NCT #NCT04484857

FibroGen, Inc.

A Phase 3b Multicenter, Open-Label Single Arm Study of Roxadustat: Either as Conversion from an Erythropoiesis Stimulating Agent (ESA), or as Initial Anemia Treatment in Hemodialysis (HD) Patients

Protocol Number: FGCL-4592-096

Amendment 1

STATISTICAL ANALYSIS PLAN

Version: **1.0**
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Approvals

I have reviewed and accept the infonnation in this document to be a tme and accurate representation of the Statistical Analysis Plan for Study FGCL-4592-096.

Initiator:

Signature: [redacted] Date: _____

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Signature Significance

The following significance is lent to the signatures on the *Approvals* page of this document.

Signature	Significance
Author	By signing, the author is attesting that the content of the document is complete and accurate.
Reviewer	By signing, the reviewer is attesting that the document's approach and contents are compliant with the study protocol, all appropriate, regulato1y requirements, and other significant guidelines. This individual(s) has reviewed the document for accuracy and completeness.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
BUN	Blood Urea Nitrogen
CHr	Reticulocyte Hemoglobin Content
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CPK	Creatine Phosphokinase
EOS	End of Study
EOT	End of Treatment
ESRD	End Stage Renal Disease
ET	Early Termination
FAS	Full Analysis Set
Hb	Hemoglobin
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hb
MCHC	Mean Corpuscular Hb Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially Clinically Significant
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class (used in MedDRA dictionary)
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TIBC	Total Iron Binding Capacity
TIW	Three Times Weekly
TSAT	Transferrin Saturation
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of efficacy and safety as outlined and/or specified in the final study protocol. Specifications of tables, figures, and data listings are contained in a separate document.

2 STUDY DESIGN

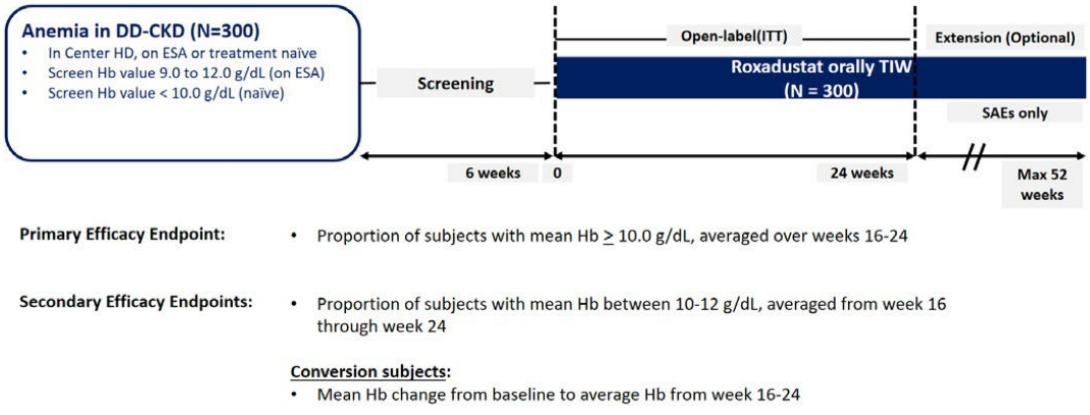
This open-label single arm study is designed to evaluate roxadustat in maintaining hemoglobin (Hb) in ESRD subjects receiving in-center hemodialysis either after conversion from a stable ESA dose: ESA use ≥ 6 weeks prior to conversion to roxadustat dosing or as initial anemia treatment, in subjects with < 6 weeks of total ESA use prior to start of roxadustat dosing.

The study periods are as follows:

- **Screening Period**: Up to 6 weeks
- **Treatment Period**: 24 weeks
- **Post-Treatment Follow-Up Period**: Subjects permanently discontinuing roxadustat, should have one final safety assessment (Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)) 28 days after the last roxadustat dose.

An extension of roxadustat treatment after 24 weeks may be offered to interested subjects within the context of the study protocol upon agreement with the study site. Data listings for the extension phase will be generated upon database lock and will include serious adverse events (SAEs), concomitant medications related to SAEs, and hospitalization records related to SAEs.

Study Design Overview



Subjects will be dosed three times weekly (TIW), except if a subject requires < 60 mg/week to maintain Hb levels, in which case dose frequency may be reduced in a stepwise fashion, e.g., to twice weekly (BIW), then once weekly (QW).

Initial Dose

Conversion from ESA to Roxadustat

The initial roxadustat dose is determined using a conversion table based on the subject's previous prescribed ESA dose in the last 4 weeks prior to enrollment (for Mircera®:in the last 8 weeks prior to enrollment) (Table 1.1).

Roxadustat treatment should start after the following intervals:

- Two days after stopping epoetin
- One week after stopping darbepoetin alfa
- Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera®)

If the converted initial dose exceeds the maximum dose of 3.0 mg/kg/dose then the next-lower dose step should be chosen as the initial dose.

Table 1.1. Conversion from ESA to Roxadustat

Previous dose of Darbepoetin alfa (mcg/week)	Previous Dose of Epoetin alfa (IU/week)	Previous Dose of Mircera® (mcg/month)	Starting Dose of Roxadustat (mg/dose TIW)
<25	<5000	<80	70
25 to 40	5000 to 8000	80 to 120	100
>40	>8000	>120	150

Initiation of Roxadustat Dosing in Subjects with < 6 weeks of Prior ESA or No Prior ESA Use

The initial roxadustat dosing is based on broad body weight categories (estimated dry weight at enrollment) as described in Table 1.2.

Table 1.2. Initial Roxadustat Dosing

Body Weight Category	**< 100 kg**	**≥ 100 kg**
Roxadustat Dose (TIW)	70 mg	100 mg

Note: Weight in HD subjects = subject's estimated dry weight at enrollment.

Dose Adjustments

During the treatment period, roxadustat dose adjustments will be made starting at Week 4 and at intervals of every 4 weeks thereafter according to the dose adjustment algorithm in Table 1.3, in order to achieve an Hb level of 11 g/dL and maintain an Hb of 11±1 g/ dL. Any potential dose escalation/dose reduction will be at pre-defined dose step increments.

Table 1.3. Roxadustat Dose Adjustment Rules

		Cunent Hblevel:			
		<10.5 g/dL	10.5 to11 9 g/dL	12.0 to 12.9 g/dL	:::13.0 g/dL
[illegible]	> 1.0 g/dL	No change	l	l	▪ Hold dosing ▪ CheckHband resume dosing when Hb <12.0 g/dL, at a dose reduced by2 steps
	-1.0 g/dL to +1.0 g/dL	t	Nochange	l	
	<-1.0 g/dL	t	t	Nochange•	

f: Increase dose by one step; ! : reduce dose by onestep.
•continue to hold dose

Notes:
Dose Increases and Reductions
- Dose increases (j) and reductions(!) are preset.
- The dose steps are as follows 20, 40, 50, 70, JOO, 150,200,250,300, and 400 mg.

If< 20 mg/dose is required, dosing frequency should be reduced in a step-wise fashion e.g., **TIW** to BIW, BIW to QW.
- The maximum dose is capped at 400 mg or 3.0 mg/kg/dose (whichever is lower). Rounding the mg/kg calculated roxadustat dose up to 10 mg may be allowed, if no safety concerns.

Roxadustat dose adjustment reviews should occur eve1y 4 weeks however, a dose reduction may be implemented at any time if the following criteria are met:

- Rate of Hb lise > 2 g/dL within 4 weeks: reduce dose by I dose step
- Hb level 13g/dL: hold dose, until Hb drops to< 12g/dL, resume dosing at 2 dose steps lower

Any dose adjustment will reset the dose-adjustment window to eve1y 4 weeks thereafter (e.g., dose adjustment for a qualified reason at Week 6 leads to next dose adjustment at Week 10).

Presclibed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower.

Dose titration decisions will be based on results from local Hb testing.

Rescue Therapy Guidelines:

Rescue therapy guidelines are provided to optimize the standardization of rescue therapy, and to ensure the safety of individual study subjects.

Blood/Red Blood Cell Transfusion

Blood/RBC transfusions should be considered if rapid conection of anemia is required to stabilize the subject's condition (e.g., acute hemonhage) or the Investigator is of the opinion that the blood transfusion is a medical necessity. Sn1dy treatment may continue during or after the RBC transfusion.

Erythropoiesis Stimulating Agent (ESA) Use
The use ofESAs as a "rescue" modality should be carefully considered, and should be restiicted to no more than one cycle of use dming the ti·eatment peliod; the Investigator may

initiate use of an approved erythropoietin (EPO) analogue if all of the following criteria are met:

- A subject's Hb level has not sufficiently responded to two or more dose increases or the maximum dose of study drug has been reached, and
- The subject's Hb is < 8.5 g/dL on two consecutive measurements (central lab) drawn at least five days apart; and
- Clinical judgment does not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in Hb, and
- Reducing the risk of alloimmunization in transplant eligible subjects and/or reduction of other RBC transfusion-related risks is a goal

ESA rescue should be started ≥ 2 days after the last dose of roxadustat.

ESA rescue should be stopped when Hb > 9 g/dL or after 4-weeks, whichever comes first. If a subject requires longer than 4 weeks therapy due to inadequate response, or in other extenuating circumstances, the Medical Monitor should be contacted.

Study treatment should be resumed after the following intervals:

- Two days after stopping epoetin
- One week after stopping darbepoetin alfa
- Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera®)

If more than one cycle of ESA rescue is required, the Investigator should permanently discontinue study drug.

Inadvertent ESA administration, such as ESA administration during a hospitalization, should not be counted as rescue unless the above criteria are met; these subjects may be allowed to restart roxadustat dosing if considered safe by the Investigator or the Medical Monitor.

ESAs and roxadustat should not be administered concomitantly.

Emergency Procedure (Therapeutic Phlebotomy)
If there are clinical concerns for a subject's high Hb levels, the Investigator may decide to perform a therapeutic phlebotomy in addition to temporarily withholding the study drug.

Iron Supplementation
Oral iron may be administered for iron supplementation without restriction. Dose and frequency of administration of oral iron are to be determined by the Investigator.

Intravenous iron (IV) should be considered for subjects with ferritin <100 ng/mL or TSAT <20%. IV iron should administered in 5 doses of 50 mg/dose. The Medical Monitor should be contacted if more IV iron is required.

Prohibited Medication:

The following medications/therapies are prohibited during the period identified:

- Any investigational drug from 4 weeks prior to screening until End of Study (EOS)
- Androgens from screening until EOS

- Iron-chelating agents (e.g., deferoxamine/desferrioxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to enrollment until EOS
- Dapsone (at any dose) from screening until EOS
- Chronic doses acetaminophen/paracetamol > 2.0 g/day from enrollment until 1 week after End of Treatment (EOT)

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

To confirm safe and effective roxadustat dosing regimens among chronic dialysis subjects converted from ESA therapy (≥6 weeks ESA treatment) or who are ESA-naïve (<6 weeks ESA treatment).

3.2 SECONDARY/EXPLORATARY OBJECTIVES

- Assessment of TEAEs and TESAEs
- Laboratory parameters, including iron indices
- Utilization of IV iron
- To test operational characteristics of converting a population of ESRD subjects from an injectable to oral anemia therapy

4 STUDY ENDPOINTS

4.1 EFFICACY ENDPOINTS

- Proportion of subjects with mean Hb level ≥ 10g/dL, averaged from Week 16 to Week 24
- Mean Hb change from baseline to average Hb from Week 16 to Week 24

Baseline Hb is defined as the mean of available central laboratory Hb values prior to first dose of study medication including the pre-dose Hb value collected on day 1.

4.2 EXPLORATORY ENDPOINTS

- Proportion of subjects with a mean Hb level within 10-12 g/dL from Week 16 to Week 24
- Proportion of subjects with Hb > 12 g/dL any time during treatment
- Proportion of subjects with Hb > 13 g/dL any time during treatment
- Percentage of time with Hb, values within 10.0 to 12.0 g/dL from Week 16 to Week 24
- Time to first RBC transfusion
- Proportion of subjects with a mean Hb level ≥10 g/dL in the first 8 weeks after conversion or initiation of treatment
- Proportion of subjects with a mean Hb level ≥10 g/dL (averaged from Week 16 to Week 24) based on baseline ESA use status ≥ 6 weeks (conversion form ESA to roxadustat based on prior ESA use) and < 6 weeks (initiation of roxadustat based on body weight)
- Evaluate the utilization of IV iron (IV iron use/4 weeks)

- Evaluate the effect on iron indices
- Evaluate dosing adherence
- Conversion subjects: Comparison of starting dose of roxadustat to roxadustat dose at Weeks 16 to 24
- Mean number of dose adjustments (including dose-hold) during study
- Proportion of subjects requiring blood/pRBC transfusion from Week 5 (Day 29) to Week 24/ET.
- Proportion of subjects requiring rescue therapy (blood/pRBC transfusion or ESA rescue) from Week 5 (Day 29) to Week 24/ET

In addition to the exploratory endpoints in the protocol, additional exploratory efficacy endpoints of interest are presented in this section.

RBC transfusion data is collected in the Blood Transfusions form of the eCRF.

For efficacy evaluation, Hb values will be censored for 4 weeks if blood/pRBC is administered during the treatment period. Hb results obtained from the central laboratory will be used to determine the Hb response.

4.3 SAFETY ASSESSMENTS

Study-specific safety will be assessed by evaluating the following:

- Incidence of TEAEs and TESAEs
- Vascular Access Thrombosis:
    - Time to a TEAE of vascular access thrombosis
    - Proportion of subjects with a TEAE of vascular access thrombosis
    - Proportion of subjects with a TEAE of vascular access thrombosis based on baseline type of vascular access
- Clinically significant changes in laboratory values from baseline
- Vital signs
- Specific adverse events (see Appendix 7)
    - Time to a TEAE for a specific adverse event
    - Proportion of subjects with a TEAE for specific adverse events

In addition to the safety assessments in the protocol, additional safety endpoints of interest are presented in this section.

Baseline vascular access (see Appendix 8) is determined using the vascular access medical history record. The start date of subject's last available vascular access medical history record must be prior to first dose of study medication and the end date must be on or after first dose of study medication.

5 GENERAL STATISTICAL CONSIDERATIONS

5.1 STATISTICAL METHODOLOGY

Safety and efficacy data will be summarized and presented by time points in summary tables. Continuous variables will be presented by descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated by frequency counts and percentages.

Lab results obtained from the central laboratory, rather than local laboratories, will be used for all efficacy and safety analyses. Local laboratory values, if collected in the eCRFs, will only be presented as data listings.

Unless otherwise stated, all confidence intervals will be two-sided 95% confidence intervals.

All analyses will be performed using SAS® Version 9.4 or higher.

5.2 SAMPLE SIZE DETERMINATION

Approximately 300 subjects with anemia of CKD (either with or without prior treatment with an ESA before enrollment) and on hemodialysis are planned in this study. This number of subjects distributed across the specified number of sites is adequate to evaluate the primary study objective.

Assuming the proportion of subjects that maintain Hb levels ≥10g/dL from Weeks 16 to 24 is at least 80%, with a sample size of 300, the study will be able to produce a two-sided 95% confidence interval (CI) with a width equal to 9.5%.

5.3 ANALYSIS POPULATIONS

5.3.1 Safety Population (SAF)

The safety analysis set will include all enrolled subjects receiving at least 1 dose of study treatment. The safety analysis set will be used for all safety endpoints and exposure to study treatment outcomes.

5.3.2 Full Analysis Set (FAS)

The FAS set will consist of all subjects who signed the informed consent, were enrolled, and provided baseline Hb data and data for at least one post baseline Hb time point. The FAS set will be used for all efficacy endpoints.

5.4 ADDITIONAL DATA HANDLING RULES AND PRESENTATION SPECIFICATIONS

The following general guidelines will apply to all statistical analyses and data presentations:

- Baseline is defined as the last available value obtained prior to the first dose of study drug, unless otherwise specified in this SAP.
- Hb baseline is defined as the mean of available values obtained during screening prior to the first dose (including pre-dose Day 1 Hb value).

- Baselines for reticulocyte count, reticulocyte hemoglobin content (CHr), serum iron parameters (transferrin, TIBC, TSAT, ferritin, sTfR, and iron) are defined as the values obtained on Day 1 (excluding screening) prior to the first dose.
- Baselines for blood pressure and heart rate are defined as the mean of values obtained during screening (including Day 1) prior to the first dose.
- Unscheduled visits within an allowable window will be grouped into the closest scheduled visits based on the visit window specified in Appendix 1. For subjects who have more than one measurement at a certain scheduled visit, the last measurements will be used, with the exception of CPK, WBC, liver function tests (i.e., ALT, AST, GGT, ALP, and total bilirubin), in which the maximum measurement will be used.
- By default, US conventional units will be used for laboratory value presentations. A separate set of laboratory tables with SI units may be required by regulators, such as the European Medicines Agency (EMA).
- Age is calculated as of date that the informed consent form was signed.
  - age = INTCK('YEAR', Birth date, date of Informed Consent, 'C') where INTCK is a SAS function.
- Duration of treatment or days on treatment is calculated as: last dose date – first dose date +1
- Body weight, height and temperatures will be converted using the following formulas:
  - kg = lb/2.2
  - cm = 2.54 x in
  - $C^o = (5/9) \times (F^o - 32)$
- Mean Arterial Pressure (MAP) will be calculated for each subject using the following formula: MAP = (2/3) * diastolic blood pressure + (1/3) * systolic blood pressure.
- All percentages will be rounded to one decimal place and lined up by the decimal place. The percentage will be suppressed when the count is zero.
- All tables and listings will have a header showing "FibroGen, Inc.", the protocol number, and the page number. Footer will indicate the program file path/name, run date and run time.
- For continuous variables that are recorded as "< X" or "> X", the value of "X" will be used in the calculation of summary statistics. The original values will be used for the listings.
- Decimal points will be presented as follows: N will be presented without decimals, minimum and maximum in same precision as in the database, mean, median in one more decimal than minimum and maximum, and SD in one more decimal than mean and median.
- Tables and figures will use derived analysis visits. Listings will use nominal visits, and the analysis visits used will be flagged. Namely, both nominal visits and analysis visits will be presented in the listing.
- Additional data handling conventions are detailed in Appendix 2.

5.5 PROTOCOL DEVIATIONS

Major protocol deviations of interest may include, but are not limited to the criteria in Table 2.

Table 2. Criteria for Assessing Major Protocol Deviations

Number	Major Protocol Deviation
1	Violation of key* inclusion or exclusion criteria which may affect the assessment of the efficacy of the study drug

Number	Major Protocol Deviation
2	Administration of ESA for more than 4 weeks before Week 16; any duration from Week 16 to Week 24
3	Study drug compliance < 75% or >125% (up to Week 24)
4	Administration of prohibited concomitant medication that may impact evaluation of efficacy of the study drug*
5	Significant noncompliance with study procedures that may impact evaluation of efficacy of the study drug will be evaluated case by base*

*Subject to Medical Monitor's decision

The number and percentage of major protocol deviations will be categorized and summarized as deemed appropriate.

6 SUBJECT ACCOUNTABILITY AND DISPOSITION

The following subject data will be summarized and presented if applicable, by number and percentage:

- Subjects enrolled at each center, and for all centers combined (using the enrolled population)
- Subjects in each analysis set (using the enrolled population)
- Subjects who prematurely discontinued during the treatment period, and by discontinuation reason for the enrolled population.
- Subjects who complete the treatment period (will be considered as "completers")
- Subjects who participated in the Post-treatment Follow-Up
- Subjects who completed the EOS Visit
- Subjects who entered extension study

Kaplan-Meier plots will be generated for premature treatment discontinuations showing one curve.

7 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

7.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic parameters and important baseline and disease characteristics will be summarized for the safety and FAS populations. These include but may not be limited to age, age group (18 to <65, 65 to <75, ≥75), sex, ethnicity, race, weight, body-mass index (BMI), Hb, baseline Hb categories (<10, ≥10 g/dL), iron repletion status at baseline, ferritin, ferritin group (<100, 100-<400, ≥400 ng/mL), TSAT and TSAT group (<20%, 20%-<40%, ≥40%), hepcidin, serum iron, iron deplete (ferritin <100 or TSAT <20%) vs. not, cardiovascular or cerebrovascular or thromboembolic medical history (yes vs. no), blood pressure (systolic ≥140 or diastolic ≥90 vs systolic <140 and diastolic <90), incident dialysis vs stable dialysis, starting dose, baseline ESA type, baseline ESA dose categories (low/medium/high/very high), vascular access at baseline.

Table 3. Baseline ESA Dose Categories

Baseline ESA dose categories	Epoetin (IU/Week)	Darbepoetin Alfa (ug/Week)	Mircera (ug/month)
Low	0 - < 5000	0 - < 25	0 - < 80
Medium	5000 - < 8000	25 – 40	80 – 120

High	8000 – 16000	> 40- 80	> 120- 200
Very High	> 16000	>80	>200

Identify dialysis based on medical history of interest CRF MHINTERM ((Dialysis (Peritoneal), Dialysis (Home Hemodialysis), and Dialysis (Hemodialysis). Dialysis start date equals to MHSTDAT if not partial. If it is partial and day is missing impute the date with 1st day of the month. If missing month and day, impute to January 1st.

ESA naive is defined as patients who started ESA for < 6 weeks prior to Day 1. ESA dependent is defined as patients who started ESA for ≥ 6 weeks prior to Day 1.

ESA baseline window is defined as 28 days prior to enrollment and the date right before first dose. For patients with more than one ESA type at baseline, the ESA type that was administered immediately before Day 1 was used.

Total duration of ESA use is calculated from first chronic ESA use to date of first dose date.

Stable dialysis is defined as patients who have been on dialysis for > 4 months at the time of enrollment into the study. Incident dialysis is defined as patients who have been on dialysis for ≤ 4 months at the time of enrollment into the study.

Dialysis duration is calculated from first chronic dialysis date to date of enrollment.

In addition, 25%-75% values of Hb and platelets will be presented. Frequency distributions (number and percentage of subjects) will be presented for categorical variables.

The baseline characteristics, iron indices, and iron IV given between ESA naïve and those converted from ESA therapy will be summarized and presented in a table.

Descriptive statistics of baseline values for other parameters will be presented in their change from baseline tables.

7.2 MEDICAL HISTORY

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Medical history of interest including Chronic Kidney Disease (CKD) history inclusive of CKD cause, cardiovascular disease, cerebrovascular disease, thrombosis history, hypertension history, diabetes history, and anemia history will be summarized by system organ class and preferred term for the safety population.

8 TREATMENT AND MEDICATIONS

8.1 STUDY DRUG EXPOSURE

Exposure to study medication will be summarized in terms of treatment duration in weeks, which is calculated using the following formula: (the date of last medication taken - the date of first dose taken +1)/7.

Total weekly study drug exposure is defined as the total actual dose (in mg and mg/kg) of study drug administered within the week (windowed by 7-day period from Day 1).

Weekly exposure and total study drug exposure will be tabulated for the safety population.

Per administration amount and administration frequency will also be tabulated for the safety population.

Patient-Exposure-Year (PEY) is defined as (Last Dose Date – First Dose Date + 1)/365.25.

8.1.1 Dosing Changes

Prescribed dose adjustments (dose increase, dose reduced, dose interrupted, and dose resumed) along with the adjustment reasons (protocol mandated dose amount adjustment, AE related, and other) recorded on the Prescribed Dose Adjustments Form in the eCRF will be tabulated by time point (Week 2, 4, 6, 8, 12, 16, 20, 24). Mean number of dose adjustments (including dose-hold) during study and number (%) of subjects with dose adjustment in each adjustment category will be summarized.

8.1.2 Treatment Compliance

Study medication dosing compliance for a specified period is defined as the total dose (mg actually taken by a patient during that period divided by the prescribed dose expected to be taken during the same period multiplied by 100. An overall per-dose compliance measure can be calculated by (total amount of actual dose administrations)/ (total amount of expected dose administrations) *100 during the subject's treatment period. Descriptive statistics for study medication compliance will be presented for the entire treatment period of the study.

Compliance will be summarized as follows:

- Descriptive statistics will be summarized for the entire treatment period.
- Percent compliance will be categorized according to the following categories for the entire treatment period for safety population:
    - less than 75% (drug noncompliance)
    - at least 75%, less than 125% (drug compliance)
    - greater or equal 125% (drug noncompliance)
    - unknown

8.2 PRIOR AND CONCOMITANT MEDICATIONS

The World Health Organization Drug Dictionary (WHO Drug) will be used to classify prior and concomitant medications by therapeutic class and generic name based on ATC code level 3. Prior medication is defined as any medication taken and stopped prior to the first dose of the study medication. Concomitant medication is defined as any medication taken between the day of first dose of the study medication and the day of last study medication date + 28 days. For subjects who complete the treatment period and decide to participate in the extension treatment, any medication taken after the Treatment Period (Week 24/EOT) will not be counted as concomitant medications for the main study, but will be listed for the extension period.

Medication start and end dates and times will be compared with the start date of study drug and classified as per Table 4.

In case of partial or missing dates, comparisons will be made based on the level of detail available. For example, if start date of study drug is 04Jan2013, and a medication has a start date of Jan2013 but missing day, the medication will be classified as concomitant.

Table 4. Classification of Prior and Concomitant Medications

End date / Start date	Before start of study drug administration	On or after start of study drug administration	Missing
Before start of study drug administration	Prior	Concomitant	Concomitant
On or after start of study drug administration	–	Treatment Emergent Concomitant	Treatment Emergent Concomitant
Missing	Prior	Concomitant	Concomitant

Both prior and concomitant medication usage will be summarized by the number and proportion of subjects. Subjects will only be counted one time in each unique ATC Class and generic name if multiple drugs are used by a subject.

Detailed analyses may be performed on prior and concomitant medications of special interests such as oral iron, blood pressure medications, and lipids medications.

9 EFFICACY ANALYSES

Efficacy analysis will be conducted on the FAS population.

9.1 ANALYSIS OF EFFICACY ENDPOINTS

9.1.1 Proportion of subjects with mean Hb ⩾ 10 g/dL, averaged from Week 16 to Week 24

The efficacy endpoint will be evaluated using the proportion (%) of subjects with mean value of Hb measurements from Week 16 to Week 24 ≥ 10 g/dL.

Proportion of responders will be presented descriptively with counts and percentages and a 95% confidence interval of the responder rate. The 95% CI of the response rate will be presented based on normal approximation.

For the Hb efficacy analysis, a multiple imputation (MI) method will be used. This will be implemented on the raw Hb values, then the Hb-relates endpoint summaries will be derived based on the imputed data (algorithm as used for the previous phase 3 studies).

The following steps will be used to conduct the MI procedure of the Hb values:

1. Generate 200 datasets, using seed 12345, where only intermittent missing Hb data will be imputed relying on non-missing data from all subjects using the Monte Carlo Markov Chain (MCMC) imputation model using baseline Hb and the available non missing Hb for each scheduled week.

The MCMC statement in the SAS PROC MI procedure with monotone option will be used. As a result, each dataset will only have missing ending data, or a monotone missing data pattern.

2. For each dataset from step 1, missing ending data (Hb up through end of evaluation period) will be imputed. As a result, 200 imputed complete datasets will be generated.

- Missing data at Week 2 will be imputed using the regression imputation model with baseline and Hb from Week 2, using the SAS PROC MI procedure with the REGRESSION option in the MONOTONE statement.

- Repeat for all other scheduled weeks sequentially (Week 4 to the end of evaluation period). Subjects whose missing data were imputed for previous weeks will contribute to the imputation for the current week.

- The regression imputation model includes an intercept and the slopes of the Hb from previous weeks.

Steps 3 and 4 will be used to analyze proportion of subjects with a mean Hb level ≥ 10 g/dL, averaged from Week 16 to Week 24 using the imputed Hb data above:

3. Analyze each imputed complete dataset to estimate proportions of responders and their standard errors using the mean of all observed or imputed Hb values within the evaluation period (Weeks 16 to 24).

Sample SAS code:

```
PROC FREQ DATA=xx;
  TABLES resp_week16_24 / cl binomial (level=2);
  BY _Imputation_;
  ODS OUTPUT BINOMIALPROP=prop;
RUN;
```

4. Combine estimates from the results for each of the 200 proportion estimates using SAS PROC MIANALYZE.

```
PROC MIANALYZE DATA=prop;
  MODELEFFECTS prop;
  STDERR prop_se;
  ODS OUTPUT PARAMETERESTIMATES=mian_prop;
RUN;
```

Report the results of the proportion of subjects with a mean Hb level ≥ 10g/dL, averaged from Week 16 to Week 24.

9.1.2 Mean Hb change from baseline to average Hb from Week 16 to Week 24

For continuous endpoints, changes from baseline will be presented descriptively. Missing Hb values will be imputed using a MI procedure.

Steps 3 and 4 below will be used to calculate the mean Hb change from baseline to average Hb from Week 16 to Week 24 using the imputed Hb data in Steps 1-2 above in section 9.1.1.

3. Analyze each imputed complete dataset to estimate the mean Hb change from baseline to average Hb and their standard errors using the mean of all observed or imputed Hb values within the evaluation period (Weeks 16 to 24).

Sample SAS code:

```
PROC MEANS DATA=xx MEAN STDERR;
  BY _imputation_;
  VAR change_Week24;
  WEIGHT covariates;
  OUTPUT OUT=avg MEAN=mean_hb STDERR=se_hb;
RUN;
```

4. Combine estimates from the results for each of the 200 proportion estimates using SAS PROC MIANALYZE.

```
PROC MIANALYZE DATA= avg;
  MODELEFFECTS mean_hb;
  STDERR se_hb;
  ODS OUTPUT PARAMETERESTIMATES=mian_mean;
RUN;
```

Report the results of the mean Hb change from baseline to average Hb from Week 16 to Week 24.

9.2 ANALYSIS OF EXPLORATORY ENDPOINTS

The analysis for the exploratory endpoints will be based on the FAS population.

9.2.1 Time to first RBC Transfusion

For a subject receiving a RBC transfusion, the Time at Risk (time up to first RBC transfusion) will be calculated (in weeks) as:

(First RBC transfusion date – First dose date of study medication + 1) / 7

For a subject not receiving a transfusion, the Time at Risk (time until they get censored) is calculated as:

(Date of last study visit – First dose date of study medication + 1) / 7

Subjects with no events were censored at the date of minimum (last dose date, last visit date, death date, Week 24*7).

Time to first RBC transfusion will be analyzed using the Kaplan-Meier method with KM curve plotted to derive the following:

- Proportion of subjects with any RBC transfusion up to Week 24

9.2.2 Hb Level

- Proportion of subjects with a mean Hb level ≥ 10 g/dL in the first 8 weeks after conversion or initiation of treatment
- Proportion of patient with a mean Hb level ≥ 10 g/dL (averaged from Week 16 to Week 24) based on baseline ESA use status ≥ 6 weeks (conversion form ESA to roxadustat based on prior ESA use) and < 6 weeks (initiation of roxadustat based on body weight)

For the Hb level exploratory analysis above, a MI method will be used. The imputation data will be generated in a method similar to the one described in section 9.1.1. Similarly, the Rubin's method will then be used to combine the estimates of the proportion of responders and standard errors from each of the PROC FREQ procedure.

- Proportion of subjects with a mean Hb within 10-12 g/dL from Week 16 to Week 24
- Proportion of subjects with Hb > 12 g/dL any time during treatment
- Proportion of subjects with Hb > 13 g/dL any time during treatment
- Percentage of time with Hb values within 10.0 to 12.0 g/dL from Week 16 to Week 24

For the Hb level exploratory analysis above, observed Hb values will be used.

9.2.3 IV iron use every 4 weeks during the treatment period

The IV iron use every 4 weeks during the treatment period will be calculated for monthly intervals. The treatment period will be divided into 28 days and the monthly mean of IV iron for each period will be calculated using the following formula:

> Monthly iron use for each subject = total IV iron in mg / [(last dose date – first dose date of IV Iron in the period +1)/ 28]

9.2.4 Iron indices

The mean change from baseline in the following endpoints will be summarized and data up to the Week 24 visit will be included in the analyses:

- Value and change from baseline in CHr at each of the selected time points (e.g., Weeks 8, 16, 24)
- Value and change from baseline in serum ferritin at each of the selected time points, total and sub-grouped by baseline values of <100 ng/mL, 100 to <400 ng/mL and ≥ 400 ng/mL.
- Value and change from baseline in TSAT at each of the selected time points, total and sub-grouped by baseline values of <20%, 20% to <40%, and ≥ 40%.
- Value and change from baseline in serum iron at each of the time points tested
- Proportion of patients with CHr > ULN at each time point tested: Weeks 8, 16, 24

9.2.5 Dosing adherence

See SAP section 8.1.2 Treatment Compliance

9.2.6 Comparison of starting dose to Weeks 16 to 24 dose

For proportion of patients with dose increased, dose decreased, and dose not changed, an analysis will be done comparing starting dose to average prescribed dose over Weeks 16 to 24.

9.2.7 Dosing adjustments

See SAP section 8.1.1 Dosing Changes

9.2.8 Blood Transfusion and ESA Usage as Rescue Therapy

Blood/pRBC transfusions will be recorded in the Blood Transfusion Form of the eCRF. ESA, as rescue therapy, will be recorded in the Concomitant Medication eCRF.

The following 2 endpoints will be analyzed:

- Proportion of patients requiring a blood/pRBC transfusion from Week 5 (Day 29) to Week 24/ET. The 95% CI of the response rate will be presented based on normal approximation.
- Proportion of patients requiring rescue therapy (blood/pRBC transfusion or ESA rescue) from Week 5 (Day 29) to Week 24/ET. The 95% CI of the response rate will be presented based on normal approximation.

9.3 SUBGROUP ANALYSIS

Primary efficacy endpoints will be presented by forest plots based on the following subgroups: sex, age group, baseline Hb categories, baseline iron status, cardiovascular/cerebrovascular/thromboembolic medical history, starting dose, participating dialysis organizations, and baseline ESA dose categories. Overall summary of TEAEs will be analyzed by subgroups of starting doses of roxadustat.

Other endpoints of interest may be analyzed by the subgroups listed above as needed.

10 SAFETY ANALYSES

The safety analysis will be performed using the safety population. Safety parameters include adverse events, laboratory parameters, vital signs, and physical examinations.

For each safety parameter, the last assessment made prior to the first dose of study medication will be used as the baseline for all analyses for that safety parameter.

10.1 ADVERSE EVENTS

Adverse events will be coded using the latest MedDRA version.

10.1.1 Proportion of Subjects with TEAE

An AE (classified by preferred term) started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study medication, or it was present prior to the first dose of study medication but increased in severity during the treatment period. For subjects who permanently discontinue roxadustat early or complete the treatment period (24 weeks) but decide not to participate in the extension treatment, all AEs that occur up to 28 days after the last roxadustat dose will be counted as a TEAE. For subjects who complete the treatment period and decide to participate in the extension treatment, an AE that occurs after the treatment period (Week 24/EOT) will not be counted as a TEAE.

The number and percentage of subjects reporting TEAEs will be tabulated separately by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study medication. If more than one event occurs with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study medication.

The distribution of TEAEs by severity and relationship to study medication will be summarized.

The incidence of common (≥ 5% of subjects) TEAEs, common non-serious (≥ 5% of subjects) TEAEs (excluding TESAE), TESAEs, and AEs leading to discontinuation of study medication will be summarized by preferred term and sorted by decreasing frequency. In addition, the incidence of deaths and SAEs with a fatal outcome (i.e., events that caused death) will be summarized separately by preferred term.

AE summaries are presented as a crude incidence rate and patient exposure year (PEY) adjusted incidence rate. The PEY-adjusted incidence rate, per 100 patient exposure years, is defined as the incidence of an event divided by 100 times the PEY which is defined as (last dose date – first dose date +1) divided by 365.25.

Listings of subjects with SAEs, adverse events leading to discontinuation, and those who died will be presented

Temporal profile of TEAEs of special interest may also be plotted showing the subjects in the y-axis and time to these TEAEs in the x-axis (Appendix 4).

10.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for laboratory values (in US conventional and SI units) and changes from baseline for each assessment time point will be presented for the following laboratory parameters collected in the study including but not limited to the following:

- Hematology: Hb, hematocrit, RBC count, MCV, MCH, MCHC, WBC count, WBC differential, platelet counts and reticulocyte count;
- Chemistry: CPK, ALP, ALT, AST, total bilirubin, LDH, total protein, albumin, glucose, phosphate, BUN, creatinine and potassium;
- Serum iron, ferritin, TIBC, TSAT, and CHr

Laboratory values are clinically significant (CS) if they meet either the low or high CS criteria. The number and percentage of subjects with post-baseline CS values will be tabulated. The percentages are to be calculated relative to the number of subjects with available baseline values and at least one post-baseline assessment. The numerator is the total number of subjects with at least one post-baseline CS value. In addition, shift tables will be presented by time point. The following 2 data listings will be presented by subject:

- A listing of lab values for all lab tests at all collected time points.
- A listing of subjects with post-baseline CS values will be provided including the baseline and post-baseline values.

10.3 VITAL SIGNS

Blood pressure and heart rate baselines are defined as the mean of values obtained from the last 6 weeks of screening including Day 1 prior to the first dose. For subjects on hemodialysis, pre-dialysis vital signs will be used. For subjects on peritoneal dialysis, vital signs may be recorded at any time during the visit.

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, MAP, heart rate, respiratory rate and temperature) and their changes from baseline at each visit and at the end of study will be presented.

10.4 COVID-19 POSITIVE PATIENTS

Patients who tested positive for COVID-19 during the study will be recorded on the Adverse Events Form in the eCRF. The following 2 data listings will be presented in COVID-19 positive patients:

- A listing of central lab Hb values with COVID-19 AE start date/stop date, mean Hb before COVID-19 diagnosis, mean Hb after COVID-19 diagnosis.
- A listing of COVID-19 related AEs leading to study drug interruption or withdrawal up to 28 days after last dose.

11 INTERIM ANALYSIS

An interim analysis may be performed to report topline results at the Sponsor's discretion. Since no statistical hypothesis testing is performed for this study, no multiplicity adjustment is required.

For better execution and understanding, certain data points (e.g., data linked to dose adjustments, iron supplementation, etc.) may be analyzed by patients participating under each dialysis organization (i.e., all patients, patients from DaVita, and patients from USRC), as needed.

12 REFERENCES

ICH Harmonized Tripartite Guideline E3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

Carpenter JR, Roge JH and Kenward MG, Analysis of longitudinal trials with protocol deviation: a Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation. Journal of Biopharmaceutical Statistics, issue 6 (November/December) in volume 23 (2013). 1352-137

Haybittle, J. L. (1971), "Repeated Assessment of Results in Clinical Trials of Cancer Treatment," British Journal of Radiology, 44, 793-797.

Peto, R., Pike, M. C., Armitage, P., Breslow, N. E., Cox, D. R., Howard, S. V., Mantel, N., McPherson, K., Peto, J., and Smith, P. G. (1976), "Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of Each Patient: I. Introduction and Design," British Journal of Cancer, 34, 585-612.

Little RJA, Rubin D.1987. Statistical Analysis with Missing Data. John Wiley and Sons.

Rubin, D. B. (1987) Multiple imputation for nonresponse in surveys. New York: Wiley.

Schafer, J. L. (1997) Analysis of incomplete multivariate data. London: Chapman and Hall.

13 APPENDIX

13.1 APPENDIX 1: SCHEDULE OF ASSESSMENTS

Visit/ Week:	Screening Visit	Day 1	Wk2to8 ± 4 days	Wk 12-24g ± 4days	Post-Treatment or ET ±7 days
Written infonned consent	X				
Eligibility criteria	X	X			
Demographics and medical history	X				
Height, weight	X	X			
Blood pressme, heart rate, temperature	X	X	X	X	X
Physical Exam	X			X	
Hemoglobin (central and local)	Xd		Xf	Xf	Xd
CBC with WBC differential	X	X	Wks4. 8	Wks 16, 24	X
Senun chemistry	X	X	Wks4, 8	Wks 16, 24	X
CPK	X	X	Wks 8	Wk 16, 24	
Senun iron, ferritin, TIBC, TSAT, CHr, reticulocytes	X	X	Wk8	Wks 16,24	
HIV ELISA, HBsAg, anti-HCV Ab	X				
Senun hCG pregnancy test	Xb			Q8Wks	X
Dose adjustment			X	X	
AE/CM recording	X	X	X	X	X
Study dmg dispensing		X	X	X	

Ab = antibo r CBC = complete blood count; CHr = reticulocyte hemoglobin content; ELISA = enzyme-Ii ed immunosorbent assay; ET = early temlination; HBsAg = hepatitis B surlace antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C vi.ms; HIV = human immunodeficiency virus; LFTs = liver ftmction tests TIBC = total iron binding capacity; TSAT = transfe1rin saturation; WBC =white blood cells; Wk(s) = week(s);

a Weight only
b Collect from female subjects of child bearing potential only
c Renal ultrasotmd examination will be perfo1med durinfl screening if norecord of a renal imaginf modality exists within 24 weeks prior to enro lment.
d Centra labs only
e 28 days post last dose of roxadustat
f Collect a separate central Hb only when CBC is not collected
g Week24=EOT

13.2 APPENDIX 2: DATA HANDLING CONVENTIONS

13.2.1 Visit Time Window

Table 5 below presents the visits assigned for efficacy and safety analyses corresponding to the range of treatment days (window) during which an actual visit may have occurred.

Table 5. Analysis Visit Windows

Derived Visit	Scheduled Visit Day[a]	Window
Baseline, Week 0	Day 1	Days ≤ 1
Week 2	Day 7*(Week #)+1	Days [Day 2, 21]
Weeks 4-6	Day 7*(Week #)+1	Days [Scheduled Day -7, Scheduled Day + 6]
Week 8	Day 7*(Week #)+1	Days [Scheduled Day -7, Scheduled Day + 13]
Weeks 12-24	Day 7*(Week #)+1	Days [Scheduled Day -14, Scheduled Day +13]
ET[b]	Last assessment between Day 2 and EOT/Week 24 visit day, match to a closest scheduled visit in protocol.	
EOS	Final visit in the Study; For subjects who permanently discontinue roxadustat early or complete the treatment period (24 weeks) but decide not to participate in the extension treatment: around 28 days after the last dose. For subjects who complete the treatment period and decide to participate in the extension treatment: EOT/Week 24 visit day.	

[a]: Relative to the first study medication date. For example, Day 1 = the first dose date of study medication.
[b]: For patients that are early terminated (ET), the ET visit will be collected on the Week 24/EOT visit eCRF.

13.2.2 Repeated or Unscheduled Assessments of Safety Parameters

If a patient has repeated assessments prior to the start of study medication, then the results from the final assessment made prior to the start of study medication will be used as baseline. If EOS assessments are repeated or unscheduled, the last post-baseline assessment will be used as the EOS assessment for generating summary statistics. However, all post-baseline assessments will be used for potentially clinically significant (PCS) value determinations and all assessments will be presented in the data listings.

13.2.3 Missing Date of Study Medication

When the last date of study medication during the study treatment phase is missing, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts, then the last dispensation visit date during the treatment period will be used in the calculation of treatment duration.

13.2.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE started prior to the first study medication, then a severity of "Mild" will be assigned. If the severity is missing for an AE started on or after the first study medication dosing, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summary, while the actual missing values will be presented in data listings.

13.2.5 Missing Relationship to Study Drug for Adverse Events

If the relationship to the study medication is missing for an AE started after baseline, a causality of "Related" will be assigned. The imputed values for relationship to study medication will be used for incidence summary, while the actual values will be presented in data listings.

13.2.6 Missing Date Information for Adverse Events

The following imputation rules only apply to the case where the start date is incomplete (i.e., partial missing) for adverse events.

- **Incomplete Start Date**

Missing day and month

- If the year is same as the year of first day on study medication, then the day and month of the start date of study medication will be assigned to the missing fields.
- If the year is not the same as the year of first day on study medication, then January 1 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

If the month and year are same as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.

If the month and year are not the same as the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.

- **Incomplete Stop Date**

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If needed, the following imputation rules apply to the case where the end date is incomplete (i.e., partially missing) for adverse events. Other partial end date will not be imputed.

Missing day and month, or Missing month only

December 31 will be assigned to the missing fields.

Missing day only

The last day of the month will be assigned to the missing day.

Table 6.1 Imputation of the Analysis Adverse Event Start Date

Reported Date	Date of First Drug Intake	Analysis Date (Derived)
--/MM/YYYY	DD/MM/YYYY	
--/02/2008	14/02/2008	14/02/2008*
--/02/2008	14/02/2007	01/02/2008
--/02/2008	14/02/2009	01/02/2008
--/--/YYYY	DD/MM/YYYY	
--/--/2008	14/02/2008	14/02/2008
--/--/2008	14/02/2007	01/01/2008
--/--/2008	14/02/2009	01/01/2008
DD/--/---- --/MM/---- --/--/----		No imputation

Table 6.2 Imputation of the Analysis Adverse Event Stop Date

Reported Date	Analysis Date (Derived) *
--/MM/YYYY	31/MM/YYYY or 30/MM/YYYY or 29/MM/YYYY or 28/MM/YYYY
--/--/YYYY	31/12/YYYY
DD/--/----, or --/MM/----, or --/--/----	No imputation

*Death has to be taken into consideration when calculating this.

13.2.7 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

- **Incomplete Start Date**

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month
If the year of the incomplete start date is the same as the year of the first dose date of study medication, then the day and month of the first dose date will be assigned to the missing fields.
If the year of the incomplete start date is not the same as the year of the first dose date of study medication, then January 1 will be assigned to the missing fields.
Missing month only
Treat day as missing and replace both month and day according to the above procedure.
Missing day only
If the month and year of the incomplete start date are the same as the month and year of the first dose date of study medication, then the day of the first dose date will be assigned to the missing day.
If the month and year of the incomplete start date are the same as the first dose date of study medication, then the first day of the month will be assigned to the missing day.

- **Incomplete Stop Date**

The following rules will be applied to impute the missing numerical fields, if needed. If the last dose date of study medication is missing, impute it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

If the year of the incomplete stop date is the same as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.
If the year of the incomplete stop date is not the same as the year of the last dose date of study medication, then December 31 will be assigned to the missing fields.
Missing month only
Treat day as missing and replace both month and day according to the above procedure.
Missing day only
If the month and year of the incomplete stop date are the same as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day.
If the month and year of the incomplete stop date are not the same as the month and year of the last dose date of double-blind study medication, then the last day of the month will be assigned to the missing day.

13.2.8 Missing Date Imputation for last dose date

Imputed last dose date = earliest date of (last drug dispense date + number of days of drug dispensed, date of death, date of EOT/EOS visit, and other dates as appropriate).

13.2.9 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table due to, for example, that a character string is reported for a parameter of the numerical type, coded value needs to be appropriately determined and used in the statistical analyses. However, the actual values as reported in the database will be presented in data listings.

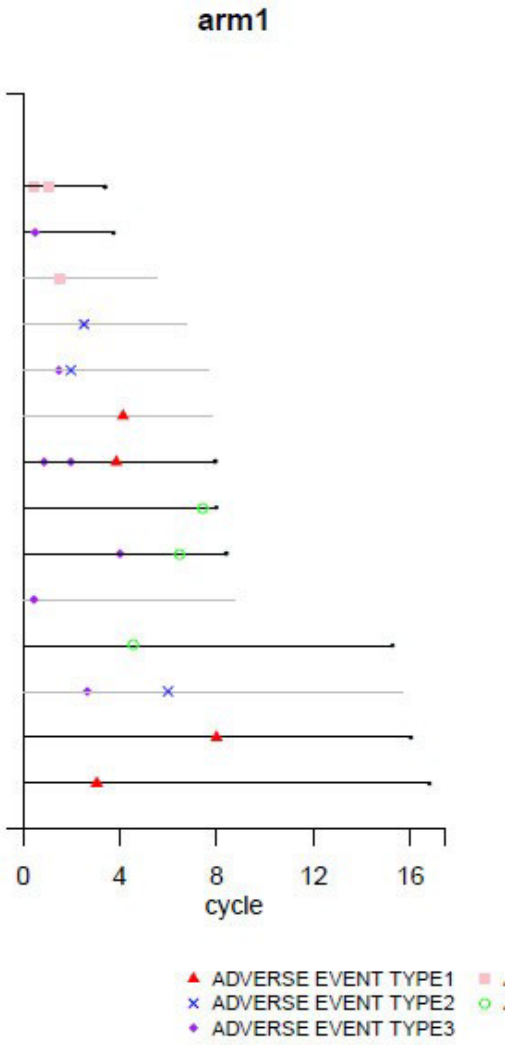
Table 7. Example for Coding of Special Character Values for Clinical Laboratory Parameters

Lab Test	Possible Lab Results (in SI unit)	Coded Value for Analysis
Urinalysis: Ketones	= OR > 8.0, ≥8.0, > 0	Positive
	≤ 0, Negative	Negative
Urinalysis: pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5,	8.5
Urinalysis: Protein	= OR > 3.0, ≥3.0, > 0	Positive
	≤ 0	Negative

13.3 APPENDIX 3: RANGES OF POTENTIALLY CLINICALLY SIGNIFICANT LAB VALUES

Parameter	SI Unit	Lower Limit	Higher Limit
CHEMISTRY			
Alanine Aminotransferase (ALT)	U/L		≥3 * ULN
Alkaline Phosphatase	U/L		≥3 * ULN
Aspartate Aminotransferase (AST)	U/L		≥3 * ULN
Severe liver abnormality			ALT or AST ≥ 3 x UL N AND Total bilirubin > =2 x ULN
GGT	U/L		≥3 * ULN
Calcium	mmol/L	<0.8*LLN	>1.2 * ULN
Potassium	µmol/L	<0.75*LLN	>1.2 * UNL
Sodium	mmol/L	<0.9*LNL	>1.1 * UNL
Total Bilirubin	µmol/L		>1.5 * UNL
Total Protein	µmol/L	<0.9*LNL	>1.1 * UNL
HEMATOLOGY			
Neutrophils	10^9/L	≤1	
Platelet Count	10^9/L	≤ 100	≥700
White Blood Cell Count	10^9/L	≤2.5	≥15
LLN: Lower limit of normal, value provided by the laboratory ULN: Upper limit of normal, value provided by the laboratory			

13.4 APPENDIX 4: TEMPORAL PROFILE OF TEAES OF SPECIAL INTEREST



13.5 APPENDIX 5: MEDICATION WHO DRUG DICTIONARY CODES

Name	Code
ESA except darbepoetin alfa	ATC level 4 = B03XA
Darbepoetin alfa	ATC level 4 = B03XA
IV Iron	ATC level 4 = B03AC
RBC transfusion	ATC level 4 = B05AX
Any investigational drug	WHODD drug code = 99999701001
Hypoxia-inducible factor HIF-PHI	ATC level 4 = B03XA
Iron-chelating agents	ATC level 4 = B03AA, B03AD, B03AE, A12CX
Androgens	ATC level 3 = G03B and G03E
Dapsone	ATC level 4 = J04BA
Acetaminophen/paracetamol	ATC level 4 = N02BE, N02AA, R05X

The following WHO-DRL codes will be classified as ESA: '00909301001', '00928301001', '02198701001', '07973701001', ‘01703101001’.

The following WHO-DRL code where route is INTRAVENOUS will be classified as IV IRON: '00023501001' and ‘90135401001’.

The following WHO-DRL code will be classified as RBC transfusion: '01186901001'.

13.6 APPENDIX 6: CARDIOVASCULAR/CEREBROVASCULAR/THROMBOEMBOLIC MEDICAL HISTORY TERMS USED IN MEDICAL HISTORY OF INTEREST CRF

Medical Condition Term
Hypertension
Myocardial infarction(STEMI or NSTEMI)
Angina, Stable
Angina, Unstable
Coronary artery bypass
Percutaneous coronary intervention
Atrial fibrillation, flutter or supraventricular tachycardia
Ventricular tachycardia or fibrillation
Stroke: Ischemic
Stroke: Hemorrhagic
Stroke: Unknown
Transient ischemic attack
Congestive heart failure (NYHA): Class I
Congestive heart failure (NYHA): Class II
Congestive heart failure (NYHA): Class III
Congestive heart failure (NYHA): Class IV
Cardiomyopathy
Peripheral vascular disease
Deep vein thrombosis
Pulmonary embolism
Vascular access thrombosis
Valvular heart disease

13.7 APPENDIX 7: SEARCH CRITERIA FOR SPECIFIC ADVERSE EVENTS

Specific Adverse Events	**Search Criteria**
Myocardial Infarction	PTs: Acute myocardial infarction Myocardial infarction
Stroke Selected PTs	PTs: Brain Stem Haemorrhage Brain Stem Infarction Brain Stem Stroke Cerebellar Infarction Cerebral Infarction Cerebral Thrombosis Cerebrovascular Accident Embolic Stroke Haemorrhagic Cerebral Infarction Haemorrhagic Stroke Ischaemic Cerebral Infarction Ischaemic Stroke Lacunar Infarction Lacunar Stroke Thalamic Infarction
Stroke SMQs	Two SMQS combined : • Haemorrhagic central nervous system vascular conditions (SMQ) • Ischaemic central nervous system vascular conditions (SMQ)
Hypertension	Hypertension Narrow SMQ
Seizures	Convulsions Narrow SMQ
Deep vein thrombosis (DVT)	PT: Deep vein thrombosis
Pulmonary embolism	PTs: Pulmonary artery thrombosis Pulmonary embolism
Infections SOC	Infections SOC
Infections SAE	Infections SOC + SAE
Infections Fatal	Infections SOC + Fatal
Sepsis	Sepsis Narrow SMQ
Malignancy	Malignant tumors SMQ

13.8 APPENDIX 8: MEDICAL HISTORY PREFERRED TERM FOR BASELINE VASCULAR ACCESS TYPE

Baseline Vascular Access Type	**Preferred Term**
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
Catheter	Central venous catheterisation

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