Dated: 19/Jul/2017) are present.

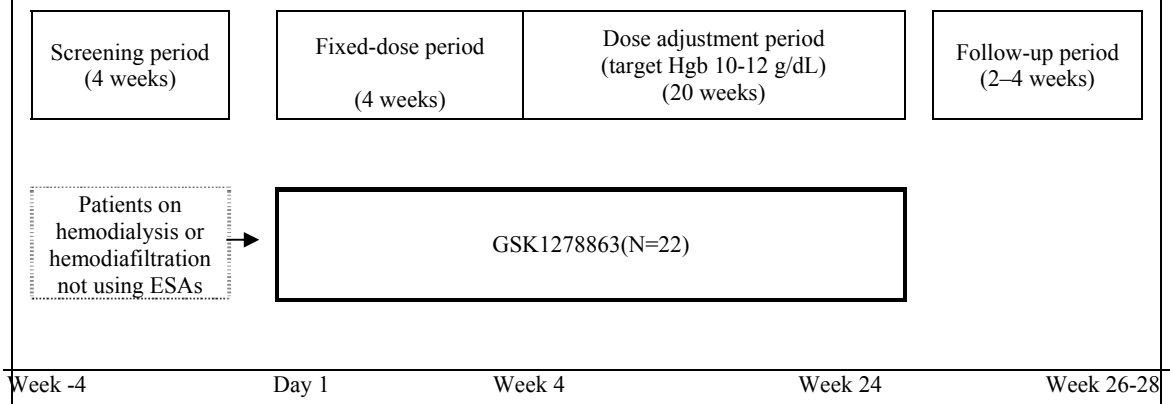
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
• To characterize the appropriateness of the starting dose of GSK1278863 in HD patients not using ESAs	• Change from baseline in Hgb at Week 4 • Number (%) of subjects by Hgb change from baseline category at Week 4
Secondary	
• To characterize overall Hgb control of GSK1278863 in HD patients not using ESAs	• Hgb and changes from baseline • Number (%) of subjects who have a Hgb level within the target range (10.0–12.0 g/dL) • Time (in days) to reach the lower target Hgb level (10.0 g/dL) • Number (%) of subjects who have a Hgb level of less than < 7.5 g/dL • Number (%) of subjects who have a Hgb increase of more than > 2-g/dL over any 4 weeks • Number (%) of subjects who have a Hgb level of more than > 13.0 g/dL and number of episodes
• To characterize the pharmacokinetics of GSK1278863	• AUC and Cmax of plasma GSK1278863
• To characterize the effect on iron use of GSK1278863 in HD patients not using ESAs	• Dose of intravenous iron • Number (%) of subjects who used intravenous iron
• To characterize the effect on iron metabolism of GSK1278863 in HD patients not using ESAs	• Change from baseline in ferritin • Change from baseline in transferrin saturation

Objectives	Endpoints
	• Changes from baseline in hepcidin, serum iron, and total iron binding capacity (TIBC)
• To characterize dose adjustment of GSK1278863 in HD patients not using ESAs	• Distribution of dose level • Frequency of dose adjustments • Duration of treatment interruption due to Hgb > 13 g/dL
Safety	
• To assess the safety and tolerability of GSK1278863 in HD patients not using ESAs	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including adverse events of special interest (AESIs) • Reasons for discontinuation of study medication • Laboratory tests, electrocardiogram (ECG), vital signs, and ophthalmology assessments

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a 24-week, Phase III, open-label, non-comparative, multi-center study to evaluate the efficacy and safety of GSK1278863 in Japanese HD patients with renal anemia not using ESAs. • This study will consist of a 4-week screening period, a 24-week treatment period (4-week fixed-dose period and a 20-week dose adjustment period), and a 2- to 4-week follow-up period.
Dosing	• Subjects meeting the eligibility criteria will receive GSK1278863 orally once daily initially at 4 mg for 4 weeks from Day 1. Subsequently, subjects will receive GSK1278863 orally once a day according to follow a pre-defined study treatment dose adjustment algorithm to achieve or maintain Hgb within the target range (10.0–12.0 g/dL). • Further details of administration schedule are provided protocol Section 6.3
Treatment Assignment	• This is an open-label, non-comparative study. All eligible subjects will take GSK1278863.
Interim Analysis	• No interim analysis is planned.

2.4. Statistical Hypotheses

This single arm study is a study with an aim of an estimation. The primary objective of this study is to evaluate the initial anemia correction of GSK1278863 in HD patients not

using ESAs. There will be no hypothesis testing performed in this study. Two-sided 95% confidence intervals will be used for efficacy estimation.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned.

3.2. Final Analyses

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

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for releasing the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screening	• Consists of all subjects who are given subject number and are corrected data at screening.	• Study Population
Enrolled	• Consist of subjects in 'All Screening' except for screen failure (who never passed screening even if rescreened).	• Study Population (some displays for EudraCT)
Assigned	• Consist of all subjects who are given randomization number regardless of whether they actually receive GSK1278863.	• Study Population
All Treated Subjects	• Consist of all subjects who received at least one dose of GSK1278863.	• Study Population • Efficacy • Safety
PK	• Consist of all subjects who received GSK1278863 with the PK samples collected and analyzed.	• PK

NOTES :

- Basically, enrolled population will be the same as assigned population because a subject is going to be given randomized number as soon as passed screening
- Please refer to Appendix 14: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- 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.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorized on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

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

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance
10.9	Appendix 9: Multicenter Studies
10.10	Appendix 10: Examination of Covariates, Subgroups & Other Strata
10.11	Appendix 11: Multiple Comparisons & Multiplicity
10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the All Treated Subjects population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Population	Data Displays Generated		
		Table	Figure	Listing
Subject Disposition				
Subject Status and Reason for Study Withdrawal	Assigned	Y		
Subject Status and Reason for Study Withdrawal by Dialysis Status	Assigned	Y		
Reasons for Subject Withdrawal	Assigned			Y
Treatment Status and Reasons for Discontinuation of Study Treatment	All Treated	Y		Y
Screening Status and Reasons for Screen Failure	All Screening	Y		Y
Subjects Enrolled by Country and Site ID	Enrolled	Y		
Protocol Deviations				
Important Protocol Deviations	Assigned	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations	Assigned	Y		Y
Populations Analyzed				
Study Populations	All Screening	Y		
Exclusions from Study Population	Assigned	Y		
Subjects Excluded from Any Population	Assigned			Y
Demographic and Baseline Characteristics				
Demographic Characteristics	All Treated	Y		Y
Demographic Characteristics by Dialysis Status	All Treated	Y		
Age Ranges	Enrolled	Y		
Race and Racial Combinations	All Treated	Y		Y [1]
Family History for CV Risk Factors	All Treated	Y		Y
Substance Use (History of Tobacco Use, Alcohol Intake)	All Treated	Y		Y
Prior and Concomitant Medications				
Current/Past Medical Conditions	All Treated	Y		Y
Current/Past Medical Conditions by Dialysis Status	All Treated	Y		
Concomitant Medications [2]	All Treated	Y		Y
Other Concomitant Medications [3]	All Treated	Y		Y

Endpoint / Parameter / Display Type	Population	Data Displays Generated		
		Table	Figure	Listing
Other Concomitant Medications [3] by Dialysis Status	All Treated	Y		
Blood products and blood supportive care products [4]	All Treated	Y		Y
Blood products and blood supportive care products [4] by Dialysis Status	All Treated	Y		
Dialysis				
Dialysis Status	All Treated	Y		Y
Baseline Mode of Dialysis	All Treated	Y		Y
Subjects with Change in Hemodialysis	All Treated			Y
Baseline Vascular Access	All Treated	Y		Y
Subjects with Vascular Therapeutic Procedures during the study period	All Treated			Y
Exposure and Treatment Compliance				
Exposure to Study Treatment	All Treated	Y		Y
Exposure to Study Treatment by Dialysis Status	All Treated	Y		
Treatment Compliance	All Treated	Y		Y

NOTES :

- Y = Yes display generated.
- Some summaries will be generated as efficacy analyses.

[1] Listing of race.
[2] Concomitant medications in prior-therapy period, on-therapy period, and post-therapy period will be summarized separately.
[3] On-therapy ESA and iron medication will be provided.
[4] On-therapy blood products and blood supportive care products will be provided.

6.1.1. Planned Summary Display Details

A subject who has multiple subject numbers (i.e. rescreened subject) will be analyzed as a unique subject based on the latest screening result.

The definition of subgroup is described in Appendix 10.

- **Subject Disposition**

Subject Status and Reason for Study Withdrawal

The number and percentage of subjects completing the study or withdrawing early from the study will be summarized overall and by reason for withdrawal. Reasons for withdrawal will be listed for subject. The subgroup analysis for dialysis status will be summarized as the same.

Treatment Status and Reasons for Discontinuation of Study Treatment

The number and percentage of subjects completing the treatment or discontinuing the treatment during the study will be summarized overall and by reason.

Screening Status and Reasons for Screen Failure

The number and percentage of subjects who failed screening and were therefore not randomized into the study, overall and by reason, will be summarized for all screening population. Note that the reasons for rescreen subjects who initially failed but subsequently enrolled are not included in the display (see Section 10.6.2).

Subjects Enrolled by Country and Site ID

The number and percentage of subjects by region, country and center will be summarized.

- **Protocol Deviations**

Important Protocol Deviations

The number and percentage of subjects who had important protocol deviations defined in PDMP will be summarized.

Subjects with Inclusion/Exclusion Criteria Deviations

The number and percentage of subjects with any Inclusion/Exclusion Criteria Deviations will be summarized, further classifying inclusion/exclusion deviations.

- **Population Analyzed**

Study Populations

The number of subjects in each analysis population (defined in Section 4) will be summarized.

Exclusions from Study Population

The number of subjects excluded from All Treated Subjects population will be summarized for the assigned population.

- **Demographic and Baseline Characteristics**

Demographic Characteristics

The number and percentage of subjects or summary statistics will be provided for the demographic and baseline characteristics: Sex, Age (years), Age Group (years), Ethnicity, Race detail, Height, Weight, and Body Mass Index. Age Group (years) will be categorized into 3 ('<=18', '19-64', '>=65'). The subgroup analysis for dialysis status will be summarized as the same.

Age Ranges

The number and percentage of subjects within each age range category will be provided. Age range will be categorized into: Adult (18-64 years), >=65-84 years, >=85 years.

Race and Racial Combinations

Summaries of race and racial combinations will be provided.

Family History for CV Risk Factors

A summary of family (first degree relatives) history for CV risk factors will be provided.

Substance Use (History of Tobacco Use, Alcohol Intake)

A summary of substance use will be provided.

- **Prior and Concomitant Medications**

Current/Past Medical Conditions

The number and percentage of subjects with current and past medical conditions recorded in eCRF will be provided. The subgroup analysis for dialysis status will be summarized as the same.

Concomitant Medications

The number and percentage of subjects reporting the use of each concomitant medication will be summarized by anatomical therapeutic chemical (ATC) Level 1, and Ingredient. Summaries of pre-therapy, on-therapy, and post-therapy medication will be provided separately. See Section 10.4.1.3 for treatment states for concomitant medications.

Other concomitant medications

The similar summary as above will be provided focusing on on-therapy ESA and iron medication. See Section 10.4.1.3 for treatment states. The subgroup analysis for dialysis status will be summarized as the same.

Blood products and blood supportive care products

The number and percentage of subjects who use blood products and/or blood supportive care products will be provided. The details for the use will also be provided. The subgroup analysis for dialysis status will be summarized as the same.

- **Dialysis**

Dialysis Status

The number and percentage of subjects with dialysis status of newly started dialysis and maintenance dialysis will be provided. Definitions of dialysis status are described in the protocol section 5.3.

Baseline Mode of Dialysis

The number and percentage of subjects with each baseline mode of dialysis (i.e. haemodialysis, haemofiltration, or haemodiafiltration) will be provided.

Baseline Vascular Access

The number and percentage of subjects with each baseline vascular access will be provided. Previous vascular access will be summarized as the same.

- **Exposure and Treatment Compliance**

Exposure to Study Treatment

Full details of exposure definition are presented in Appendix 6.

Daily dose, cumulative dose, and days on study drug will be summarized using mean, standard deviation, median, minimum, and maximum. Regarding days on study drug, the number and percentage of subjects within each category (i.e. 1-28, 29-56, 57-84, 85-112, 113-140, 141-168, >168 (days)) will also be provided. The subgroup analysis for dialysis status will be summarized as the same.

Treatment Compliance

Full details of treatment compliance definition are presented in Appendix 6.

The number and percentage of subjects within each category of treatment compliance will be provided and the categories will be classified into <80%, 80% to 120%, and >120%.

7. PRIMARY STATISTICAL ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Overview of Planned Primary Efficacy Analyses

The primary efficacy analyses will be based on the All Treated Subjects population, unless otherwise specified.

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 3 Overview of Planned Primary Efficacy Analyses

Endpoint / Parameter/ Display Type	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Change from baseline in Hgb at Week 4				Y			
Number (%) of subjects by Hgb change from baseline category at Week 4 [1]				Y			
Change from baseline in Hgb at Week 4 by Dialysis Status				Y			
Number (%) of subjects by Hgb change from baseline category at Week 4 [1] by Dialysis Status				Y			

NOTES :

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

[1] ≤-2, -2 to -1, -1 to 0, 0 to 1, 1 to 2, and >2 g/dL. In addition, within ±1 g/dL and over ±2 g/dL.

7.1.2. Planned Efficacy Statistical Analyses

Primary Analyses
Endpoint(s)
• Change from baseline in Hgb at Week 4 • Number (%) of subjects by Hgb change from baseline category at Week 4
Model Specification
• Hgb values from central laboratory 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 (See Section 10.6.3). • The primary analysis is to assess modest increase in Hgb in initial response to GSK1278863 (i.e., Hgb increase by ≤ 2 g/dL after 4 weeks of treatment), on the basis of the mean change from baseline in Hgb at Week 4 as well as the number (%) of subjects by Hgb change from baseline category at Week 4 as the primary efficacy endpoints. • For the change from baseline in Hgb at Week 4, the summary statistics will be calculated,

along with the two-sided 95% confidence interval based on t-distribution.

- The change in Hgb at Week 4 will be classifieds into different categories (i.e., ≤-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, and >2 g/dL), and the number (%) of subjects in each category will be summarized. In addition, 'within ± 1 g/dL (i.e., ≥-1 and ≤1 g/dL)' and 'over ± 2 g/dL (i.e., <-2 and >2 g/dL)' categories will be provided.

7.1.3. Planned Summary Display Details

The definition of subgroup is described in Appendix 10.

Change from baseline in Hgb at Week 4

This summary will be included within a summary of change from baseline in Hgb at each assessment visit (See Section 8.1.2). The values will be summarized using mean, standard deviation, 95%CI, minimum, P25, median, P75, and maximum at Week 4 visit. The subgroup analysis will be summarized as the same.

Number (%) of subjects by Hgb change from baseline category at Week 4

The number and percentage of subjects within each category will be provided and the categories will be classified into ≤-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, and >2 g/dL). In addition, 'within ± 1 g/dL (i.e., ≥-1 and ≤1)' and 'over ± 2 g/dL (i.e., <-2 and >2)' categories will be provided. The subgroup analysis will be summarized as the same.

8. SECONDARY STATISTICAL ANALYSES

8.1. Secondary Efficacy Analyses

8.1.1. Overview of Planned Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the All Treated Subjects population, unless otherwise specified.

Table 4 provides an overview of the planned secondary efficacy analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 4 Overview of Planned Efficacy Analyses

Endpoint / Parameter/ Display Type	Absolute					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Hgb						
Hgb at each assessment visit			Y	Y		Y
Hgb at each assessment visit by Dialysis Status			Y	Y		
Change from baseline at each assessment visit			Y	Y		Y
Change from baseline at each assessment visit by Dialysis Status			Y	Y		
Number (%) of subjects with Hgb within the target range at each assessment visit [1]			Y	Y		
Number (%) of subjects with Hgb within the target range at each assessment visit [1] by Dialysis Status			Y	Y		
Time (in days) to reach the lower target Hgb level (10.0 g/dL) [2] [3]	Y	Y				
Time (in days) to reach the lower target Hgb level (10.0 g/dL) [2] [3] by Dialysis Status	Y	Y				
Number (%) of subjects who have an Hgb level of less than 7.5 g/dL [3]			Y			Y
Number (%) of subjects who have an Hgb level of less than 7.5 g/dL [3] by Dialysis Status			Y			
Number (%) of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks [3]			Y			Y
Number (%) of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks [3] by Dialysis Status			Y			
Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes [3]			Y			Y
Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes [3] by Dialysis Status			Y			
Hemocue Hgb						Y

Endpoint / Parameter/ Display Type	Absolute					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L
Scatter plot of Hgb assessments: Central Laboratory vs. HemoCue		Y				
Iron use						
Dose of i.v. iron during the treatment period			Y			Y
Dose of i.v. iron during the treatment period by Dialysis Status			Y			
Number (%) of subjects who use iron during the treatment period			Y			
Number (%) of subjects who use iron during the treatment period by Dialysis Status			Y			
Iron Parameters (ferritin, TSAT [4], hepcidin [4], serum iron, and TIBC)						
Raw observed value at each assessment visit			Y			Y
Raw observed value at each assessment visit by Dialysis Status			Y			
Change from baseline at each assessment visit			Y	Y		
Change from baseline at each assessment visit by Dialysis Status			Y			
Dose adjustment [5]						
Dose level (mg) at each assessment visit			Y	Y		Y
Dose level (mg) at each assessment visit by Dialysis Status			Y	Y		
Duration (days) of treatment interruption due to Hgb >13.0 g/dL [3]			Y			
Duration (days) of treatment interruption due to Hgb >13.0 g/dL [3] by Dialysis Status			Y			
Dose adjustment			Y			
Dose adjustment by Dialysis Status			Y			
Number (%) of subjects with each dose level at each assessment visit			Y			
Number (%) of subjects with each dose level at each assessment visit by Dialysis Status			Y			
Number of dose adjustment to reach the lower Hgb target Hgb level (10.0 g/dL)			Y			
Number of dose adjustment to reach the lower Hgb target Hgb level (10.0 g/dL) by Dialysis Status			Y			
Other						
Scatter plot of change from baseline in Hgb at Week 4 vs. candidate covariates [6]				Y		
Scatter plot of mean dose vs. candidate covariates [6]				Y		

NOTES :

[1] Not only within the target range, but also subjects with above and below target range will be assessed.

[2] Time to first reach the lower target Hgb level will be estimated by Kaplan-Meier method using P25, median and P75. Subjects who could not reach lower target will be regarded as censored.

Endpoint / Parameter/ Display Type	Absolute					
	Stats Analysis		Summary		Individual	
	T	F	T	F	F	L

[3] On-therapy Hgb values observed in scheduled visits will be included. On-therapy Hgb values observed in unscheduled visits will be included if specified (see Section 8.1.2)
[4] Based on literature review the distributions of TSAT and hepcidin are skewed and require a log-transformation.
[5] Summaries for dose adjustment will be based on HemoCue Hgb values including those of unscheduled visits.
[6] Figures will include the candidate covariates of body weight and baseline Hgb, and will be produced for overall and dialysis status groups.

8.1.2. Planned Efficacy Table Displays

- **Hgb**

Hgb at each assessment visit

The values will be summarized using mean, standard deviation, 95%CI, minimum, P25, median, P75, and maximum at each assessment visit. Graphical summaries will be provided using mean and 95% CI over time. The subgroup analysis for dialysis status will be summarized as the same.

Change from baseline at each assessment visit

The values will be summarized using mean, standard deviation, 95%CI, minimum, P25, median, P75, and maximum at each assessment visit. Graphical summaries will be provided using mean and 95% CI over time. This will be also summarized by baseline dialysis status.

Number (%) of subjects with Hgb within the target range at each assessment visit

The number and percentage of subjects with Hgb within, above and below the target range at each assessment visit will be summarized. This will be also summarized by baseline dialysis status.

Time (in days) to reach the lower target Hgb level (10.0 g/dL)

The time (in days) will be summarized using P25, median, and P75 by Kaplan-Meier method. Kaplan-Meier plot of time to event will be provided using on-therapy Hgb values. Subjects who could not reach lower target will be regarded as censored. This will be also summarized by baseline dialysis status.

Number (%) of subjects who have an Hgb level of less than 7.5 g/dL

The number and percentage of subjects who have an Hgb level of less than 7.5 g/dL will be summarized. On-therapy Hgb values observed in both scheduled and unscheduled visits will be included in the summary. This will be also summarized by baseline dialysis status.

Number (%) of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks

The number and percentage of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks will be summarized. On-therapy Hgb values will be used for the summary. This will be also summarized by baseline dialysis status. See Section 10.6.3 for detailed derivation.

Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes

The number and percentage of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes will be summarized. On-therapy Hgb values observed in both scheduled and unscheduled visits will be included in the summary. This will be also summarized by baseline dialysis status.

Scatter plot of Hgb assessments: Central Laboratory vs. HemoCue

A scatter plot of Hgb values measured by Central Laboratory versus Hgb values measured by Hemocue will be produced along with Pearson's correlation coefficient. All available pairs of Hgb (i.e. non-missing values in both from central laboratory and from the corresponding HemoCue measurement) will be used.

- **Iron Use**

Dose of i.v. iron during the treatment period

Average quarterly i.v. iron dose (See Section 10.6.3) will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. Quarter 1 (Day 1 to Week 12) and Quarter 2 (Week 12 to Week 24) will be used. This will be also summarized by baseline dialysis status.

Number (%) of subjects who use iron during the treatment period

The number and percentage of subjects who use iron (both i.v. and oral iron) during the treatment period will be summarized. This will be also summarized by baseline dialysis status.

- **Iron Parameter (ferritin, TSAT, hepcidin, serum iron, and TIBC)**

Based on literature review the distributions of TSAT and hepcidin are skewed and require a log-transformation (See Section 10.6.3).

Raw observed value at each assessment visit

Ferritin, serum iron, and TIBC values will be summarized using mean, standard deviation, 95%CI, minimum, P25, median, P75, and maximum at each assessment visit. TSAT and hepcidin values will be summarized using geometric mean, standard error, coefficient of

variation, and 95%CI based on log-transformed parameters, and median, minimum, and maximum based on original scale at each assessment visit. This will be also summarized by baseline dialysis status.

Change from baseline at each assessment visit

Change from baseline in Ferritin, serum iron, and TIBC values will be summarized using mean, standard deviation, 95%CI, minimum, P25, median, P75, and maximum at each assessment visit. Percent Change from baseline in TSAT and hepcidin values will be summarized using geometric mean and 95%CI based on log-transformed parameters, and median, minimum, and maximum based on original scale at each assessment visit. Graphical summaries will be provided using mean and 95% CI over time. This will be also summarized by baseline dialysis status.

- **Dose adjustment**

The dose adjustment algorithm is described in Section 10.6.3, based on HemoCue Hgb values including those in both scheduled and unscheduled visits

Dose level (mg) at each assessment visit

The values will be summarized using mean, standard deviation, minimum, P25, median, P75, mode, and maximum at each assessment visit. The mean dose during Week 12 to 24 will also be summarized. This will be also summarized by baseline dialysis status.

Duration (days) of treatment interruption due to Hgb >13.0 g/dL

The number and percentage of subjects who have a period of treatment interruption due to Hgb >13.0 g/dL will be summarized. On subjects who have a period of treatment interruption due to Hgb >13.0 g/dL, the duration (in days) of treatment interruption due to Hgb >13.0 g/dL per subject will be summarized using mean, standard deviation, minimum, P25, median, P75, and maximum. Hgb values observed in both scheduled and unscheduled visits will be counted in the summary. This will be also summarized by baseline dialysis status.

Dose adjustment

The number and percentage of subjects with dose adjustments will be provided. Number of dose adjustments will be summarized using mean, standard deviation, minimum, median, mode, and maximum. For dose adjustments frequency, the number and percentage of subjects will be provided by the number of dose adjustments (i.e. zero, one, two, three, four, and five or more). For timing of dose adjustments, the number and percentage of subjects with dose adjustments by each assessment visit will be provided. This will be also summarized by baseline dialysis status.

Number (%) of subjects with each dose level at each assessment visit

The number and percentage of subjects with each dose level adjustments will be provided. Graphical summaries will be provided with the number of subjects in each dose level. Dose level categories will be classified into 10; W/d (early withdrawal), 0 mg (treatment interruption), 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 18 mg, and 24 mg). This will be also summarized by baseline dialysis status.

Number of dose adjustment to reach the lower Hgb target (10.0 g/dL)

The number and percentage of subjects with dose adjustments to reach the lower Hgb target will be provided on the basis of on-therapy Hgb. Number of dose adjustment to reach the lower Hgb target will be summarized using mean, standard deviation, minimum, median, mode, and maximum. For dose adjustments frequency, the number and percentage of subjects will be provided by the number of dose adjustments (i.e., zero, one, two, three, four, five or more). Subjects who does not reach the lower Hgb target during treatment period will be excluded from the summary. This will be also summarized by baseline dialysis status.

- **Other**

The following two sorts of scatter plots of interest will be produced for overall and dialysis status groups:

Change from baseline in Hgb at Week 4 versus the candidate covariates

Mean dose during Week 12 to 24 versus the candidate covariates

See Appendix 10 for the candidate covariates and Section 10.6.3 for the detailed derivations.

8.1.3. Planned Hgb Efficacy Statistical Analyses

Secondary Hgb Analyses
Endpoint(s)
• Hgb and changes from baseline • Number (%) of subjects who have a Hgb level within the target range (10.0–12.0 g/dL) • Time (in days) to reach the lower target Hgb level (10.0 g/dL) • Number (%) of subjects who have a Hgb level of less than 7.5 g/dL • Number (%) of subjects who have a Hgb increase of more than 2.0 g/dL over any 4 weeks • Number (%) of subjects who have a Hgb level of more than 13.0 g/dL and number of episodes
Model Specification
• Hgb values from central laboratory 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 (See Section 10.6.3). • The secondary analysis is to assess appropriate control of Hgb within the target range, on the basis of the Hgb mean at Week 24 and the number (%) of subjects with Hgb within the target

Secondary Hgb Analyses
range as secondary endpoints. • For the Hgb, the summary statistics will be calculated, along with the two-sided 95% confidence interval based on t-distribution. • The percentage of subjects with Hgb within the target range will be calculated at Week 24, with calculation of exact two-sided 95% confidence interval based on binomial distribution. • The time (in days) to reach first the lower target Hgb level (10.0 g/dL) will be calculated in each subject, and summarized descriptively by Kaplan-Meier method using P25, median, and P75. Subjects who could not reach lower target will be regarded as censored at Study Treatment Stop Date (See Section 10.6.1).

8.2. Safety Analyses

The safety analyses will be based on the All Treated Subjects population, unless otherwise specified.

Table 5, Table 6, and Table 7 provide overviews of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

8.2.1. Overview of Planned Adverse Events Analyses

All AEs will be categorized by the MedDRA (version 20.0 or higher if available) system organ class and preferred term to tabulate the number and incidence.

AEs of special interest will be manually-selected at patient-level (i.e. following case-by-case review by members of the SRT including representatives from the local Japan team) and not at preferred term level.

Table 5 Overview of Planned AEs Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
On-therapy AEs by SOC and PT	Y		Y
On-therapy AEs by SOC and PT by Dialysis Status	Y		
On-therapy AEs by SOC and PT and Maximum Intensity	Y		
On-therapy AEs up to Week 4 by SOC and PT	Y		
On-therapy AEs up to Week 4 by SOC and PT by Dialysis Status	Y		
On-therapy AEs up to Week 4 by SOC and PT and Maximum Intensity	Y		
Post-therapy AEs by SOC and PT	Y		Y
Post-therapy AEs by SOC and PT and Maximum Intensity	Y		
On-therapy Drug-Related AEs by SOC and PT	Y		
On-therapy Drug-Related AEs by SOC and PT by Dialysis Status	Y		
On-therapy Drug-Related AEs by SOC and PT and Maximum Intensity	Y		
On-therapy Drug-Related AEs up to Week 4 by SOC and PT	Y		
On-therapy Drug-Related AEs up to Week 4 by SOC and PT by Dialysis Status	Y		
On-therapy Drug-Related AEs up to Week 4 by SOC and PT and Maximum Intensity	Y		
Post-therapy Drug-Related AEs by SOC and PT	Y		
Post-therapy Drug-Related AEs by SOC and PT and Maximum Intensity	Y		
On-therapy Common (>= 5 %) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y		

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT & Verbatim Text			Y
Serious and Other Significant AEs			
Fatal Serious AEs			Y
Non-Fatal Serious AEs			Y
On-therapy Serious AEs	Y		
Post-therapy Serious AEs	Y		
Serious AEs in Screening Period [1]			Y
Reasons for Considering as a Serious AE			Y
Serious AEs by SOC and PT (Subjects & No. of Occurrences)	Y		
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT	Y		Y
CV Events			Y
AEs of special interest [2]			
On-therapy AEs of special interest	Y		Y
On-therapy AEs of special interest by Dialysis Status	Y		
Post-therapy AEs of special interest	Y		Y
Other Safety Summary for Plain Language Summary			
On-therapy Serious Drug-Related AEs	Y		
On-therapy Non-Serious Drug-Related AEs	Y		

NOTES:

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

[1] Listing will be based on All Screening Population.
[2] See Section 10.6.4.

8.2.1.1. Planed AE Analyses Displays

- **Adverse Events**

AEs by SOC and PT

The number and percentage of subjects reporting at least one AE will be provided. These events will be summarized by primary system organ class and preferred term. On-therapy, on-therapy up to week 4, and post-therapy AEs will be summarized separately. On-therapy AE will be also summarized by baseline dialysis status.

AEs by SOC and PT and Maximum Intensity

AEs will be summarized by Maximum Intensity (not applicable, mild, moderate, or severe) by primary system organ class and preferred term. Subjects who experience the same event several times with different intensities will only be counted with the maximum intensity in the order of (not applicable < mild < moderate < severe). On-therapy, on-therapy up to week 4, and post-therapy AEs will be summarized separately.

Drug-Related AEs by SOC and PT

The number and percentage of subjects reporting at least one drug-related AE will be provided. These events will be summarized by primary system organ class and preferred term. On-therapy, on-therapy up to week 4, and post-therapy AEs will be summarized separately. On-therapy AE will be also summarized by baseline dialysis status.

Drug-Related AEs by SOC and PT and Maximum Intensity

Drug-related AEs will be summarized by Maximum Intensity (not applicable, mild, moderate, or severe) by primary system organ class and preferred term. Subjects who experience the same event several times with different intensities will only be counted with the maximum intensity in the order of (not applicable < mild < moderate < severe). On-therapy, on-therapy up to week 4, and post-therapy AEs will be summarized separately.

On-therapy Common (>= 5 %) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)

The number and percentage of subjects reporting at least one on-therapy common (≥ 5 %) non-serious AE will be provided. The number of on-therapy non-serious AE occurrences will also be provided. These events will be summarized by primary system organ class and preferred term.

- **Serious and Other Significant AEs**

Serious AEs

The number and percentage of subjects reporting at least one Serious AE will be provided. These events will be summarized by primary system organ class and preferred term. On- and post-therapy serious AEs will be summarized separately.

On-therapy Serious AEs by SOC and PT (Subjects & No. of Occurrences)

The number and percentage of subjects reporting at least one on-therapy serious AE will be provided. The number of on-therapy serious AE occurrences will also be provided. These events will be summarized by preferred term.

AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT

The number and percentage of subjects reporting each on-therapy AE leading to discontinuation of study treatment will be summarized. These events will be summarized by preferred term.

- **AEs of Special Interest (AESIs)**

How to identify the AESIs is described in Section 10.6.4.

AEs of Special Interest

The number and percentage of subjects reporting at least one AESI will be provided. These events will be summarized by each AESI term (See Section 10.6.4). On-therapy and post-therapy AESIs will be summarized separately. On-therapy AE will be also summarized by baseline dialysis status.

- **Other Safety Summary for Plain Language Summary**

Serious/Non-serious Drug-Related AEs

The number and percentage of subjects with on-therapy serious or non-serious drug-related AEs will be summarized by preferred term. The serious AEs and the non-serious AEs will be summarized separately.

8.2.2. Overview of Planned Clinical Laboratory Analyses

Table 6 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Values by Visit	Y		Y	Y		
Percent change from Baseline in Lipid Parameters [1] (total cholesterol, LDL cholesterol, and HDL cholesterol)			Y	Y	Y	
Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	Y					
Worst Case Chemistry Results Relative to PCI Criteria Post-Baseline Relative to Baseline	Y					
Hematology						
Hematology Values by Visit	Y		Y	Y		
Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	Y					
Worst Case Hematology Results Relative to PCI Criteria Post-Baseline Relative to Baseline	Y					
Other Laboratory Tests [2]						

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Other Laboratory Values by Visit [2]	Y		Y	Y		
Worst Case Other Laboratory Results Relative to Normal Range Post-Baseline Relative to Baseline [2]	Y					
Worst Case Other Laboratory Results Relative to PCI Criteria Post-Baseline Relative to Baseline [2]	Y					
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting	Y					
Hepatobiliary Laboratory Abnormalities	Y					
Medical Conditions for Subjects with Liver Stopping Events			Y			
Substance Use for Subjects with Liver Stopping Events			Y			
Scatter Plot of Maximum vs. Baseline for ALT		Y[3]				
Scatter Plot of Maximum ALT vs Maximum Total Bilirubin		Y[3]				
All Laboratory						
All Laboratory Data for Subjects with any Value of Potential Clinical Concern/PCI			Y			
Laboratory Values of PCI			Y			

NOTES:

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

[1] Lipid parameters will be log-transformed and the percent change from baseline will be reported.
[2] Only iPTH will be collected as other laboratory tests.
[3] This figure may not be provided in this study because this is required for 'larger study' by the GSK Core RAP requirements in the RAP Template.

8.2.2.1. Planned Clinical Laboratory Analyses Displays

- ***Chemistry/Hematology/Other Laboratory Tests***

Clinical Laboratory Values by Visit

The values will be summarized using mean, standard deviation, median, minimum, and maximum at each assessment visit and baseline. Chemistry values, hematology values, and other laboratory values will be summarized separately.

Percent change from Baseline in Lipid Parameters

Lipid parameters will be log-transformed and the percent change from baseline will be reported. The percent change from baseline in each lipid parameter, including baseline values, will be summarized using geometric mean, 95% CI, minimum, median, and maximum at each assessment visit. In baseline values, the coefficient of variation will also be provided.

Clinical Laboratory Changes from Baseline by Visit

The values will be summarized using mean, standard deviation, median, minimum, and maximum at each assessment visit. Change from baseline in chemistry, hematology, and other laboratory will be summarized separately.

Worst Case Laboratory Results Relative to Normal Range/PCI Criteria Post-Baseline Relative to Baseline

The number of subjects with worst laboratory results relative to normal range/potential clinical importance (PCI) criteria which are post-baseline relative to baseline, including unscheduled assessments, will be summarized by test and category. Summaries for normal range and PCI will be provided separately. The categories for normal range are: To Low, To Normal or No Change, To High; the categories for PCI criteria are: To Low, To w/in Range or No Change, To High. The categorization is determined by comparing the baseline category to the worst case post-baseline category.

- ***Hepatobiliary (Liver)***

Details of liver chemistry stopping criteria are described in the protocol.

Liver monitoring/stopping events will be summarized.

Hepatobiliary laboratory abnormalities will be summarized.

A scatter plot of maximum on-therapy ALT values versus baseline ALT values will be produced if larger data permit.

A scatter plot of maximum total bilirubin (xULN) versus maximum ALT (xULN) values on-therapy will be produced if larger data permit.

8.2.3. Overview of Planned Other Safety Analyses

Table 7 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings by Visit	Y		Y			
ECG Values by Visit			Y	Y		
Abnormal ECG Findings			Y			
Vital Signs						
Vital Signs by Visit	Y		Y	Y		
Worst Case Vital Sign Results Relative to PCI Criteria Post-Baseline Relative to Baseline	Y					

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
All Vital Signs for Subjects with Values of PCI			Y			
Ophthalmology						
Ophthalmologic Exams at Screening	Y		Y			
On-Therapy Ophthalmologic Exams	Y		Y			

NOTES:

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

8.2.3.1. Planned Other Safety Analyses Displays

- ***ECG***

ECG findings ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will be summarized by each assessment visit. Findings without regard to visits (labelled "Worst Case Post-Baseline", only the worst case finding for each subject, will also be provided. All ECG measures (heart rate, PR interval, QRS duration, QT (uncorrected) interval and QTcB (calculated), result of ECG) will be included in a subject listing.

- ***Vital Signs***

Vital sign values will be summarized using mean, standard deviation, minimum, median, and maximum for each assessment visit. Separate summary statistics of pre- and post-dialysis vital signs will be provided for raw values and change from baseline. In a summary of change from baseline, each baseline value (i.e. pre- and post-dialysis baseline) will be used for calculation (Section 10.5.2).

The number of subjects with worst case vital sign results relative to PCI criteria which are post-baseline relative to baseline, including unscheduled assessments, will also be summarized by test and category. The categories for PCI criteria are: To Low, To w/in Range or No Change, To High. The categorization is determined by comparing the baseline category to the worst case post-baseline category.

- ***Ophthalmology Exams***

The responses to each question will be summarized using number and percentage at each assessment visit. The response will be classified into 'Yes' and 'No'. Ophthalmology exam at screening and at on-therapy will be summarized separately. The number of subjects with worst case after-screening ophthalmology exams (i.e., the response is 'Yes' at least once during whole treatment period, including unscheduled visits) will also be summarized by each question.

8.3. Pharmacokinetic Analyses

8.3.1. Overview of Planned Pharmacokinetic Analyses

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

Table 8 provides an overview of the planned analyses, with full details being presented in Appendix 14: List of Data Displays. Summaries will be produced for week 12, week 24, and pooled.

Table 8 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Plasma Concentrations of GSK1278863	Y [1] [2]	Y	Y [1]	Y				
Derived PK Parameters	Y [3]	Y [3]	Y[3]	Y		Y[3]		
Dose Normalized PK Parameters	Y [3]	Y [3]	Y[3]	Y		Y[3]		

NOTES :

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

1. Linear and Semi-Log plots will be created on the same display.
2. Separate Mean (± SD) and Median plots will be generated.
3. Individual PK parameters calculated less than 4 time point concentration or any time deviated concentration will be omitted from summaries and figures.

8.3.2. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).

Concentrations of GSK1278863 in plasma will be listed and summarized by dose group and nominal time. Individual plasma concentration-time profiles and median/mean profiles by dose group will be plotted. Each of figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. a log-linear plot).

8.3.3. Pharmacokinetic Parameters

8.3.3.1. Deriving Pharmacokinetic Parameters

- Derivation of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Pharmacology & Science Promotion Office, GlaxoSmithKline K.K.
- Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).
- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Win Nonlin (version 6.3 or higher).
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 9 will be determined from the Plasma GSK1278863 concentration-time data, as data permits.

Table 9 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-4)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(last)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the linear trapezoidal for each decremental trapezoid. The concentration at 0 hr will be set to 0.
AUC(0-7)	Area under the concentration-time curve from time zero to seven will be calculated using the linear trapezoidal rule for each incremental trapezoid and the linear trapezoidal for each decremental trapezoid. The concentration at 0 hr and 7 hr will be set to 0.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to first occurrence of Cmax will be obtained directly from the concentration-time data.

NOTES:

- Additional parameters may be included as required.
- C(last) is expected to be the concentration observed at 4hours after the most recent dose.

8.3.4. Population Pharmacokinetic (PopPK) Analyses

No population pharmacokinetic analysis is planned.

8.4. Pharmacodynamic Analyses

No pharmacodynamic analysis is planned.

8.5. Pharmacokinetic / Pharmacodynamic Analyses

No pharmacokinetic / pharmacodynamic analysis is planned.

9. REFERENCES

N/A

10. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Treatment States & Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic
Section 10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.8	Appendix 8: Values of Potential Clinical Importance
Section 10.9	Appendix 9: Multicenter Studies • Laboratory Values • ECG • Vital Signs
Section 10.10	Appendix 10: Examination of Covariates and Subgroups
Section 10.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.13	Appendix 13: Abbreviations & Trade Marks
Section 10.14	Appendix 14: List of Data Displays
Section 10.15	Appendix 15: Example Mock Shells for Data Displays

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

Per Protocol Population will not be defined in this study.

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

Period	Screening		Treatment								Follow-up
Visits **All assessments pre-dialysis, unless noted.**		Week -4	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early withdrawal [10]	2–4 weeks after Week 24 or early withdrawal
Allowable window (days)		±7	-	±3	±3	±3	±3	±3	±3	-	±3
Informed consent	X										
Inclusion/exclusion		X	X								
Medical history, demography, height, body weight [1]		X									
IWRS call		X	X	X	X	X	X	X	X	X	X
Study medication dispensing [2]			X	X	X	X	X	X			
Study medication compliance				X	X	X	X	X	X	X	
Vital signs (before and after dialysis) [3]		X	X	X		X			X	X	X
Ophthalmology examination [4]		X [11]				↔		↔		↔	
ECG		X				X			X		
HemoCue Hgb			X	X	X	X	X	X	X		
Hematology		X [12]	X	X	Hgb only	X	Hgb only	Hgb only	X	X	X
Clinical chemistry		X	X	X		X			X	X	X
Ferritin, TSAT		X	X	X		X			X	X	
Serum iron, TIBC, UIBC, serum transferrin, hepcidin			X	X		X			X	X	
Serum pregnancy test [5]		X	X	X		X			X	X	X
Estradiol [5], FSH [6]		X									
Pharmacokinetics [7]						X			X		
iPTH			X	X		X			X		
Genetics sample [8]			X								
Adverse event assessment [9]			↔								
Concomitant medication assessment		↔									

1. Body weight is measured after dialysis.
2. If a subject visit the study site only to receive study medication, only the IWRS call, study medication dispensing, and study medication compliance will be required
3. At visits without dialysis, only one measurement of each parameter will be obtained.
4. Ophthalmology exams should be conducted at the following time points.
   - Screening: anytime after consenting and prior to first dose of study medication (Day 1)
   - Week 12: window from weeks 10-14 (inclusive)
   - End of study: window from weeks 20-24 (inclusive)
   - Early study medication discontinuation or study withdrawal: withdrawal eye exam as close to the last dose as possible. Re-conduct is not required if the exam is conducted within two weeks prior to withdrawal visit.
5. Only for females of reproductive potential.
6. Only at determination of menopausal status in female subjects (Section 5.1).
7. See Table 7
8. For optional genetic research, informed consent should be obtained before the specimen collection.
9. See Section 7.4.1.
10. For examination at early withdrawal, the specified assessments should be performed as far as possible
11. The previous result of ophthalmology exam at the screening may be used if the subject meets all of the following criteria and the investigator judges it appropriate.
    - There were no findings that would suggest a repeat ophthalmology exam performed within the next 3 months at the latest screening ophthalmology exam.
    - Subjects had no new eye-related symptoms or complaints since the latest screening ophthalmology exam.
    - The latest screening ophthalmology exam was performed within 3 months prior to anticipated Day 1.
12. Exam should be conducted at least one week after ESA treatment.

- Blood Sampling Schedule for Pharmacokinetics

PK sample	Week 12 [2]	Week 24 [2]
Blood sampling timing [1]	1, 2, 3, and 4 h after administration of GSK1278863	

Subjects must take the study medication in consideration of blood sampling time. Subjects will record the date and time of the last two study medication doses taken prior to blood sampling in the medication diary. Preferably, there should be an interval of at least 12 h between these two doses.

1. Blood sampling should be completed within +/- 30 min of the planned collected time.
2. Blood sampling not performed at this visit may be postponed until the following visits.

10.3. Appendix 3: Assessment Windows

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Permissible range at each visit was specified in time & event table (See Appendix 2). Records in the eCRF unscheduled visit will not be slotted to a particular time point, but remain as unscheduled if they are either summarized or listed unless otherwise specified.

10.3.1. Definitions of Analysis Time Point

Analysis Time Point	Definitions
Screening [1]	Data collected in Screening visit
Day 1 [1]	Data collected in Day 1 visit
Week 4	Data collected in Week 4 visit
Week 8	Data collected in Week 8 visit
Week 12	Data collected in Week 12 visit
Week 16	Data collected in Week 16 visit
Week 20	Data collected in Week 20 visit
Week 24	Data collected in Week 24 visit
Follow-up	Data collected in Follow-up visit

Note: Any unscheduled visit will not be slotted to a particular time point.
[1] For rescreened subjects, data collected in screening-pass visit will be used for analysis. They may have multiple records at Screening and/or Day 1 visit, which associates with a screening-pass visit and screening failure visit(s)

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment States

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

10.4.1.1. Treatment States for Hgb Data

Treatment State	Definition
Pre-therapy	Date ≤ Randomization Date
On-therapy	Randomization Date < Date ≤ Study Treatment Stop Date + 1 day
Post-therapy	Date > Study Treatment Stop Date + 1 day

NOTES:

- If Randomization date is missing then the assessment will be consider to be Pre-therapy
- If study treatment stop date is missing then the assessment will be considered to be On-therapy

10.4.1.2. Treatment States for AE Data

Treatment State	Definition
Pre-therapy	AE Start Date < Randomization Date
On-therapy	If AE onset date is on or after randomization date & on or before Study Treatment Stop Date + 1 day Randomization Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 day
Post-therapy	If AE onset date is after Study Treatment Stop Date + 1 day AE Start Date > Study Treatment Stop Date + 1 day
Duration (Days)	AE Resolution Date – AE Onset Date + 1 day
Drug-related	If relationship is marked 'YES' on eCRF or value is missing.

NOTES:

- If Randomization date is missing then the assessment will be consider to be Pre-therapy
- If study treatment stop date is missing then the AE will be considered to be On-therapy.

10.4.1.3. Treatment States for Concomitant Medications Data

Treatment State	Definition
Pre-therapy	Concomitant Medication Start Date ≤ Randomization Date
On-therapy	Define as (A) or (B) (A): If concomitant medication start date is on or after randomization date & on or before Study Treatment Stop Date • Randomization Date ≤ Concomitant Medication Start Date ≤ Study Treatment Stop Date If Study Treatment Stop Date is missing, just check if the start date is on or after randomization date. (B): If concomitant medication start date is before randomization date & concomitant medication stop date is on or after randomization date • Concomitant Medication Start Date < Randomization Date

Treatment State	Definition
	• Randomization Date ≤ Concomitant Medication Stop Date
Post-therapy	Concomitant Medication Stop Date > Study Treatment Stop Date If Study Treatment Stop Date is missing: • post-therapy = blank where Concomitant Medication Stop Date ≥ Randomization Date • post-therapy = Y where concomitant medication stop date are missing • post-therapy = N where Concomitant Medication Stop Date < Randomization Date

NOTES:

- If Randomization date is missing then the assessment will be consider to be Pre-therapy
- Data of concomitant medication includes ESA, iron, and blood products and blood supportive care products.

Illustrations of the pre-therapy, on-therapy, and post-therapy treatment states for concomitant medications are included below:

	Pre-therapy	On-therapy			Post-therapy		Pre-therapy medication	On-therapy medication	Post-therapy medication
		Randomization Date		Study Treatment Stop Date	Study Treatment Stop Date + 1 Days				
(a)	x——x						Y	N	N
(b)	x——		——x				Y	Y	N
(c)	x——		———			———x	Y	Y	Y
(d)			x——x				N	Y	N
(e)			x——			———x	N	Y	Y
(f)						x——x	N	N	Y
(g)	?—— x						Y	N	N
(h)	?———		——x				Y*	Y	N
(i)	?———		———			———x	Y*	Y*	Y
(j)	x———		———			———?	Y	Y**	Y**
(k)			x——			———?	N	Y	Y**
(l)						x——?	N	N	Y
(m)	?— ——		———			———?	Y***	Y***	Y***
(n)	x———	x					Y	Y	N
(o)	?— ——	x					Y*	Y	N
(p)		x	——x				N	Y	N
(q)		x	———	x			N	Y	N
(r)				x	—	———x	N	Y	Y
(s)				x	—	———?	N	Y	Y**
(t)					x	———x	N	N	Y
(u)					x	———?	N	N	Y
(v)			x——	—	x		N	Y	Y

x = start/stop date of medication

? = missing start/stop date of medication

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

** If a medication is started Pre-therapy or On-therapy 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-therapy phase to the Post-therapy phase

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order
D1	GSK1278863	GSK1278863	1

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

The baseline value will be the latest pre-dose assessment. This is generally expected to be the pre-dose value from the Day 1 visit, except for ECG. For ECG, screening assessment will be used as a baseline.

For vital signs, the baseline value at pre- and post-dialysis will be defined differently.

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
Change from Baseline For Vital Signs	• Pre-dialysis: = Post-Dose Visit Value from Pre-Dialysis Assessment – Baseline from Pre-Dialysis Assessment • Post-dialysis: = Post-Dose Visit Value from Post-Dialysis Assessment – Baseline from Post-Dialysis Assessment
% Change from Baseline For TSAT, Hepcidin, and Lipid Parameters	1. Log-transform the data at both the baseline and the specified timepoint 2. Calculate a change from baseline using the log-transformed data for each subject 3. Calculate the mean, and 95%CI and standard error (SE) of the log-transformed data 4. Exponentially back-transform to the original scale 5. Subtract 1, then multiply everything by 100% So, geometric mean for percent change from baseline = { exp(Mean [ln(Post-Dose Visit Value) – ln(Baseline)]) – 1 }x 100

Definition	Reporting Details
	Coefficient of variation will be calculated as CV%=[exp(Var in log scale)-1]$^{1/2}$ x 100 where 'Var in log scale' represents variance of percent change from baseline in log scale.

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 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 will be set to missing.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software and S-Plus will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: /arenv/arprod/gsk1278863/mid204716/final_01
QC Spreadsheet	: /arenv/arprod/gsk1278863/mid204716/final_01/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & ADaM IG Version 1.0. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• Not generated.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF.
Planned and Actual Time

Reporting Standards	

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

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables, unless otherwise specified. • If unscheduled visits are included in a summary, it will be provided how a summary will be produced as appropriate. • Unscheduled visits will not be included in figures, unless otherwise specified. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1: This does not apply to the output of statistical models or when the standard list is inappropriate. • Hgb and iron summary statistics will include 95%CI and percentiles (P25 and P75). • Dose level and dose adjustment frequency summary statistics will include mode.
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log-transformed data and between geometric coefficient of variation (CVb (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables. • For multiple measurements at Screening and Day 1 visit, the screening-pass visit record will be used for analysis (See Appendix 3).
Study Day

• Calculated as the number of days from randomization 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

Unique Subject ID
• All subjects have unique subject ID for analyses even if a subject was enrolled after rescreened. Tables/figures/listings will be produced based on unique subject ID. • For a rescreened subject, the unique subject ID will be derived from the first-assigned subject number though he or she seems to have multiple subject numbers in eCRF records by screening assessment. The other subject numbers, which are to be recorded within a supplemental domain, will be associated with the unique subject ID.
Rescreening Subjects
• For rescreened subjects, data collected in screening-pass visit will be used for analysis. They may have multiple records at Screening and/or Day 1 visit, which associates with a screening-pass visit and screening failure visit(s) • Regarding a listing of SAEs in screening period, all pre-therapy SAEs captured in eCRF will be provided including screen failure records of rescreened subjects.
Study Treatment Start Date
• First randomized treatment start date
Study Treatment Stop Date
• Latest end date of treatment • Note that the end date of treatment will be captured as the end date when subjects were intended to end the treatment, rather than when subjects have actually ended the treatment.
Time Definitions (per GSK standard principles)
• 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days

10.6.2. Study Population

Subject Disposition and Study Population

• Screening status and reason for screening failure for a subject who has multiple subject numbers will be unique in the unique subject ID.
  ○ The screening status of a subject who failed screening but passed rescreening will be 'enrolled', and the reason for failure will not be counted.
  ○ The screening status of a subject who failed more than one screening and never passed will be 'failed', and the reason for failure will be derived from the latest failure record.
• Study population of subjects will be derived from the above unique screening status.

Demographics and Baseline Characteristics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ A date and month will be imputed as '30th June' as it will not be captured.
• Randomization date will be used as reference date of calculation.
  ○ If randomization date is missing, screening date will be used.

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

Exposure
Prescribed Dose and Actual Dose
• Prescribed dose will be derived from a dose record captured in eCRF. • In principle, actual dose will be the same as prescribed dose except for a case in which inconsistency between a prescribed dose and prescribed bottle(s) occurs. If such an inconsistency case (e.g. wrong treatment) is detected by study team, the actual dose may be replaced with a plausible value by case-by-case review.
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Sum of [Exposure Duration at Each Visit] where Exposure Duration at Each Visit = Treatment Stop date - Treatment Start date + 1 If dose is interrupted in a visit according to dose adjustment algorithm, duration in the period will be included in duration of exposure. • Cumulative dose will be based on the formula using prescribed dose: Cumulative Dose = Sum of (Exposure Duration x Dose) at Each Visit • Daily Dose Cumulative Dose / Duration of Exposure in Days
Treatment Compliance
• Listing will include treatment compliance up to Week 4 and overall. Overall Compliance(%) = [(Total # of tablets actual taken)/(Total # of tablets planned

Exposure
taken)]*100 Compliance (%) up to Week 4 = [(# of tablets actual taken up to Week 4)/(# of tablets planned taken up to Week 4)]*100 where Total # of tablets actual taken = Sum of (Numbers of Tablets Taken at Each Visit) Total # of tablets planned taken = Sum of [(Treatment Stop Date – Treatment Start Date + 1) x Planned # of tablet/day in the Visit] # of tablets actual taken up to Week 4 = Numbers of Tablets Taken of Day 1 record # of tablets planned taken up to Week 4= (Treatment Stop date of Day 1 record – Treatment Start Date of Day 1 record + 1) Planned # of tablet/day is defined as follows according to the protocol: ○ 0 mg → 0 tablet/day ○ 1 mg → 1 tablet/day ○ 2 mg → 1 tablet/day ○ 4 mg → 1 tablet/day ○ 6 mg → 1 tablet/day ○ 8 mg → 2 tablets/day ○ 12 mg → 2 tablets/day ○ 18 mg → 3 tablets/day ○ 24 mg → 4 tablets/day where dose records are derived from prescribed doses.

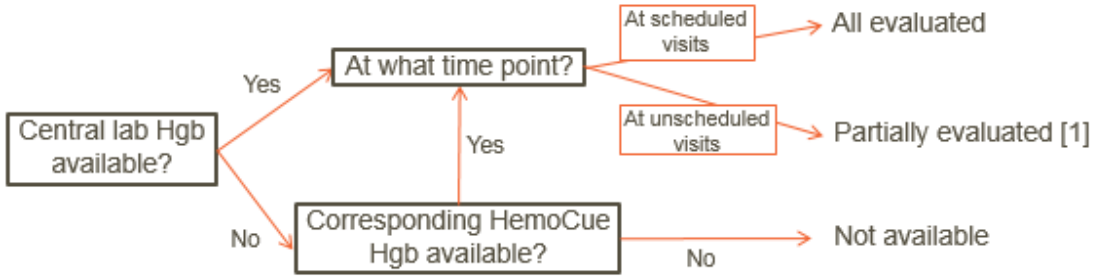
10.6.3. Efficacy

Hgb Values for Efficacy Analyses
Central laboratory and HemoCue Hgb Values
• 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, which is associated with the identical subject number and visit, will be used.
Evaluable Hgb Values
• Note that this will not be applicable for reporting summaries and figures, but applicable for reporting listings. • Evaluable Hgb values will be based on on-therapy central laboratory and/or HemoCue Hgb values that are not taken within the 8 weeks following a transfusion or within the 8 weeks following a non-randomized ESA medication (except protocol-specified ESA treatment in screening period). If an Hgb record meets at least one following criteria, the Hgb record will have a flag of evaluable Hgb = 'N'. ○ Blood Product Administration Date < Date of Hgb data ≤ Blood Product Administration Date + 56 (days)

Hgb Values for Efficacy Analyses

- ESA Start Date < Date of Hgb data ≤ ESA Stop Date + 56 (days)

Flowchart for Hgb efficacy analyses



- Basically, scheduled visits between Day 1 and Week 24 will be applicable to this flowchart, but analyses including by-visit summaries may include other schedued visits (ie. screening and follow-up visit).

[1] Regarding partially evaluated Hgb values, the following summaries of Hgb will include a unscheduled visit:

- Summary of Number (%) of subjects who have an Hgb level of less than 7.5 g/dL
- Summary of Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes

Hgb increase of more than 2 g/dL over any 4 weeks

- For this reporting purpose, Hgb values from central laboratory will be used as previously described.
- A subject who has at least one record with Hgb increase of more than 2 g/dL over any 4 weeks will be counted.
- Hgb increase will be calculated for scheduled visits between Day 1 and Week 24 if available (i.e. Week 4 Hgb - Day 1 Hgb, Week 8 Hgb - Week 4 Hgb, ...)

Illustration of calculation (example in case of Week 12 missing)

Hgb (g/dL)	Lab Date	Study Day	Visit	Hgb increase
9.1	01FEB2017	1	Day 1	Not calculated
9.8	02MAR2017	30	Week 4	0.7
11.9	02APR2017	61	Week 8	2.1
12.6	07JUN2017	127	Week 16	Not calculated
12.7	08JUL2017	158	Week 20	0.1
12.3	02AUG2017	183	Week 24	-0.4

Scatter plot of Hgb assessments: Central Laboratory vs. HemoCue

- All available pairs of Hgb (i.e. non-missing values in both from central laboratory and from the corresponding HemoCue measurement) will be used. The figure will include Pearson's

Hgb Values for Efficacy Analyses

correlation coefficient.

Scatter plot of Change from Baseline in Hgb at Week 4 vs. Candidate Covariates

- The following scatter plot figures will be produced for overall and dialysis status groups:
  - Change from baseline in Hgb at Week 4 vs. Body Weight at Screening
  - Change from baseline in Hgb at Week 4 vs. Baseline Hgb
- Vertical axis will indicate the change from baseline in Hgb (g/dL) at Week 4, horizontal axis will indicate the candidate covariates; body weight (kg) at screening or baseline Hgb (g/dL).

Scatter plot of Mean Dose during Week 12 to 24 vs. Candidate Covariates

- The following scatter plot figures will be produced for overall and dialysis status groups:
  - Mean Dose during Week 12 to 24 vs. Body Weight at Screening
  - Mean Dose during Week 12 to 24 vs. Baseline Hgb
- Vertical axis will indicate the mean dose (mg), horizontal axis will indicate the candidate covariates; body weight (kg) at screening or baseline Hgb (g/dL).
- Mean dose will be calculated from the arithmetic mean using the latest 3 exposure records (i.e., for completers Week 12, 16, and 20), which are based on the prescribed doses and the scheduled visits.
- Subjects who has less than 3 dosing records will be excluded from the figures.
- Mean dose during Week 12 to 24 will also be summarized and listed.

Dose Adjustment

Dose adjustment algorithm

- Dose Adjustment algorithm will be based on HemoCue Hgb values at scheduled visits. No Hgb values measured at unscheduled visits will be included.
- Dose will be derived from prescribed dose recorded in eCRF, not actual dose associated with container numbers.
- The following table illustrates the algorithm using analysis flags as below:
  - (FL_A): Adjustment flags will be counted if prescribed dose recorded in eCRF is changed from that of the previous visit.
  - (FL_B): Over 13 g/dL flags will be counted if HemoCue Hgb >13 g/dL is observed.
  - (FL_C): Interruption flags will be counted if prescribed dose recorded in eCRF is zero.

  Treatment durations will be calculated based on the following formula:
  - Duration (days) = Treatment Stop Date – Treatment Start Date + 1

Illustration of dose adjustment algorithm

Visit (Example)	Treatment Start date/ Stop date	Duration	HemoCue Hgb (g/dL)	Dose (mg)	(FL_A) Adjust-ment	(FL_B) Over 13 g/dL	(FL_C) Inter-ruption
Day 1	01FEB2017/ 01MAR2017	29	11.1	4	N	N	N
Week 4	02MAR2017/	14	11.4	4	N	N	N

Dose Adjustment

	15MAR2017						
Week 8	02APR2017/ 01MAY2017	30	11.8	2	Y	N	N
Week 12	02MAY2017/ 01JUN2017	31	13.4	0	Y	Y	Y
Week 16	02JUN2017/ 01JUL2017	30	11.6	1	Y	N	N
Week 20	02JUL2017/ 01AUG2017	31	12.7	0	Y	N	Y
Week 24	-	-	12.3	-	-	N	-

For summary tables, how to use flags is described within the next items;

- 'Duration (days) of treatment interruption due to Hgb >13 g/dL'
- 'Dose adjustment'

Duration (days) of treatment interruption due to Hgb >13 g/dL

Calculation of duration of treatment interruption due to Hgb >13 g/dL will be based on the above algorithm and the below formula.

- Duration (days) = Sum of $[Duration]_n$

  where

  $[Duration]_n$ represents exposure duration at visit n.

  If over 13 g/dL flag (FL_B) = 'Y' and interruption flag (FL_C) = 'Y':
  - Duration (days) = Treatment Stop Date - Treatment Start Date + 1

  If else:
  - Duration (days) = 0

Frequency of dose adjustment

Calculation of frequency of dose adjustment will be based on the above algorithm.

- Number of dose adjustment will be counted for each subject as follows:
  - Counts of adjustment flag = 'Y'

Number of dose adjustment to reach the lower Hgb target (10.0 g/dL)

Number of dose adjustment to reach the lower Hgb target will be counted for each subject as follows

- Counts of adjustment flag ='Y' at visits before Date to reach the lower Hgb target, including a record which firstly achieved the lower Hgb target.

Iron Endpoints

Subjects who used i.v. and oraliron

- Number of subjects who used i.v. and/or oral iron will be summarized
- Subjects who used i.v. and oral iron will be defined as follows:
  - Subjects with on-therapy i.v. and/or oral iron medication collected in a specific eCRF form (CONMEDS-IRON).

Quarterly IV Iron Dose

- Records of on-therapy iron medication will be used for the following calculations
- Monthly average i.v. iron by quarter = Total i.v. iron dose during each quarter (mg) / (duration in a quarter (days) / 30.4375 days).
- Total i.v. iron dose during each quarter (mg) will be carried with the following formula using each record. Duration will be derived from iron medication start/stop date:
    - Total i.v. iron dose in each quarter (mg) = (iron dose$_1$*frequency$_1$*duration$_1$) + ... + (iron dose$_n$*frequency$_n$*duration$_n$)
    - Duration (days) = (stop date$_1$ - start date$_1$ + 1) + ... + (stop date$_n$ - start date$_n$ + 1)

  Frequency is defined as follows:
    - If subject receives iron dose with once daily → frequency = 1
    - If subject receives iron dose with BID → frequency = 2
    - If subject receives iron dose with TID → frequency = 3
    - If subject receives iron dose with QID → frequency = 4
- Quarters will be defined as follows:
    - Quarter 1:start date = Randomization Date
      end date = Treatment Start Date at Week 12 - 1 (day)
    - Quarter 2:start date = Treatment Start Date at Week 12
      end date = Study Treatment Stop Date
    - If treatment start date at Week 12 is missing (i.e. early withdrawal before Week 12), the end date of Quarter 1 will be replaced with Study Treatment Stop Date. Quarter 2 will not be generated.
    - Iron medication start/stop date will be defined newly for the analyses in addition to Quarter start/end date to derive amount of iron dose within a specified quarter (analysis flags may be used to judge which quarters the iron records should belong to).
- If iron medication start date < randomization date, the iron medication start date will be replaced with randomization date for the analyses.
- If iron medication end date > Study Treatment Stop Date, the iron medication stop date will be replaced with Study Treatment Stop Date for the analyses.
    - If iron medication start date and stop date step over quarters, the iron medication record will be divided; the end date in the former record and the start date in the latter record will be replaced with the quarter end date and the next quarter start date, respectively.

Quarter State of Iron Medication	Definition
Quarter 1	Iron Medication End Date ≤ Quarter 1 End Date
Quarter 2	Quarter 2 Start Date ≤ Iron Medication Start Date
Quarter 1 & 2 (will be divided as described above)	Iron Medication Start Date ≤ Quarter 1 End Date and Quarter 2 Start Date ≤ Iron Medication Stop Date

NOTES: • Only on-therapy iron medication will be evaluated. • If no start or stop date is recorded on iron medication, the date will be replaced with Randomization Date or Study Treatment Stop Date, respectively.
TIBC
• TIBC will be calculated automatically by the central laboratory using: o TIBC = UIBC + total iron
TSAT
• Based on literature review the distribution of TSAT is skewed and requires a log-transformation. Calculation of statistics on log-transformed data are described in Section 10.5.2.2. • TSAT will be calculated automatically by the central laboratory using: o TSAT = 100 * (Serum Iron/TIBC)
Hepcidin
• Based on literature review the distribution of hepcidin is skewed and requires a log-transformation. Calculation of statistics on log-transformed data are described in Section 10.5.2.2.

10.6.4. Safety

Adverse Events
AE up to Week 4
Cut-off date of Week 4 for individuals will be based on Week 4 visit date which is associated with the earliest date throughout Week 4 records (i.e., SDTM.SVSTDTC).
AE of Special Interest
AEs of special interest are manually-selected at patient-level (i.e. following case-by-case review by members of the SRT including representatives from the local Japan team) and not at preferred term level. Adverse events of special interest are classified as follows: • Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis • Death, MI, stroke, heart failure, thromboembolic events, thrombosis of vascular access • Cardiomyopathy • Pulmonary artery hypertension • Cancer-related mortality and tumor progression and recurrence • Esophageal and gastric erosions • Proliferative retinopathy, macular edema, choroidal neovascularization • Exacerbation of rheumatoid arthritis

CV Events
Basically, patient profiles of CV events will be provided according to records captured in eCRF, except for Peripheral Arterial Thrombosis Embolism (PAT) form. CV events in PAT form will be provided only when a related AE sequence number is not present. This is because several records in PAT form are captured just for AESI information, instead of CV events.

Laboratory Parameters
Imputation
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1 • The following laboratory values will not be applicable for this imputation: o Hgb, serum iron, serum ferritin, serum transferrin, TIBC, UIBC, TSAT, and Hepcidin • The default convention for reporting of clinical laboratory units will be the international system of units (SI units).
Log-transformation
• Lipid parameters will be log-transformed and the percent change from baseline will be reported. Based on literature review the distributions of hepcidin and TSAT are skewed and require a log-transformation. Other endpoints may also be log-transformed if deemed appropriate (See Section 10.5.2.2).
Others
Just for summaries of PCI cutoffs, the absolute neutrophils and lymphocytes count will be calculated by multiplying the percentages given for each subject by the absolute white blood count.

10.6.5. Pharmacokinetic

Dose level
• Summaries by dose level and used tablet strength will be based on an actual dose associated with a container number. (See Section 10.6.2). Tablet strength is defined as follows: o Actual dose = 0 mg → 0 mg tablet strength o Actual dose = 1 mg → 1 mg tablet strength o Actual dose = 2 mg → 2 mg tablet strength o Actual dose = 4 mg → 4 mg tablet strength

○ Actual dose = 6 mg → 6 mg tablet strength ○ Actual dose = 8 mg → 4 mg tablet strength ○ Actual dose = 12 mg → 6 mg tablet strength ○ Actual dose = 18 mg → 6 mg tablet strength ○ Actual dose = 24 mg → 6 mg tablet strength • Dose level will be derived from an actual dose of the visit (including unscheduled visits) which meets the following: ○ Treatment Start Date ≤ Date of last dose taken prior to PK sampling ≤ Treatment Stop Date
Others
• Dose normalized PK parameters will be derived from [PK parameters/actual dose (mg)]. • In pooled analyses, data collected in Week 12 and Week 24 will be aggregated. • For the PK parameters calculation, the concentration at 0 hr and 7 hr will be set to 0. • Individual's PK parameters calculated less than 4 time point concentration or any time deviated (beyond ± 30 min of scheduled timepoints) concentration will be omitted from summaries and figures.

10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completing all periods of the study including the follow-up visit. • The study will be completed with the last subject's last study visit • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. 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 subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Concomitant Medications /Dialysis	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. The recorded partial date will be displayed in listings.

10.7.2.2. Handling of Missing Data for Statistical Analysis

If a central laboratory Hgb value is missing, a corresponding non-missing HemoCue Hgb value will be used. Any other imputation will not be conducted for Hgb.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag	High Flag
Albumin (serum)	g/L	< 30 g/L	>55 g/L
Aspartate Aminotransferase	IU/L	N/A	≥ 3x ULRR
Alanine Aminotransferase	IU/L	N/A	≥ 3x ULRR
Bilirubin (total)	μmol/L	N/A	≥ 2x ULRR
Calcium (albumin-adjusted)	mmol/L	< 1.87 mmol/L	> 2.56 mmolL
Bicarbonate (total)	mmol/L	< 20 mmol/L	> 32 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
Sodium (serum)	mmol/L	< 130 mmol/L	> 150 mmol/L

Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag (< x)	High Flag (>x)
Platelet Count	GI/L	< 80 GI/L	> 500 GI/L
WBC Count	GI/L	< 1x LLRR	>5x ULRR
Neutrophils	GI/L	< 1.0 GI/L	N/A
Lymphocytes	GI/L	< 0.5 GI/L	N/A

Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag (< x)	High Flag (>x)
Ferritin	μg/L	< 100 μg/L	> 1200 μg/L
TSAT	%	<15 %	>40 %
iPTH	ng/L	N/A	> 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	beats/min	< 40 beats/min	> 110 beats/min

10.9. Appendix 9: Multicenter Studies

It is anticipated that subject accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative. Therefore, data from all participating centers will be just pooled prior to analysis.

10.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

10.10.1. Handling of Covariates, Subgroups & Other Strata

- The following is a list of covariates that may be used in descriptive summaries by subgroups.
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to database freezing.

Category	Covariates and / or Subgroups
Covariates[1]	Body Weight (kg) at Screening Baseline Hgb (g/dL)
Subgroup	Dialysis Status · Newly started dialysis (Dialysis newly started < 12 weeks before screening): Patients not using ESAs after the start of dialysis · Maintenance dialysis (Dialysis started >= 12 weeks before screening): Patients not using ESAs within 8 weeks before screening (including interruption of ESA therapy)

[1] This category will be used only to produce exploratory figures of scatter plot.

10.11. Appendix 11: Multiple Comparisons & Multiplicity

10.11.1. Handling of Multiple Comparisons & Multiplicity

There is no hypothesis to be tested.

10.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

There is no statistical analysis assumption.

10.13. Appendix 13 – Abbreviations & Trade Marks

10.13.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DP	Decimal Places
eCRF	Electronic Case Record Form
Hgb	Hemoglobin
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IP	Investigational Product
IV	Intravenous
GUI	Guidance
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
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
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
UIBC	Unsaturated Iron Binding Capacity
GSK	GlaxoSmithKline

10.13.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
N/A

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin
SAS
HemoCue

10.14. Appendix 14: List of Data Displays

10.14.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.32	N/A
Efficacy	2.1 to 2.48	2.1 to 2.16
Safety	3.1 to 3.46	3.1
Pharmacokinetic	4.1 to 4.8	4.1 to 4.15
Section	**Listings**	
ICH Listings	1 to 28	
Other Listings	29 to 69	

10.14.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in 10.15: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

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

10.14.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Subject Disposition					
1.1.	Assigned	ES8	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.2.	Assigned	ES8	Summary of Subject Status and Reason for Study Withdrawal by Dialysis Status		Y
1.3.	All Treated Subjects	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	Y
1.4.	All Screening	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	Y
1.5.	Enrolled	NS1	Summary of Subjects Enrolled by Country and Site ID	EudraCT/clinical operations	Y
Protocol Deviations					
1.6.	Assigned	DV1	Summary of Important Protocol Deviations	ICH E3	Y
1.7.	Assigned	IE1	Summary of Inclusion/Exclusion Criteria Deviations	ICH E3	Y
Populations Analysed					
1.8.	All Screening	SP1	Summary of Study Populations	IDSL	Y
1.9.	Assigned	SP2A	Summary of Exclusions from All Treated Subjects Population	IDSL	Y
Demographic and Baseline Characteristics					
1.10.	All Treated Subjects	DM1	Summary of Demographic Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.11.	All Treated Subjects	DM1	Summary of Demographic Characteristics by Dialysis Status		Y

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
1.12.	Enrolled	DM11	Summary of Age Ranges	EudraCT	Y
1.13.	All Treated Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, GSK CTR, FDAAA, EudraCT	Y
1.14.	All Treated Subjects	FH1	Summary of Family History for CV Risk Factors	IDSL	Y
1.15.	All Treated Subjects	SU1	Summary of Substance Use (History of Tobacco Use, Alcohol Intake)	IDSL	Y
Prior and Concomitant Medications					
1.16.	All Treated Subjects	MH4	Summary of Current Medical Conditions	ICH E3	Y
1.17.	All Treated Subjects	MH4	Summary of Current Medical Conditions by Dialysis Status		Y
1.18.	All Treated Subjects	MH4	Summary of Past Medical Conditions	ICH E3	Y
1.19.	All Treated Subjects	MH4	Summary of Past Medical Conditions by Dialysis Status		Y
1.20.	All Treated Subjects	CM1	Summary of Concomitant Medications (Prior-Treatment)	ICH E3	Y
1.21.	All Treated Subjects	CM1	Summary of Concomitant Medications (On-therapy)	ICH E3	Y
1.22.	All Treated Subjects	CM1	Summary of Concomitant Medications (Post-therapy)	ICH E3	Y
1.23.	All Treated Subjects	CM1	Summary of Other Concomitant Medication (On-therapy)		Y

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
1.24.	All Treated Subjects	CM1	Summary of Other Concomitant Medication by Dialysis Status (On-therapy)		Y
1.25.	All Treated Subjects	POP_T1	Summary of Blood Products and Blood Supportive Care Products (On-therapy)		Y
1.26.	All Treated Subjects	POP_T1	Summary of Blood Products and Blood Supportive Care Products by Dialysis Status (On-therapy)		Y
Dialysis					
1.27.	All Treated Subjects	POP_T2	Summary of Dialysis Status		Y
1.28.	All Treated Subjects	POP_T3	Summary of Baseline Hemodialysis		Y
1.29.	All Treated Subjects	POP_T4	Summary of Baseline Vascular Access		Y
Exposure and Treatment Compliance					
1.30.	All Treated Subjects	POP_T5	Summary of Exposure to Study Treatment	ICH E3	Y
1.31.	All Treated Subjects	POP_T5	Summary of Exposure to Study Treatment by Dialysis Status		Y
1.32.	All Treated Subjects	POP_T6	Summary of Treatment Compliance		Y

10.14.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Hgb					
2.1.	All Treated Subjects	EFF_T1	Summary of Change from Baseline in Hgb by Visit		Y
2.2.	All Treated Subjects	EFF_T1	Summary of Change from Baseline in Hgb by Visit by Dialysis Status		Y
2.3.	All Treated Subjects	EFF_T2	Summary of Number (%) of subjects by Hgb change from baseline category at Week 4		Y
2.4.	All Treated Subjects	EFF_T2	Summary of Number (%) of subjects by Hgb change from baseline category at Week 4 by Dialysis Status		Y
2.5.	All Treated Subjects	EFF_T1	Summary of Hgb by Visit		Y
2.6.	All Treated Subjects	EFF_T1	Summary of Hgb by Visit by Dialysis Status		Y
2.7.	All Treated Subjects	EFF_T3	Summary of Number (%) of subjects with Hgb within the target range by Visit		Y
2.8.	All Treated Subjects	EFF_T3	Summary of Number (%) of subjects with Hgb within the target range by Visit by Dialysis Status		Y
2.9.	All Treated Subjects	EFF_T4	Summary of Time (in days) to reach the lower target Hgb level (10.0 g/dL)		Y
2.10.	All Treated Subjects	EFF_T4	Summary of Time (in days) to reach the lower target Hgb level (10.0 g/dL) by Dialysis Status		Y
2.11.	All Treated Subjects	EFF_T5	Summary of Number (%) of subjects who have an Hgb level of less than 7.5 g/dL		Y

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.12.	All Treated Subjects	EFF_T5	Summary of Number (%) of subjects who have an Hgb level of less than 7.5 g/dL by Dialysis Status		Y
2.13.	All Treated Subjects	EFF_T5	Summary of Number (%) of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks		Y
2.14.	All Treated Subjects	EFF_T5	Summary of Number (%) of subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks		Y
2.15.	All Treated Subjects	EFF_T6	Summary of Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes by Dialysis Status		Y
2.16.	All Treated Subjects	EFF_T6	Summary of Number (%) of subjects who have an Hgb level of more than 13.0 g/dL and number of episodes by Dialysis Status		Y
Iron Use					
2.17.	All Treated Subjects	EFF_T7	Summary of Dose of i.v. iron during the treatment period		Y
2.18.	All Treated Subjects	EFF_T7	Summary of Dose of i.v. iron during the treatment period by Dialysis Status		Y
2.19.	All Treated Subjects	EFF_T8	Summary of Number (%) of subjects who use iron during the treatment period		Y
2.20.	All Treated Subjects	EFF_T8	Summary of Number (%) of subjects who use iron during the treatment period by Dialysis Status		Y
Iron Parameters (ferritin, TSAT, hepcidin, serum iron, and TIBC)					
2.21.	All Treated Subjects	LB1	Summary of Ferritin (ug/L) by Visit	Includes Baseline values	Y
2.22.	All Treated Subjects	LB1	Summary of Ferritin (ug/L) by Visit by Dialysis Status	Includes Baseline values	Y

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.23.	All Treated Subjects	LB1	Summary of Ferritin (ug/L) Change from Baseline by Visit		Y
2.24.	All Treated Subjects	LB1	Summary of Ferritin (ug/L) Change from Baseline by Visit by Dialysis Status		Y
2.25.	All Treated Subjects	EFF_T9	Summary of Transferrin Saturation (%) by Visit	Includes Baseline values	Y
2.26.	All Treated Subjects	EFF_T9	Summary of Transferrin Saturation (%) by Visit by Dialysis Status	Includes Baseline values	Y
2.27.	All Treated Subjects	EFF_T10	Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit		Y
2.28.	All Treated Subjects	EFF_T10	Summary of Transferrin Saturation (%) Percent Change from Baseline by Visit by Dialysis Status		Y
2.29.	All Treated Subjects	EFF_T9	Summary of Hepcidin (nmol/L) by Visit	Includes Baseline values	Y
2.30.	All Treated Subjects	EFF_T9	Summary of Hepcidin (nmol/L) by Visit by Dialysis Status	Includes Baseline values	Y
2.31.	All Treated Subjects	EFF_T10	Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit		Y
2.32.	All Treated Subjects	EFF_T10	Summary of Hepcidin (nmol/L) Percent Change from Baseline by Visit by Dialysis Status		Y
2.33.	All Treated Subjects	LB1	Summary of Serum Iron (umol/L) by Visit	Includes Baseline values	Y
2.34.	All Treated Subjects	LB1	Summary of Serum Iron (umol/L) by Visit by Dialysis Status	Includes Baseline values	Y

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.35.	All Treated Subjects	LB1	Summary of Serum Iron (umol/L) Change from Baseline by Visit		Y
2.36.	All Treated Subjects	LB1	Summary of Serum Iron (umol/L) Change from Baseline by Visit by Dialysis Status		Y
2.37.	All Treated Subjects	LB1	Summary of Total Iron Binding Capacity (umol/L) by Visit	Includes Baseline values	Y
2.38.	All Treated Subjects	LB1	Summary of Total Iron Binding Capacity (umol/L) by Visit by Dialysis Status	Includes Baseline values	Y
2.39.	All Treated Subjects	LB1	Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit		Y
2.40.	All Treated Subjects	LB1	Summary of Total Iron Binding Capacity (umol/L) Change from Baseline by Visit by Dialysis Status		Y
Dose adjustment					
2.41.	All Treated Subjects	EFF_T11	Summary of Dose level (mg) by Visit	Includes mean dose (mg) during Week 12 to 24	Y
2.42.	All Treated Subjects	EFF_T11	Summary of Dose level (mg) by Visit by Dialysis Status	Includes mean dose (mg) during Week 12 to 24	Y
2.43.	All Treated Subjects	EFF_T12	Summary of Duration (days) of treatment interruption due to Hgb >13.0 g/dL		Y
2.44.	All Treated Subjects	EFF_T12	Summary of Duration (days) of treatment interruption due to Hgb >13.0 g/dL by Dialysis Status		Y
2.45.	All Treated Subjects	EFF_T13	Summary of Dose Adjustment		Y
2.46.	All Treated	EFF_T13	Summary of Dose Adjustment by Dialysis Status		Y

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
	Subjects				
2.47.	All Treated Subjects	EFF_T14	Summary of Number (%) of Subjects with Each Dose Level by Visit		Y
2.48.	All Treated Subjects	EFF_T14	Summary of Number (%) of Subjects with Each Dose Level by Visit by Dialysis Status		Y

10.14.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Hgb					
2.1.	All Treated Subjects	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CI for Change from Baseline over Time		Y
2.2.	All Treated Subjects	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CI for Change from Baseline over Time by Dialysis Status		Y
2.3.	All Treated Subjects	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CI over Time		Y
2.4.	All Treated Subjects	EFF_F1	Plot of Mean Hgb (g/dL) and 95% CI over Time by Dialysis Status		Y
2.5.	All Treated Subjects	EFF_F2	Figure of Number (%) of subjects with Hgb within the target range over time	Like Fig. 2.7.6.2.3.1-2 in NESP CTD 2.7.6	Y
2.6.	All Treated Subjects	EFF_F2	Figure of Number (%) of subjects with Hgb within the target range over time by Dialysis Status		Y
2.7.	All Treated Subjects	EFF_F3	Kaplan-Meier plot of Time (in days) to reach the lower target Hgb level (10.0 g/dL)		Y
2.8.	All Treated Subjects	EFF_F3	Kaplan-Meier plot of Time (in days) to reach the lower target Hgb level (10.0 g/dL) by Dialysis Status		Y
2.9.	All Treated Subjects	EFF_F4	Scatter plot of Hgb assessments: Central Laboratory vs. HemoCue		Y
Dose Adjustment					
2.10.	All Treated Subjects	EFF_F5	Histogram of GSK1278863 Dose by Visit		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.11.	All Treated Subjects	EFF_F6	Subject Profiles of Hgb and Dose over Time		Y
Iron Parameters					
2.12.	All Treated Subjects	EFF_F1	Plot of Mean and 95% CI for Ferritin Change from Baseline over time		Y
2.13.	All Treated Subjects	EFF_F1	Plot of Geometric Mean and 95% CI for Transferrin Saturation Percent Change from Baseline over time		Y
2.14.	All Treated Subjects	EFF_F1	Plot of Geometric Mean and 95% CI for Hepcidin Percent Change from Baseline over time		Y
2.15.	All Treated Subjects	EFF_F1	Plot of Mean and 95% CI for Serum Iron Change from Baseline over time		Y
2.16.	All Treated Subjects	EFF_F1	Plot of Mean and 95% CI for Total Iron Binding Capacity Change from Baseline over time		Y
Other					
2.17.	All Treated Subjects	EFF_F7	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Body Weight		Y
2.18.	All Treated Subjects	EFF_F7	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Body Weight by Dialysis Status		Y
2.19.	All Treated Subjects	EFF_F7	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Baseline Hgb		Y
2.20.	All Treated Subjects	EFF_F7	Scatter Plot of Change from Baseline in Hgb at Week 4 vs. Baseline Hgb by Dialysis Status		Y
2.21.	All Treated Subjects	EFF_F7	Scatter Plot of Mean Dose during Week 12 to 24 vs. Body Weight		Y

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
2.22.	All Treated Subjects	EFF_F7	Scatter Plot of Mean Dose during Week 12 to 24 vs. Body Weight by Dialysis Status		Y
2.23.	All Treated Subjects	EFF_F7	Scatter Plot of Mean Dose during Week 12 to 24 vs. Baseline Hgb		Y
2.24.	All Treated Subjects	EFF_F7	Scatter Plot of Mean Dose during Week 12 to 24 vs. Baseline Hgb by Dialysis Status		Y

10.14.6. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Adverse Events (AEs)					
3.1.	All Treated Subjects	AE1	Summary of On-Therapy AEs by SOC and PT	ICH E3	Y
3.2.	All Treated Subjects	AE1	Summary of On-Therapy AEs by SOC and PT by Dialysis Status		Y
3.3.	All Treated Subjects	AE5	Summary of On-Therapy AEs by SOC and PT and Maximum Intensity	ICH E3	Y
3.4.	All Treated Subjects	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT	ICH E3	Y
3.5.	All Treated Subjects	AE1	Summary of On-Therapy AEs up to Week 4 by SOC and PT by Dialysis Status		Y
3.6.	All Treated Subjects	AE5	Summary of On-Therapy AEs up to Week 4 by SOC and PT and Maximum Intensity	ICH E3	Y
3.7.	All Treated Subjects	AE1	Summary of Post-Therapy AEs by SOC and PT	ICH E3	Y
3.8.	All Treated Subjects	AE5	Summary of Post-Therapy AEs by SOC and PT and Maximum Intensity	ICH E3	Y
3.9.	All Treated Subjects	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT	ICH E3	Y
3.10.	All Treated Subjects	AE1	Summary of On-Therapy Drug-Related AEs by SOC and PT by Dialysis Status		Y
3.11.	All Treated Subjects	AE5	Summary of On-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity	ICH E3	Y

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.12.	All Treated Subjects	AE1	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT	ICH E3	Y
3.13.	All Treated Subjects	AE1	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT by Dialysis Status		Y
3.14.	All Treated Subjects	AE5	Summary of On-Therapy Drug-Related AEs up to Week 4 by SOC and PT and Maximum Intensity	ICH E3	Y
3.15.	All Treated Subjects	AE1	Summary of Post-Therapy Drug-Related AEs by SOC and PT	ICH E3	Y
3.16.	All Treated Subjects	AE5	Summary of Post-Therapy Drug-Related AEs by SOC and PT and Maximum Intensity	ICH E3	Y
3.17.	All Treated Subjects	AE15	Summary of On-Therapy Common (>=5%) Non-Serious AEs by SOC and PT (Subjects & No. of Occurrences)	FDAAA, EudraCT	Y
Serious and Other Significant AEs					
3.18.	All Treated Subjects	AE1	Summary of On-Therapy Serious AEs	GSK CTR	Y
3.19.	All Treated Subjects	AE1	Summary of Post-Therapy Serious AEs	GSK CTR	Y
3.20.	All Treated Subjects	AE16	Summary of Serious AEs by SOC and PT (Subjects & No. of Occurrences)	FDAAA, EudraCT	Y
3.21.	All Treated Subjects	AE1	Summary of AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT	IDSL	Y
AEs of Special Interest					
3.22.	All Treated Subjects	SAFE_T1	Summary of On-Therapy AEs of special interest		Y
3.23.	All Treated	SAFE_T1	Summary of On-Therapy AEs of special interest by Dialysis Status		Y

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
	Subjects				
3.24.	All Treated Subjects	SAFE_T1	Summary of Post-Therapy AEs of special interest		Y
Laboratory Chemistry					
3.25.	All Treated Subjects	LB1	Summary of Chemistry Values by Visit	ICH E3 Includes Baseline values	Y
3.26.	All Treated Subjects	LB1	Summary of Chemistry Changes from Baseline by Visit	ICH E3	Y
3.27.	All Treated Subjects	SAFE_T2	Summary of Percent change from Baseline in Lipid Parameters (total cholesterol, LDL cholesterol and HDL cholesterol) by Visit		Y
3.28.	All Treated Subjects	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	Y
3.29.	All Treated Subjects	LB17	Summary of Worst Case Chemistry Results Relative to PCI Criteria Post-Baseline Relative to Baseline	ICH E3	Y
Hematology					
3.30.	All Treated Subjects	LB1	Summary of Hematology Values by Visit	ICH E3 Includes Baseline values	Y
3.31.	All Treated Subjects	LB1	Summary of Hematology Changes from Baseline by Visit	ICH E3	Y
3.32.	All Treated Subjects	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	Y
3.33.	All Treated Subjects	LB17	Summary of Worst Case Hematology Results Relative to PCI Criteria Post-Baseline Relative to Baseline	ICH E3	Y
Other Laboratory Tests					
3.34.	All Treated	LB1	Summary of Other Laboratory Values by Visit	ICH E3	Y

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
	Subjects			Includes Baseline values	
3.35.	All Treated Subjects	LB1	Summary of Other Laboratory Changes from Baseline by Visit	ICH E3	Y
3.36.	All Treated Subjects	LB15	Summary of Worst Case Other Laboratory Results Relative to Normal Range Post-Baseline Relative to Baselinet	ICH E3	Y
3.37.	All Treated Subjects	LB17	Summary of Worst Case Other Laboratory Results Relative to PCI Criteria Post-Baseline Relative to Baseline	ICH E3	Y
Hepatobiliary (Liver)					
3.38.	All Treated Subjects	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	Y
3.39.	All Treated Subjects	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria	IDSL Listing may be sufficient if few events.	Y
ECG					
3.40.	All Treated Subjects	EG1	Summary of ECG Findings	IDSL	Y
3.41.	All Treated Subjects	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	Y
Vital Signs					
3.42.	All Treated Subjects	SAFE_T3 based on VS1	Summary of Vital Signs by Visit	Summarized by each assessment status (i.e. pre-dialysis and post-dialysis)	Y
3.43.	All Treated Subjects	SAFE_T3 based on VS1	Summary Change from Baseline in Vital Signs by Visit	Summarized by each assessment status (i.e. pre-dialysis and post-dialysis)	Y
3.44.	All Treated Subjects	SAFE_T4 based on VS7	Summary of Worst Case Vital Sign Results Relative to PCI Criteria Post-Baseline Relative to Baseline	Summarized by each assessment status (i.e. pre-dialysis and post-dialysis)	Y
Ophthalmology					

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
3.45.	All Treated Subjects	SAFE_T5	Summary of Ophthalmologic Exams at Screening		Y
3.46.	All Treated Subjects	SAFE_T6	Summary of On-Therapy Ophthalmologic Exams		Y
Safety Summaries for a Plain Language Summary					
3.47.	All Treated Subjects	AE3	Summary of On-Therapy Serious Drug-Related AEs		Y
3.48.	All Treated Subjects	AE3	Summary of On-Therapy Non-Serious Drug-Related AEs		Y

10.14.7. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Clinical Laboratory Analyses					
3.1.	All Treated Subjects	SAFE_F1	Plot of Percent change from Baseline in Lipid Parameters (total cholesterol, LDL cholesterol, and HDL cholesterol) over time		Y

10.14.8. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Plasma GSK1278863 Concentrations					
4.1.	PK	PK01	Summary of GSK1278863 Plasma Concentration by Dose level (non-transformed)		Y
4.2.	PK	PK_T1 based on PK05	Summary of GSK1278863 Plasma Concentration by Dose level (loge-transformed)		Y
PK parameters					
4.3.	PK	PK03	Summary of GSK1278863 Pharmacokinetic Parameters by Dose level (non-transformed)		Y
4.4.	PK	PK05	Summary of GSK1278863 Pharmacokinetic Parameters by Dose level (loge-transformed)		Y
4.5.	PK	PK03	Summary of Dose Normalized GSK1278863 Pharmacokinetic Parameters by Dose level (non-transformed)		Y
4.6.	PK	PK05	Summary of Dose Normalized GSK1278863 Pharmacokinetic Parameters by Dose level (loge-transformed)		Y
4.7.	PK	PK03	Summary of Dose Normalized GSK1278863 Pharmacokinetic Parameters by Used Tablet Strength (non-transformed)		Y
4.8.	PK	PK05	Summary of Dose Normalized GSK1278863 Pharmacokinetic Parameters by Used Tablet Strength (loge-transformed)		Y

10.14.9. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Plasma GSK1278863 Concentrations					
4.1.	PK	PK24	Individual GSK1278863 Plasma Concentration-Time Plots	(Linear and Semi-Log) (by Dose)	Y
4.2.	PK	PK17	Mean GSK1278863 Plasma Concentration-Time Plots	(Linear and Semi-Log) (by Dose)	Y
4.3.	PK	PK19	Mean (+SD) GSK1278863 Plasma Concentration-Time Plots	(Linear and Semi-Log) (by Dose)	Y
4.4.	PK	PK20	Median GSK1278863 Plasma Concentration-Time Plots	(Linear and Semi-Log) (by Dose)	Y
PK Parameters					
4.5.	PK	PK_F1	Individual Plot of GSK1278863 Dose level and PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.6.	PK	PK_F2	Mean (+SD) Plot of GSK1278863 Dose level and PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.7.	PK	PK_F3	Median Plot of GSK1278863 Dose level and PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.8.	PK	PK_F1	Individual Plot of GSK1278863 Dose level and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.9.	PK	PK_F2	Mean (+SD) Plot of GSK1278863 Dose level and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.10.	PK	PK_F3	Median Plot of GSK1278863 Dose level and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.11.	PK	PK_F4	Box Plot of GSK1278863 Dose level and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.12.	PK	PK_F1	Individual Plot of GSK1278863 Used Tablet Strength and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
4.13.	PK	PK_F2	Mean (+SD) Plot of GSK1278863 Used Tablet Strength and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.14.	PK	PK_F3	Median Plot of GSK1278863 Used Tablet Strength and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y
4.15.	PK	PK_F4	Box Plot of GSK1278863 Used Tablet Strength and Dose Normalized PK Parameters (AUC (0-4), AUC (0-7), Cmax)	will provide only pooled data	Y

10.14.10. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Study Populations					
Subject Disposition					
1.	Assigned	ES2	Listing of Reasons for Study Withdrawal	ICH E3	Y
2.	All Treated Subjects	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	Y
3.	All Screening	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	Y
Protocol Deviations					
4.	Assigned	DV2	Listing of Important Protocol Deviations	ICH E3	Y
5.	Assigned	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	Y
Populations Analysed					
6.	Assigned	SP3	Listing of Subjects Excluded from All Treated Subjects Population	ICH E3 Note: IDSL shell for SP3a in development. e.g., subjects screened but not randomized, subjects randomized but not treated, subjects with deviations leading to exclusion from per protocol population (can be separate listing per population).	Y
Demographic and Baseline Characteristics					
7.	All Treated Subjects	DM2	Listing of Demographic Characteristics	ICH E3	Y
8.	All Treated Subjects	DM9	Listing of Race	ICH E3	Y

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Dialysis					
9.	All Treated Subjects	POP_L1	Listing of Dialysis Status		Y
Exposure and Treatment Compliance					
10.	All Treated Subjects	POP_L2 based on EX3	Listing of Exposure Data	ICH E3	Y
11.	All Treated Subjects	POP_L3	Listing of Treatment Compliance	ICH E3 Up to Week 4 and overall compliance will be provided.	Y
Efficacy					
Hgb					
12.	All Treated Subjects	EFF_L1	Listing of Hgb Data		Y
13.	All Treated Subjects	EFF_L2	Listing of Subjects who have an Hgb level of less than 7.5 g/dL		Y
14.	All Treated Subjects	EFF_L2	Listing of Subjects who have an Hgb increase of more than 2.0 g/dL over any 4 weeks		Y
15.	All Treated Subjects	EFF_L2	Listing of Subjects who have an Hgb increase of more than 13.0 g/dL		Y
16.	All Treated Subjects	LB5	Listing of Iron Parameter Data	Ferritin, TSAT, hepcidin, serum iron, and TIBC will be included.	Y
Safety					

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Adverse Events					
17.	All Treated Subjects	AE8	Listing of All Adverse Events	ICH E3	Y
18.	All Treated Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	Y
19.	All Treated Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	Y
Serious and Other Significant Adverse Events					
20.	All Treated Subjects	AE8	Listing of Fatal Serious Adverse Events	ICH E3 Fatal and Non-Fatal SAEs are combined into a single listing for ClinPharm studies (i.e., "Listing of Serious Adverse Events").	Y
21.	All Treated Subjects	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Fatal and Non-Fatal SAEs are combined into a single listing for ClinPharm studies (i.e., "Listing of Serious Adverse Events").	Y
22.	All Screening	AE8	Listing of Serious AEs in Screening Period	All pre-therapy SAEs captured in eCRF will be provided including screen failure records of rescreened subjects.	Y
23.	All Treated Subjects	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	Y
24.	All Treated Subjects	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	Y

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
25.	All Treated Subjects	SAFE_L1	Listing of Adverse Events of Special Interest	ICH E3 Displays will be produced with AESI category in addition of AE8 template.	Y
All Laboratory					
26.	All Treated Subjects	LB5	Listing of All Chemistry Data for Subjects with Any Value Outside of Normal Range/of PCI	ICH E3 May be split into separate listings by chemistry, hematology, urinalysis, etc. Display ALL labs for a subject who experienced a value of potential clinical concern/importance.	Y
27.	All Treated Subjects	LB5	Listing of All Hematology Data for Subjects with Any Value Outside of Normal Range/of PCI	ICH E3	Y
28.	All Treated Subjects	LB5	Listing of All Other Laboratory Data for Subjects with Any Value Outside of Normal Range/of PCI	ICH E3	Y
29.	All Treated Subjects	LB14	Listing of Laboratory Data with Character Results	IDSL Rationale: This listing is required to ensure character laboratory results are presented.	Y

10.14.11. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Study Population					
Demographic and Baseline Characteristics					
30.	All Treated Subjects	FH4	Listing of Family Members with History of Cardiovascular Risk Factors		Y
31.	All Treated Subjects	SU2	Listing of Substance Use History		Y
Prior and Concomitant Medications					
32.	All Treated Subjects	MH2	Listing of Medical Conditions		Y
33.	All Treated Subjects	CM2	Listing of Concomitant Medications		Y
34.	All Treated Subjects	POP_L4	Listing of ESA Concomitant Medications		Y
35.	All Treated Subjects	POP_L5	Listing of Iron Concomitant Medications		Y
36.	All Treated Subjects	POP_L6	Listing of Blood Products and Blood Supportive Care Products		Y
Dialysis					
37.	All Treated Subjects	POP_L7	Listing of Baseline Hemodialysis and Changes in Hemodialysis		Y
38.	All Treated Subjects	POP_L8	Listing of Baseline Vascular Access		Y

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
39.	All Treated Subjects	POP_L9	Listing of Subjects with Vascular Therapeutic Procedures during the Study Period		Y
Efficacy					
Safety					
Suicidality-Related Adverse Event					
40.	All Treated Subjects	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Sections 1-2)		Y
41.	All Treated Subjects	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)		Y
42.	All Treated Subjects	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: (Section 4)		Y
43.	All Treated Subjects	IDSL standard	Listing of Possible Suicidality-Related Adverse Event Data: (Section 5-8)		Y
Clinical Laboratory, ECG, Vital Sign, and Ophthalmology Exam					
44.	All Treated Subjects	LB5	Listing of Chemistry Data		Y
45.	All Treated Subjects	LB5	Listing of Hematology Data		Y
46.	All Treated Subjects	LB5	Listing of Other Laboratory Data		Y
47.	All Treated Subjects	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	This listing is required for medical review of subjects with liver stopping events.	Y
48.	All Treated Subjects	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	This listing is required for medical review of subjects with liver stopping events.	Y

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
49.	All Treated Subjects	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		Y
50.	All Treated Subjects	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score		Y
51.	All Treated Subjects	LIVER7	Listing of Liver Biopsy Details		Y
52.	All Treated Subjects	LIVER8	Listing of Liver Imaging Details		Y
53.	All Treated Subjects	EG3	Listing of ECG Values		Y
54.	All Treated Subjects	EG5	Listing of ECG Findings		Y
55.	All Treated Subjects	VS4	Listing of Vital Signs		Y
56.	All Treated Subjects	VS4	Listing of All Vital Signs for Subjects with Values of PCI		Y
57.	All Treated Subjects	SAFE_L2	Listing of Ophthalmologic Exams		Y
Pharmacokinetic Parameters					
58.	PK	PK07	Listing of GSK1278863 Pharmacokinetic Concentration-Time Data by Dose level		Y
59.	PK	PK13	Listing of Derived GSK1278863 Pharmacokinetic Parameters by Dose level		Y

10.14.12. Patient Profile Listings

Patient Profile Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**SAC**
Safety					
60.	All Treated Subjects	IDSL standard	Patient Profile Listing of Arrhythmias		Y
61.	All Treated Subjects	IDSL standard	Patient Profile Listing of Congestive Heart Failure		Y
62.	All Treated Subjects	IDSL standard	Patient Profile Listing of Cerebrovascular Events/Stroke/ Transient Ischemic Attack		Y
63.	All Treated Subjects	IDSL standard	Patient Profile Listing of Deep venous Thrombosis/ Pulmonary Embolism		Y
64.	All Treated Subjects	IDSL standard	Patient Profile Listing of Myocardial Infarction /Unstable Angina		Y
65.	All Treated Subjects	IDSL standard	Patient Profile Listing of Peripheral Arterial Thrombosis Embolism	Events will be provided only when a related AE sequence number is present (Section 10.6.4).	Y
66.	All Treated Subjects	IDSL standard	Patient Profile Listing of Pulmonary Hypertension		Y
67.	All Treated Subjects	IDSL standard	Patient Profile Listing of Revascularization		Y
68.	All Treated Subjects	IDSL standard	Patient Profile Listing of Valvulopathy		Y
69.	All Treated Subjects	IDSL standard	Patient Profile Listing of Deaths		Y

10.15. Appendix 15: Example Mock Shells for Data Displays

These are provided with separated documents.

10.16. Appendix 16: RAP Amendment(s)

Minor wording changes are not included in below.

Reporting and Analysis Plan_204716_Amendment_Final_V1.1 [11-Oct-2017]		
Section # and Name	**Description of Change**	**Brief Rationale**
2.1 Changes to the Protocol Defined Statistical Analysis Plan	Deleted the table and added statement of ''Modified text to align with the latest version of protocol as follow: 1. No interim analysis is planned. 2. The change in Hgb at Week 4 will be classified into different categories (i.e., ≤-2, >-2 to -1, >-1 to 0, >0 to 1, >1 to 2, and >2 g/dL)	Protocol was amended. 1. The interim analysis was just aiming to meet the clinical result disclosure obligation. Given our POLICY update, the due date of disclosure was changed to 'within 12 months of PCA' from 'within 8 months of PCA'. Therefore, a final analysis of 204716 study can meet the current disclosure due date. 2. Specifying the categories and ensuring there is no overlap.
4 Analysis populations	The term of 'randomized population' has been changed to 'assigned population'	'Assigned' would be more appropriate for this single arm study.
6.1.1 Planned Summary Display Details 10.6.2 Study Population	Clarifications were made for a subject who has multiple numbers as follows: • A subject who has multiple subject numbers (i.e. rescreened subject) will be analyzed as a unique subject based on the latest screening result. • Screening status and reason for screening failure for a subject who has multiple subject numbers will be unique in the unique subject ID. Minor wording changes were also made.	Clarification
7.1 Primary Efficacy Analyses	Updates were made to the summaries for adding categories; within ±1 g/dL and over ±2 g/dL.	These categories would facilitate review the drug efficacy results.
8 Secondary statistical analyses 10.6.3 Efficacy	It has been clarified that, on-therapy Hgb will be used for several Hgb endpoints and evaluable Hgb. In addition, 95%CI has been added to descriptive summary statistics for continuous data.	Correction and Clarification

Reporting and Analysis Plan_204716_Amendment_Final_V1.1 [11-Oct-2017]		
Section # and Name	**Description of Change**	**Brief Rationale**
8.1.2 Planned Efficacy Table Displays	Added the following clarifications in a model specification of Kaplan Meier Method: Subjects within target range at baseline will be excluded from the summary. Subjects who could not reach lower target will be regarded as censored at EoT. In addition, in dose adjustment summary, it has been clarified that what subjects will be included in summaries of duration of treatment interruption and number of dose adjustments.	Clarification
8.1.2 Planned Efficacy Table Displays	Added summary tables and planed displays detail for number (%) of subjects with each dose level by visit	Tables corresponding to histogram of dose level by visit (Fig. 2.10) are necessary.
8.2.1.1 Planed AE Analyses Displays	1. Clarifications were made for the maximum intensity of AEs category and how to treat different intensities in the same AE. 2. It has been modified how to display serious adverse event, for both primary system organ class and preferred term.	1. Clarification 2. SOC for SAE summary provides a consistent presentation style that facilitates review
8.2.2 Overview of Planned Clinical Laboratory Analyses 8.2.3 Overview of Planned Other Safety Analyses	Updates were made to the summaries for normal range/PCI criteria. Only the worst case results relative to normal range/PCI criteria post-baseline relative to baseline will be provided.	IDSL templates based on GSK Core RAP requirements in the RAP template are updated.
8.2.3.1 Planned Other Safety Analyses Displays 10.5.2 Baseline Definition & Derivations 10.14.6 Safety Tables	Updates were made to the indicated sections of RAP to describe how to summarize vital sign assessment. Pre- and post-dialysis assessment will be summarized separately and non-dialysis assessment will not be summarized.	Vital sign assessment in non-dialysis day would be unlikely, so summarization would not be necessary.
8.2.3.1 Planned Other Safety Analyses Displays	Text added to make sure the summary display for ECG findings.	Clarification
8.2.3.1 Planned Other Safety Analyses Displays	Additional summary added to ophthalmology exam, displayed along with a summary of on-therapy ophthalmology exam. No additional table is required for this update.	Worthwhile to add another way of summarization
8.3.3.1 Deriving Pharmacokinetic Parameters	Modifications were made for the definition of C(last), last quantifiable concentration.	To make sure that the definitions of the parameters are consistent
10.3.1 Definitions of Analysis Time Point 10.6.1 General	Text added to make sure data derivation for multiple measurements at Screening and Day 1 visit. The screening-pass visit record will be used for analysis if multiple records are present.	Clarification

Reporting and Analysis Plan_204716_Amendment_Final_V1.1 [11-Oct-2017]		
Section # and Name	**Description of Change**	**Brief Rationale**
10.4.1.3 Treatment States for Concomitant Medications Data	Updates were made considering the case of EoT missing	To ensure the definition of treatment state to cover all possible cases
10.5.3 Reporting Process & Standards	Further clarification has been made about descriptive summary statistics.	Clarification
10.6.2 Study Population	Age Reference date for age calculation was updated Exposure Text deleted	Age Using randomization date as reference may be more appropriate rather than using screening date based on SDTM standard derivations (Note that IG suggests to only expect AGE for treated subjects, but the study expect AGE for randomized subjects). Exposure Deleted because it may not be suitable for this section
10.6.3 Efficacy	Iron Endpoints: Quarterly IV Iron Dose Quarterly IV iron dose will be calculated using randomization date and EoT to support on-therapy iron definition.	To ensure that on-therapy iron and the quarterly iron are consistently defined.
10.6.4 Safety	Adverse Events Corrections were made to the categories of adverse events of special interest. In a second bullet of the categories, heart failure was added and venous thromboembolism was corrected to thromboembolic events CV Events Updates were added to clarify how to provided patient profiles in PAT form.	For AEs. protocol was amended for AESI terminology. For CV events, to make sure how to output CV records based on team discussion
10.6.5 Pharmacokinetic	1. Derivation of tablet strength was clarified. 2. Derivation of dose level was updated to see whether PK sampling date is included within a period of exposure for each visit as follows: • Treatment Start Date ≤ Date of last dose taken prior to PK sampling ≤ Treatment Stop Date	1. Clarification 2. To make sure that the derivation can apply to an irregular PK sampling such as sampling at unscheduled visit within

Reporting and Analysis Plan_204716_Amendment_Final_V1.1 [11-Oct-2017]		
Section # and Name	**Description of Change**	**Brief Rationale**
	Dose level is derived from actual dose of a visit which meets the above exposure record.	allowance of visit window.
10.8 Appendix 8: Values of Potential Clinical Importance	PCI values were updated in Section 10.8.1.	To maintain consistency between global and Japan Ph3 program, use the same PCI cut off values.
10.14 Appendix 14: List of Data Displays	The following bullets were modified: • General Changed from 'Randomized population' to 'Assigned population' • Table 1.9, Listing 6 Corrected title from 'Exclusions from Randomized Population' to 'Exclusions from All Treated Subjects Population' • Table 2.13, 2.14, 2.19, 2.20, 2.43 to 2.46, 3.27, Figure 3.1 Corrected titles • Table 2.47, 2.48 Added summary tables for number (%) of subjects with each dose level by visit • Table 3.18, 3.19 Corrected example shell ID • Table 3.42, 3.43, 3.44 Excluded statement to non-dialysis in Programming Notes of Vital Signs • Listing 2,3, 22 Corrected analysis population • Listing 16 Added iron parameter listing • Listing 25 Deleted duplicate (listing 39) and updated IDSL example • Listing 38, 39 Modified titles • Listing 65 Added programming notes	Corrections and Clarifications

Reporting and Analysis Plan_204716_Amendment_Final_V1.2 [29-NOV-2017]		
Section # and Name	**Description of Change**	**Brief Rationale**
6.1 Overview of Planned Analyses	Modification was made for the title; from 'Baseline Dialysis' to 'Baseline Mode of Dialysis'	Correction
8.1 Secondary Efficacy Analyses	1. Added summaries of number of dose adjustment to reach the lower Hgb target Hgb level (10.0 g/dL) 2. For the summary of time to reach the lower target Hgb level, modification was made to include all subjects in the analysis.	1. This will facilitate review of the study results 2. Correction according to team discussion
8.1.2 Planned Efficacy Table Displays	1. Text added to clarify that the analysis of scatter plot includes Pearson's correlation coefficient. 2. Updates were made to the summaries of dose level (mg) for adding P25 and P75. 3. In dose adjustment summary, it has been re-corrected that all subjects including those with no dose adjustment will include a summary.	1. Clarification 2. These will facilitate review of the study results. 3. Reconsideration clinically for the dose adjustment summary.
8.2 Safety Analyses 10.14 Appendix 14: List of Data Displays	Added additional tables: • On-therapy Serious Drug-Related AEs • On-therapy Non-Serious Drug-Related AEs	Required for a Plain Language Summary (PLS) for GSK
10.4.1 Treatment States	Clarification has been made for treatment states of follow-up visit assessments.	Clarification
10.6.1 General	Updates were made for definitions of treatment states; use study treatment stop date instead of end of treatment date (EoT). In addition to general changes of the treatment states due to this, note that this change has impact on the following endpoints for specific derivations: • Time (in days) to reach the lower target Hgb level (10.0 g/dL) • Dose of i.v. iron during the treatment period	For daprodustat, the treatment states will be more explainable on the basis of study treatment stop date derived from the exposure record rather on the basis of EoT derived from the assessment visit.
10.6.2 Study Population	Text added for treatment compliance up to Week 4.	Compliance up to Week 4 will facilitate review of the study results.
10.6.3 Efficacy	Deleted text that mentioned the baseline Hgb value might include that at unscheduled visits.	Missing the Hgb value at Day 1 will never happen so that no need to mention the unscheduled visits for the baseline Hgb derivation.
10.6.3 Efficacy	Added the candidate covariates (body weight at screening and baseline Hgb) to provide the	This will facilitate review of

Reporting and Analysis Plan_204716_Amendment_Final_V1.2 [29-NOV-2017]		
Section # and Name	**Description of Change**	**Brief Rationale**
10.10.1 Handling of Covariates, Subgroups & Other Strata 10.14.5 Efficacy Figures	following scatter plot figures: • Change from baseline in Hgb at Week 4 vs. candidate covariates • Mean dose vs. candidate covariates	appropriateness of starting dose or maintenance dose.
10.6.4 Safety	1. Clarification has been made for the definition of AEs up to Week 4 2. It has been corrected how to display the CV events in PAT form.	Clarification and correction
10.6.5 Pharmacokinetic	Clarifications were made for the derivation of dose normalized PK parameters and the definition of time deviated concentration.	Clarification