Statistical Analysis Plan

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ALTAI: An Open-Label, Randomized, Active-Controlled, Parallel Design, Multicenter Phase IV Study to Investigate the Effect of Roxadustat versus Recombinant Human Erythropoietin (rHuEPO) on Oral Iron Absorption in Chinese Patients with Anemia of Chronic Kidney Disease (CKD)

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LIST OF ABBREVIATIONS

Abbreviation or special term	**Explanation**
ATC	Anatomical therapeutic chemical
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of covariance
AUC	Area under the curve
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CSP	Clinical study protocol
DCO	Data cut off
DD	Dialysis dependent
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	estimated Glomerular Filtration Rate
EOS	End of study
FAS	Full analysis set
FSGS	Focal Segmental Glomerulosclerosis
FWER	Familywise error rate
GI	Gastrointestinal
Hb	Hemoglobin
HD	hemodialysis
hs-CRP	High sensitivity C-reactive protein
MedDRA	Medical Dictionary for Regulatory Activities
NDD	Non-dialysis dependent
PCS	Potentially Clinically Significant
PD	Peritoneal dialysis
PP	Per-protocol
rHuEPO	Recombinant human erythropoietin
TEAE	Treatment emergent adverse event
TELVC	Treatment emergent laboratory/vital signs change
TESAE	Treatment emergent serious adverse event

Abbreviation or special term	**Explanation**
TIBC	Total iron binding capacity
TLF	Tables, listings and figures
TSAT	Transferrin saturation
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	20 Nov 2020	Run-in period removed	Yes	Protocol amendment #2 approved 24 June 2020.
Statistical analysis method for the primary or secondary endpoints	20 Nov 2020	Models are updated to account for new strata from protocol amendment	Yes	Protocol amendment #2 approved 24 June 2020.
Other	20 Nov 2020	ECG text updated because only measured once (not triplicate).	Yes	Protocol amendment #2 approved 24 June 2020.
Other	20 Nov 2020	Number of subjects screened increased to account for potentially higher screen failure rate due to COVID-19 pandemic.	Yes	Protocol amendment #2 approved 24 June 2020.
Statistical analysis method for the primary or secondary endpoints	20 Nov 2020	Subgroup analyses has been added for the primary and secondary efficacy endpoints within the DD and NDD subgroups (DD-rHuEPO users, NDD-rHuEPO users, NDD-rHuEPO naïve)	Yes	Protocol amendment #2 approved 24 June 2020.
Statistical analysis method for the primary or secondary endpoints	20 Nov 2020	Details of multiple imputation methods have been added to Section 4.1.2	Yes	Protocol amendment #2 approved 24 June 2020.

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1 STUDY DETAILS

1.1 Study objectives

Primary objective [a]:	**Endpoint/variable:**
Evaluate the main effect of roxadustat versus rHuEPO on gastrointestinal iron absorption.	The main treatment effect on: the difference from baseline (Day 1) to Day 15 in log-transformed AUC of iron absorption from 0-3 hours based on the change in serum iron levels obtained just prior to T0 (time when single dose of oral iron is administered) and over the subsequent 3-hour period following oral administration (see Section 4.3.1).
Secondary Objectives [a]:	**Endpoints/variables:**
Assess the effect and interaction with key baseline variables of roxadustat versus rHuEPO on iron absorption.	The main treatment effect and key interaction effects on the difference from baseline (Day 1) to Day 15 in log-transformed AUC of iron absorption from 0-3 hours based on the change in serum iron levels obtained just prior to T0 (time when single dose of oral iron is administered) and over the subsequent 3-hour period following oral administration (see Section 4.3.2).
Assess the effect and interaction with key baseline variables of roxadustat versus rHuEPO on the indices of iron metabolism (ie, serum iron, ferritin, TIBC, TSAT, transferrin, soluble transferrin receptor) and hepcidin levels.	The main treatment effect and key interaction effects on the difference from baseline (Day 1) to Day 15 prior to administration of oral iron: in serum iron, ferritin, TIBC, TSAT, transferrin, soluble transferrin receptor and hepcidin levels, log-transformed as appropriate (see Section 4.3.2).
Safety Objective:	**Endpoint/variable:**
Safety evaluation.	Safety assessed by incidence of AEs, and measurement of vital signs (tympanic

	temperature, BP, pulse and respiratory rate), laboratory variables (see Section 4.3.3).

[a] The primary and secondary objectives will be analyzed using the Full Analysis Set (FAS), see Section 2.1 for further details.

AE=Adverse event; AUC=Area under the curve; BP=Blood pressure; rHuEPO=recombinant human erythropoietin; TIBC=total iron binding capacity; TSAT=transferrin saturation.

1.2 Study design

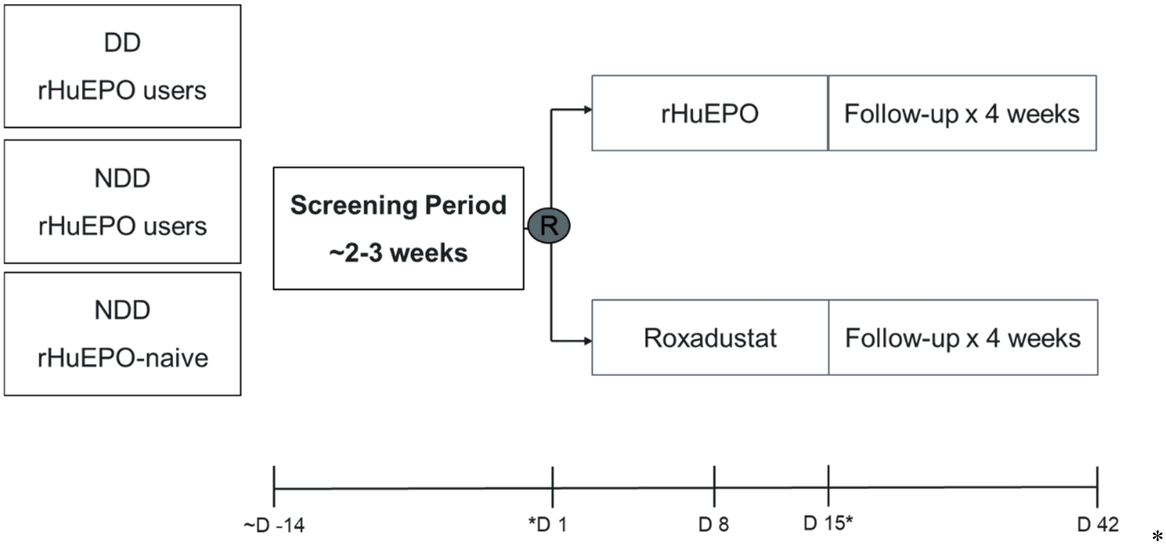
This is a Phase IV, randomized, active-controlled, open-label, parallel design, multicenter prospective study to evaluate the effect of roxadustat versus recombinant human erythropoietin (rHuEPO) treatment on the gastrointestinal (GI) iron absorption in patients with anemia of Stage 4 and Stage 5 chronic kidney disease (CKD). The study consists of 3 periods; the Screening Period, Treatment Period and Follow-up Period. The enrolled patients will have a maximum of 7 study visits (Figure 1).

This study will enroll eligible dialysis and non-dialysis patients who are either dialysis-dependent (DD) and are being treated with rHuEPO 4 weeks prior to screening, or are non-dialysis-dependent (NDD) and are being treated with rHuEPO (stable dose within 4 weeks prior to screening), or are rHuEPO-naïve at screening (no treatment with erythropoietin stimulating agents [ESAs] for > 6 weeks). At randomization, patients will be stratified by the following: Non-Dialysis Dependent rHuEPO-users (NDD-rHuEPO users), NDD-rHuEPO-naïve, dialysis dependent patients on peritoneal dialysis (DD-PD), dialysis dependent patients on hemodialysis (DD-HD) with approximately equivalent number of patients in each stratum.

Patients will be assessed for hs-CRP at the Screening Visit to check whether the measurement is either ≤ the upper limit of normal (ULN), or > the ULN, to control the number of inflamed patients being randomized in the study (maximum of 23 low hs-CRP patients will be randomized).

The Screening Period will be followed by randomization (Day 1, Visit 2) at a 1:1 ratio to receive either roxadustat or rHuEPO for 2 weeks. At Visit 2, all patients randomized to rHuEPO will receive a uniform brand of short-acting rHuEPO according to the dosage approved in the rHuEPO China Package Insert. Patients who were previously on rHuEPO (before Screening) will receive a uniform brand of short-acting rHuEPO based upon their previous dose of rHuEPO, and according to the dosage approved in the rHuEPO China Package Insert. For patients on a weekly dose of rHuEPO of 6000 IU, dosing will be 2 times a week (BIW) and for patients on a weekly dose of rHuEPO of > 6000 IU, dosing will be 3 times a week (TIW). For DD patients, the rHuEPO can be administered either IV or SC depending on the route of administration used before the Treatment Period. The rHuEPO will be administered via the SC route for all patients who are NDD. On Days 1 and 15, immediately **before** time T0 of the ferrokinetic study, a blood sample will be collected to measure baseline serum iron level and total iron binding capacity (TIBC), immediately followed by administration of a defined single dose of oral iron after which the remaining blood samples for the ferrokinetic study will be collected over 3 hours to measure serum iron levels. Serum levels of hepcidin and hs-CRP will be measured as biomarkers that reflect both altered iron metabolism and inflammation. Both biomarkers will be assessed throughout the study. Safety will be evaluated in all consented patients.

Figure 1 Study design



The Screening Period will be approximately 2-3 weeks long, but may be greater or lesser, to ascertain the Hb eligibility criteria with up to 3 hemoglobin (Hb) tests. During the Screening Period, all patients who were on rHuEPO before entering the study will remain on the rHuEPO treatment they received. The rHuEPO dose may be adjusted for patients who were on rHuEPO before the Screening Period depending on the patient's Hb levels, at the discretion of the Investigator, in accordance with the rHuEPO China Package Insert.
The ferrokinetic study on Day 1 must be completed prior to randomization. Patients will be randomly assigned in 1:1 ratio to either roxadustat or rHuEPO. Study treatment to be administered after randomization at Day 1.
*Ferrokinetic study at T0 (before single dose of oral iron [12.5 mL [100 mg elemental iron]), and 1, 2 and 3 hours following the administration of a single dose of oral iron.
The blood samples for the ferrokinetic study (serum iron and TIBC) at the T0 timepoint must be taken immediately **before** the single dose of oral iron is administered.
On Days 1, 8, and 15 hemoglobin levels will be tested in the central laboratory for all patients. Additionally, for patients randomized to rHuEPO, Hb levels will be tested in the local laboratory on Days 1 and 8 for initial dose determination and dose adjustment. The rHuEPO dose may be adjusted on Day 8 of the Treatment Period, depending on the patient's Hb levels, for safety reasons, as determined by the Investigator, in accordance with the rHuEPO China Package Insert. On Day 15 (or at the discontinuation visit), Hb levels will be tested in the local laboratory for all patients who were on rHuEPO prior to the study, to decide what rHuEPO dose to restart patients on, or another appropriate course of treatment for anemia, after study treatment stops. For patients who were rHuEPO-naïve before entering the study, Hb levels may be tested in the local laboratory on Day 15 (or at the Discontinuation Visit) at the discretion of the Investigator, to determine an appropriate course of treatment for anemia in each patient.
D=day; DD=dialysis-dependent, NDD=non-dialysis-dependent, R=randomization; rHuEPO=recombinant human erythropoietin.

1.3 Number of subjects

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

2 ANALYSIS SETS

2.1 Definition of analysis sets

For purposes of analysis, the following populations are defined.

2.1.1 All-patients analysis set

The all-patients analysis set will consist of all patients who are screened for the study. This analysis set will be used for listings.

2.1.2 Full analysis set

The full analysis set (FAS) includes all randomized patients who have complete baseline (Day 1) measurements for any of the efficacy endpoints (as defined in Sections 4.3.1 and 4.3.2), with patients being analyzed as randomized, rather than as treated. The FAS will be used for the primary endpoint and all secondary endpoints. The FAS will also be used for the presentation of all demographic and disposition data.

2.1.3 Per-protocol analysis set

The per-protocol (PP) analysis set will include all randomized patients who received at least 1 dose of study treatment, have baseline (Day 1) and at least 1 post-baseline iron absorption measurement, and are without important protocol violations. The PP analysis set will be used as a sensitivity analysis population for the primary and secondary endpoints. Section 2.2 describes the protocol violations which are considered important for this study.

2.1.4 Safety analysis set

The safety analysis set will include all randomized patients receiving at least 1 dose of study treatment, with patients being analyzed as treated, rather than as randomized. The safety analysis set will be used for the safety endpoints. Exposure to study treatment will also be presented using the safety analysis set.

2.2 Violations and deviations

Important protocol deviations are defined in Table 1. Important protocol deviations will be summarized by treatment group and overall and presented in a data listing. Important protocol deviations relating specifically to the global pandemic of COVID-19 will be presented separately.

Table 1 Criteria for Assessing Important Protocol Deviations

Number	Important Protocol Deviations	Level of Deviation [a]
1	Violation of inclusion or exclusion criteria. The key inclusion criteria are numbers 9 and 10. The key exclusion criteria are numbers 14, 15, 24, and 26. The full list of inclusion and exclusion criteria is available in the CSP.	Subject
2	Administration of wrong type or dose of study drug (i.e. the one not randomized to).	Visit
3	Administration of prohibited concomitant medication or non-drug therapy as defined in the protocol.	Visit
4	Study drug compliance <75%, where drug compliance is measured by comparing dispensed and returned drug (see Section 4.2.7).	Visit
5	Any transfusion or rescue therapy received during or within a week of the randomized treatment period.	Visit
6	Any of the two doses of oral iron are missed	Subject

[a] Subject-level deviations refer to important protocol deviations that will cause subjects to be excluded from the Per Protocol set, and therefore all their collected data from analyses based on this population. Visit-level deviations refer to important protocol deviations that will cause only some data for subjects to be excluded from analyses based on the Per Protocol set, while the subjects remain in the Per Protocol set given that they did not meet any subject-level deviations. Data to be excluded from the Per Protocol analyses could be either data from a certain date, at which the deviation was met for the first time, onwards to the end of the study, or data during a period defined by the start and end dates of the deviation.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy variables

3.1.1 Primary efficacy variable: GI iron absorption

The primary outcome for this study is the GI iron absorption change from baseline (Day 1) to Day 15. At Days 1 and 15, serum iron level and TIBC will be determined followed by administration of a defined single dose of oral liquid elemental iron containing $FeSO_4$ to all patients at time T0. Serum iron level at 1, 2, and 3 hours following administration of the single oral iron dose (timepoints T1, T2, and T3) will then be determined. Gastrointestinal iron absorption will then be assessed by the total area under the curve (AUC) adjusted for serum iron level from sample obtained just prior to T0. Iron absorption data will be provided by Covance, with log-transformations to be done during programming, where applicable. The primary endpoint is defined in Section 4.3.1.

3.1.2 Secondary efficacy variables

The secondary outcomes of interest assess direct treatment and interaction effects in iron absorption and the indices of iron metabolism and hepcidin levels and are described in Section 4.3.2. The relative change from baseline (Day 1) to Day 15 will be calculated for the following variables:

- Serum iron
- Ferritin
- TIBC
- TSAT
- Transferrin
- Soluble transfer receptor
- Hepcidin

3.2 Safety assessment

Safety will be assessed throughout the study. A complete baseline profile of each patient will be established through demographics, medical history (events before ICF signing), clinical laboratory values, vital signs, and physical assessments. During the course of the study, vital signs (tympanic temperature, systolic and diastolic BP, pulse and respiratory rate) and laboratory tests will be performed at regular intervals.

Adverse events, SAEs and ongoing concomitant medication usage will be monitored and recorded throughout the study. Serious adverse events reports will be evaluated individually to assess for the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. Serious adverse events and

AEs will be followed until resolved, stable or until the patient's End of Study (EOS) visit. Safety will be assessed by evaluating the following:

- Frequency counts and incidence rates of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)
- Changes from baseline in vital signs and physical examination
- Mean change from baseline in clinical laboratory values
- Frequency counts and incidence rates of clinically significant changes from baseline in vital signs and ECG values.

4 ANALYSIS METHODS

4.1 General principles

The following general principles will be followed throughout the study:

- Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category; including proportion of missingness.
- The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place, and the standard deviation will be reported to two more decimal places, than the raw data recorded in the database.
- Percentages will be presented to one decimal place.
- SAS® version 9.3 or later will be used for all analyses.

Study Day 1 is defined as the date of 1st dose of randomized study treatment. For visits (or events) that occur on or after first dose, study day is defined as (date of visit [event] - date of first dose of randomized treatment + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] - date of first dose of randomized treatment).

All efficacy variables, safety variables and patient characteristics will be summarized by study treatment groups using descriptive statistics. Data will be summarized by visit and randomization strata as applicable.

For safety variables, the last observation before the first dose of randomized treatment will be considered the baseline measurement unless otherwise specified.

In all summaries, change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (postbaseline value - baseline value) / baseline value ×100.

The primary endpoint, all secondary efficacy endpoints, study population and demography data will be summarized and analyzed based on the FAS. The safety analysis set will be used for the safety endpoints. The PP analysis set will be used as a sensitivity analysis population for the primary and secondary endpoints.

All statistical tests will be conducted at a 2-sided significance level of 5% unless otherwise specified. Where appropriate, model-based point estimates, together with their 95% confidence intervals (CIs) will be presented along with the 2-sided p-values for the tests.

The primary analysis will be performed when all patients have completed Day 15, and will include production of all the tables, listings and figures (TLF), which will be specified and finalized in a separate TLF shell document before database lock. A final analysis will be performed when all patients have completed the study and will include production of all TLFs.

4.1.1 Multiple testing

For each of the secondary endpoints, the Holm-Bonferroni method will be implemented to control the familywise error rate (FWER) for each of the treatment effect p-values (Holm 1979). Both the unadjusted error (based on a significance level α=0.05) and a Holm-Bonferroni adjusted significance level will be implemented due to multiple testing.

Let P1, P2…Pn be the p-values for each of the *n* separate hypotheses tests. The Holm-Bonferroni adjustment ranks these p-values from smallest to largest ($P_{[1]}$, $P_{[2]}$…$P_{[n]}$) and the associated hypotheses $H_{(1)}$, $H_{(2)}$…$H_{(n)}$.

For a pre-specified significance level, α, let *k* be the smallest value for which $P_{(k)}>\frac{\alpha}{n+1-k}$ where *n* is the total number of p-values being adjusted for.

Testing of further p-values will stop, all corresponding preceding null hypotheses $H_{(1)}$, $H_{(2)}$…$H_{(k-1)}$ will be rejected, and none of the rest of the null hypotheses $H_{(k)}$, $H_{(k+1)}$, $H_{(k+2)}$…$H_{(n)}$ will be rejected. This ensures that the FWER $\leq\alpha$.

The adjusted p-values are calculated as follows:

$$\tilde{p}_i = \max_{k\leq i}\{(n-k+1)p_k\}_1\,, where\ \{x\}_1 \equiv min(x,1)\ and\ i\ is\ the\ number\ of\ hypotheses$$

Primary endpoint

The primary endpoint will be tested at a significance level of 0.05. If significant then all secondary endpoints will be assessed using the Holm-Bonferroni method described above. If the primary endpoint is not significant (p>0.05) then testing will stop and the null hypotheses for the secondary endpoints will be accepted.

Secondary endpoints

If multiple testing is applied to the secondary endpoints, then the following rules will apply. Each model is described in section 4.3.2, with a corresponding number. For models (1) the FWER will be implemented across the seven treatment-effect p-values.

For models (2) and (3), these will be tested against a nominal p-value of 0.05 and will be treated as exploratory.

4.1.2 Handling of missing data

4.1.2.1 Multiple imputation for missing visits

Multiple imputations (MI) will be implemented for the primary and secondary analyses to account for missing data, due to the increased risk of this occurring during the COVID-19 pandemic.

For the primary and secondary efficacy analysis, MI will be used as the primary analysis method. This will be implemented on the raw data values on the log scale for the respective endpoint. If a subject has missing Day 15 but has an early discontinuation visit, the early discontinuation visit will be allocated as Day 15. Any subject with missing post-baseline measurement will have their data imputed. It will be conducted with the following steps (using AUC of iron absorption as an illustrative example, but applicable to all iron indices data):

- Step 1 - Imputation preparation step: Create a dataset, one for each treatment group, of subjects with observed values and those needing estimation by multiple imputation. Subjects with missing baseline data will be excluded.
- Step 2 – Imputation step: For each treatment group separately, missing Day 15 values will be imputed using Monotone Regression in SAS PROC MI. The imputation model will include the stratum variable (NDD-rHuEPO user, NDD-rHuEPO naïve, DD-HD, DD-PD), the baseline hs-CRP level (≤ULN, >ULN), the Day 1 value and the day 15 value (observed or missing). A total of 200 imputations will be performed using a seed of 1456. Note that a different seed will be used for each endpoint and each model within an endpoint, as shown in Table 2.
- Step 3 – Derivation step: Set the two treatment group imputed datasets together. Derive d_i as described in Section 4.3.1.
- Step 4 – Analysis step: Perform the ANCOVA analysis as described in Section 4.3.1 by imputation.
- Step 5 – Pooling step: Combine the results from the 200 ANCOVA analyses using Rubin's rules in PROC MIANALYZE. Back-transformation of estimated to the original scale (as appropriate) will be performed after the pooling step.

Table 2 Seed for Multiple Imputation

Endpoint	Seed (Model 1)	Seed (Model 2)	Seed (Model 3)
AUC iron absorption	1456	3209	4291
Serum iron	687	290	4210
Ferritin	9341	1321	7897
TIBC	6782	9200	6172
TSAT	2935	3401	201
Transferrin	5340	637	7222

Endpoint	Seed (Model 1)	Seed (Model 2)	Seed (Model 3)
Soluble transfer receptor	4782	2221	102
Hepcidin	3817	38882	2032

4.1.2.2 Partial or missing dates

When the last dose date is missing, it will be imputed as the earliest date of last drug dispense date + number of days of drug dispensed, date of death, date of EOT visit or date of EOS visit.

Where dates are missing or partially missing, medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose or after the last dose of randomized treatment.

Partial AE and concomitant medication start dates will be imputed as follows:

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start date, then use the date of first dose
- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use the 1st of January of the year of the start date
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.

Imputation of Partial Stop Dates

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31st of that year
- If the stop date is completely unknown, do not impute the stop date.

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant, or an adverse event was treatment emergent, the medication will be considered as concomitant or the adverse event will be considered treatment emergent.

4.2 Analysis methods

4.2.1 Patient disposition

The total number of patients screened (including screening failures), re-screened, randomized, patients who received any randomized treatment and patients who did not receive any randomized treatment, patients who completed randomized treatment and patients who discontinued treatment and the reason for treatment discontinuation, patients who completed the study and patients who discontinued the study and the reason for study discontinuation will be summarized by treatment group and overall.

The number and percentage of patients included in the analysis sets and the number of patients recruited by center will be also presented by treatment group and overall.

By-subject listings of patient disposition and analysis set exclusions will be presented.

4.2.2 Protocol deviations

All identified important protocol deviations, as described in Section 2.2, will be listed and summarized for the FAS by treatment group and overall. All protocol deviations will be identified and classified as important or not important before database lock.

A by-subject listing of important protocol deviations will be presented.

4.2.3 Demographics and other baseline characteristics

Demographic and baseline subject characteristics will be listed and summarized for the FAS by treatment group and overall. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Weight (kg)
- eGFR (mL/min/1.73m^2) at screening
- Duration of dialysis
- Duration of CKD

In addition to the standard descriptive statistics, the geometric mean and CV (%) will be presented for the following:

- Serum iron AUC
- Serum iron
- Ferritin
- TIBC
- TSAT
- Transferrin
- Soluble transfer receptor
- Hepcidin

The total counts and percentages of patients will be presented for the categorical variables of:

- Age group (years) (≥18-<50, ≥50-<65, ≥65-<75, ≥75)
- Weight (kg) (<70, ≥70-<100, ≥100 kg)
- Sex (male, female)
- Race (Black or African American, Asian, White, other)
- Ethnic group (Hispanic or Latino, not Hispanic or Latino)
- Dialysis history
  - Type of dialysis (PD, HD)
  - Hemodialysis access type (arteriovenous fistula, arteriovenous graft, tunneled catheter, other)
- rHuEPO use during 4 weeks prior to Visit 2
  - frequency (every week, 2 times per week, 3 times per week, 4 times per week, QM [every month], other), dose, route (parenteral, intravenous, subcutaneous, intraperitoneal, unknown, not applicable)
- Baseline CKD, most likely etiology (ischaemic/hypertensive nephropathy, chronic glomerulonephritis, renal artery stenosis, chronic pyelonephritis (infectious), chronic interstitial nephritis, obstructive nephropathy, cystic kidney disease - policystic kidney disease, cystic kidney disease - medullary kidney disease, cystic kidney disease - medullary sponge kidney, cystic kidney disease – other, diabetic nephropathy - type 1, diabetic nephropathy - type 2, unknown, other)
- Chronic Glomerulonephritis Type (IgA nephropathy, focal segmental glomerulosclerosis [FSGS], membranous nephropathy, minimal change, lupus nephritis, other primary or secondary glomerulonephritis)
- rHuEPO status at randomization (rHuEPO-user, rHuEPO-naïve)
- hs-CRP (≤ULN [10.0 mg/L], >ULN [10.0 mg/L])
- eGFR category (<10 mL/min/1.73m^2, 10-<15 mL/min/1.73m^2, 15-<30 mL/min/1.73m^2, ≥30mL/min/1.73m^2)

4.2.4 Medical and surgical history

All reported relevant medical and abdominal and pelvic surgical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized (number and percentage of patients) for the FAS by system organ class (SOC) and preferred term (PT), for each treatment group and overall.

4.2.5 Concomitant medication

Prior and concomitant medications are defined as follows:

- Prior medications are medications taken prior to or during screening with a stop date prior to the first dose of randomized treatment.

- Concomitant medications are medications with or without a stop date on or after the date of first dose of randomized treatment (and could have started prior to or during treatment).

Concomitant medication will be summarized using frequency tables by Anatomical therapeutic chemical (ATC) classification code (based on World Health Organization (WHO) classification) based on the FAS. Intravenous iron, rHuEPO and triferic in dialysate during the 4 weeks prior to Visit 1 will be listed. A by-subject listing of all concomitant medications taken on entry and during the study will be presented for randomized subjects.

4.2.6 Exposure

The following descriptive statistics will be produced for the Safety Analysis Set, by treatment group:

- Total exposure to study treatment (weeks) = (min(last dose date, death date) - first dose date +1) / (365.25/52)
- Time on study – defined as the time in days from the start date of treatment to the date of last study assessment or the date of withdrawal.

The following summaries will be produced for the Safety Analysis Set, by treatment group:

- Number of and reasons for dose interruptions
- Number of and reasons for dose reductions

4.2.7 Treatment Compliance

Subjects will be asked to return all unused study medication and empty packages to the clinic at each visit. The amount of dispensed and returned study medication will be recorded in the eCRF. The percentage treatment compliance will be calculated as:

$$(\text{Overall amount of dose actually taken}/\text{Overall amount of dose to be taken})*100$$

Subjects taking ≥75% and ≤125% of planned study medication are considered to be compliant.

Compliance will be summarized based on the FAS as follows:

- Descriptive statistics will be summarized by the two treatment groups
- Percent compliance will be categorized according to the following three categories:
  - <50% or ≥150% (significant drug non-compliance)
  - ≥50% and <75% or >125% and <150% (moderate drug non-compliance)
  - ≥75%, ≤125% (drug compliance)

4.3 Statistical analyses

4.3.1 Primary efficacy endpoint

The primary efficacy endpoint is measured through change from baseline (Day 1) to Day 15 in log-transformed AUC of iron absorption from 0-3 hours based on the change in serum iron levels obtained just prior to T0 (time when single dose of oral iron is administered) and over a 3-hour period. If a patient withdraws before Day 15, their discontinuation visit will be used as the post-baseline primary measurement. Multiple imputation, as described in Section 4.1.2.1, will be implemented on missing data for subjects with no post-baseline primary measurement.

The AUC curve (for the calculation of the primary endpoint and associated secondary endpoints) will be determined for each patient at baseline (Day 1) and post-baseline, then the average of the changes from baseline (Day 1) will be evaluated for each treatment group. This is to be calculated for patient *i* as the sum of the area of each trapezium under the curve, adjusted for any iron present in sample obtained just prior to time T0. Let *Pj* be the serum iron level at timepoint *Tj* then the AUC for patient *i* at Visit X is

$$\mathrm{AUC}_{\mathrm{x,i}}=\sum_{\mathrm{j=0}}^{2}\left(\frac{\mathrm{P}_{\mathrm{j+1}}+\mathrm{P}_{\mathrm{j}}}{2}-\mathrm{P}_{0}\right)$$

Let *di* be the change from baseline for patient *i* and is defined as:

$$d_i = \log(AUC)_{Day15,i} - \log(AUC)_{Baseline,i}$$

The difference in log (AUC) from baseline (Day 1) to Day 15 will be analyzed using an ANCOVA model, adjusting for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD patients), and baseline hs-CRP level (≤ ULN, > ULN).

A summary table will be presented to show the change from baseline (Day 1) to Day 15 in log-transformed AUC of iron absorption, by treatment group. Estimates of the geometric mean and coefficient of variation in each treatment group will also be presented. A separate table will show the treatment group comparisons, along with estimates, 95% CIs, and p-values from the ANCOVA model. Estimates will be back-transformed (exponentiated) and presented on the original scale.

Should the residuals in the primary analysis fail to satisfy normality, AUC will be analyzed on the original observation scale instead. The following procedure will be used. If the Shapiro-Wilks test rejects the null hypothesis of normality of the residuals at a significance level of 0.05 and the residuals present with left skew when analyzing the difference in log(AUC), the change in AUC will be analyzed as the difference in AUC. A second test of normality will be conducted. If the Shapiro-Wilk test rejects the null hypothesis of normality of the residuals when analyzed on the untransformed scale and the residuals present with right skew, then the analysis will revert to the log scale.

In the event that the AUC instead will be evaluated on the untransformed scale (Section 1.3), the absolute difference in AUC from baseline (Day 1) to Day 15 will be analyzed using a type III sum of squares ANCOVA model, adjusting for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD on hemodialysis [DD-HD], and DD on peritoneal dialysis [DD-PD], and baseline hs-CRP (≤ ULN, > ULN) level.

If any of the values required to calculate the AUC are missing, then the following rules will apply:

- If either measurement for timepoints T0 or T1 are missing, then the AUC cannot be reasonably calculated and will be deemed missing.
- Else If only T2 is missing, then the midpoint for T1 and T3 should be used.
- Else If T3 or T2 and T3 are missing, then LOCF from T1 should be used.

A sensitivity analysis will be performed, which will exclude all patients with any missing measurements required for the AUC calculation.

The hypothesis to be assessed is as follows:

H_0: There is no difference in the average change from baseline in the ferrokinetic measurement between rHuEPO and roxadustat.

H_A: There is a difference in the average change from baseline in the ferrokinetic measurement between rHuEPO and roxadustat.

A subgroup analysis will be performed on the primary and secondary efficacy endpoints within the DD and NDD subgroups (DD-HD, DD-PD, NDD-rHuEPO-users, NDD-rHuEPO-naïve).

4.3.2 Secondary efficacy endpoints

The secondary efficacy outcomes for this study are outlined in Section 3.1.2. The secondary endpoints of interest assess direct treatment and interaction effects in the indices of iron metabolism (ie, serum iron, ferritin, TIBC, TSAT, transferrin, soluble transfer receptor) and hepcidin levels, and are described below. When hs-CRP level or hs-CRP interaction is included in the below models, this refers to the continuous measurement of baseline hs-CRP.

Relative difference in AUC

2. The relative difference in AUC from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hepcidin value, and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
3. The relative difference in AUC from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-HuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

Relative difference in serum iron

1. The relative difference in serum iron from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD-PD, and DD-HD) and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
2. The relative difference in serum iron from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hepcidin value and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
3. The relative difference in serum iron from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

Relative difference in ferritin

1. The relative difference in ferritin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD-PD, and DD-HD) and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
2. The relative difference in ferritin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hepcidin value and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
3. The relative difference in ferritin baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

Relative difference in TIBC

1. The relative difference in TIBC from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD-PD, and DD-HD) and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
2. The relative difference in TIBC from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD),

baseline hepcidin value and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.

3. The relative difference in TIBC from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

Relative difference in TSAT

1. The relative difference in TSAT from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD-PD, and DD-HD) and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
2. The relative difference in TSAT from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hepcidin value and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
3. The relative difference in TSAT from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

Relative difference in transferrin

1. The relative difference in transferrin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD-PD, and DD-HD) and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
2. The relative difference in transferrin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hepcidin value and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
3. The relative difference in transferrin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

Relative difference in soluble transfer receptor

1. The relative difference in soluble transfer receptor from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD-PD, and DD-HD) and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
2. The relative difference in soluble transfer receptor from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hepcidin value and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.

3. The relative difference in soluble transfer receptor from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

Relative difference in hepcidin

1. The relative difference in hepcidin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO users, NDD-rHuEPO-naïve, DD-PD, and DD-HD) and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
2. The relative difference in hepcidin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hepcidin value and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
3. The relative difference in hepcidin from baseline (Day 1) to Day 15, adjusted for study treatment, stratum (NDD-rHuEPO-users, NDD-rHuEPO-naïve, DD-PD, and DD-HD), baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

These secondary endpoints will be analyzed using ANCOVA models, similar to that described in Section 4.3.1. The outcome variables (indices of iron metabolism and AUC) are to be log-transformed prior to analysis and the result back-transformed to the original scale to aid interpretability. Log-transformed baseline hepcidin and baseline hs-CRP are to be used as covariates. When back-transformed onto the original scale these estimates become exponents of hepcidin and hs-CRP.

A summary table will be presented to show the outcomes of interest, by treatment group. Estimates of the geometric mean and coefficient of variation in each treatment group will also be presented. A separate table will show the treatment group comparisons, along with estimates, 95% CIs, and p-values from the ANCOVA models, as described above. Figures to show the relationship between hepcidin values and hs-CRP values and the relative change from baseline in outcomes of interest on both the log-transformed and original scales will be produced to show the moderating effects of hepcidin and hs-CRP in the models, to aid interpretation on the original scale.

A subgroup analysis will be performed on the primary and secondary efficacy endpoints within the DD and NDD subgroups (DD-HD, DD-PD, NDD-rHuEPO-users, NDD-rHuEPO-naïve).

4.3.3 Safety assessment analysis

All safety analyses will be performed on the safety analysis set and will be analyzed descriptively. Safety parameters include adverse events (AE), laboratory parameters, vital signs, ECG variables and physical examinations. For each safety variable, the last assessment before the first dose of randomized treatment will be considered the baseline measurement for all analyses, unless specified otherwise.

4.3.3.1 Adverse events

Adverse events will be coded using the most recent version of MedDRA.

An AE (classified by preferred term) started during the treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present prior to the first dose of randomized treatment. An AE that starts more than 28 days after the last dose of study medication will not be counted as a TEAE.

The number, percentage and percentage per patient exposure year (PEY) of subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class; by system organ class, preferred term, and relationship to study medication as assessed by the investigator. If more than one event occurs with the same preferred term for the same subject, the subject 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 event rate per 100 PEY is defined as

$$\left(\frac{number\ of\ subjects\ with\ AE}{sum\ of\ days\ at\ risk\ for\ AE\ in\ treatment\ period + 28\ days}\right) \times 365.25 \times 100$$

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

A summary of adverse events in any category will be presented by treatment. The incidence of common (≥10% of subjects in any treatment group) TEAEs, common treatment-emergent serious AEs (TESAE), and AEs leading to discontinuation of study medication will be summarized by system organ class, preferred term and treatment group, sorted in decreasing overall (across treatments) frequency. The summaries of TESAEs, TESAEs that are related to study medication and TEAEs leading to discontinuation of study medication will be presented overall, and by treatment compliance category (See Section 4.2.7). Moreover, TEAEs leading to hospitalization will also be presented. Related deaths will be summarized separately by treatment group, system organ class and preferred term. TEAEs with outcome of deaths will also be presented. In addition, all fatal SAEs (i.e., events that caused death) will be summarized. Summaries of the number of subjects with related AEs and related SAEs will be presented by treatment group, system organ class and preferred term. The number of subjects with AEs with maximum severity will be presented by treatment group, system organ class and preferred term.

Listings will be presented of subjects with SAEs, AEs leading to discontinuation, and subjects who died. A listing will be presented of subjects with AEs, detailing whether these are SAEs, AEs leading to discontinuation, or result in death. A listing will be presented for AEs related to COVID-19 pandemic.

4.3.3.2 Laboratory variables

Descriptive statistics for laboratory values, mean percent changes and selected treatment-emergent laboratory/vital signs change (TELVC) from baseline at each assessment time point will be presented by treatment group for the following laboratory variables:

- Hematology: Hb, leukocyte count, leukocyte differential count, platelet count, red blood cell count, hematocrit, mean corpuscular volume, reticulocytes, HbA1c.
- Chemistry: creatinine, total bilirubin, alkaline phosphatase, aspartate transaminase, alanine aminotransferase, albumin, potassium, total calcium, sodium, glucose, bicarbonate, chloride, blood urea nitrogen, magnesium, phosphorus.
- Serum iron, ferritin, TIBC, TSAT, transferrin, soluble transferrin receptor.
- Urinalysis: blood, protein, glucose (for non-dialysis patients and dialysis-dependent patients who are not anuric).
- Vitamin B12, folate, intact parathyroid hormone, hepcidin and hs-CRP.

The laboratory values will be presented in SI units.

Potential Hy's law

The following summaries will include the number (%) of patients who have: Elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin during the study. ALT or AST ≥3×ULN and total bilirubin ≥2×ULN during the study (potential Hy's law): the onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation.

Liver biochemistry test results over time for patients with elevated ALT or AST (i.e., ≥3×ULN) and elevated total bilirubin (i.e., ≥2×ULN) at any time will be plotted.

Individual patient data where ALT or AST plus total bilirubin are elevated at any time will be listed (i.e., ALT and/or AST ≥3×ULN and total bilirubin ≥2×ULN, at any time).

4.3.3.3 Vital signs

Descriptive statistics for vital signs and their changes from baseline at each visit and at the end of study will be presented by treatment group for the following variables:

- Tympanic temperature
- Systolic and diastolic blood pressure

- Pulse rate
- Respiratory rate

Blood pressure at baselines is defined as the last non-missing prior to first dose of randomized treatment. In the event more than 1 vital sign value is recorded at a certain visit, the average of these measurements will be used for analysis.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria listed in Table 3 below. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group.

Table 3 Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change
Systolic Blood Pressure (mmHg)	High	≥170	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic Blood Pressure (mmHg)	High	≥110	Increase of ≥15
	Low	≤45	Decrease of ≥15
Pulse Rate (bpm)	High	≥120	Increase of ≥20
	Low	≤50	Decrease of ≥20

[b] A post-baseline pre-dialysis or post-dialysis value is considered as a PCS value if it meets both criteria for observed value and change from pre-dialysis or post-dialysis baseline

4.3.3.4 Electrocardiogram

QTc interval will be calculated using both Bazett ($QTcB = QT/(RR)^{1/2}$) and Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/HR in the correction formula.

Descriptive statistics for ECG variables (PR, QRS, QT, QTcF) will be presented by treatment group.

ECG values are PCS if they meet or exceed the upper limit values listed in Table 4 below. The number and percentage of subjects with PCS values will be tabulated by treatment group. The numerator is the total number of subjects with a PCS ECG value at screening.

Table 4 Criteria for Potentially Clinically Significant ECG

ECG Parameter	Unit	High Limit
QRS interval	Msec	≥150
PR interval	Msec	≥250
QTc interval	Msec	>500

4.3.3.5 Physical examination

Incidence of physical examination abnormalities will be summarized for the screening visit by treatment group.

5 INTERIM ANALYSES

No interim analysis specific to this study will be conducted.

6 CHANGES OF ANALYSIS FROM PROTOCOL

To account for multiple testing, the Holm-Bonferroni method will be applied for each of the secondary endpoints if the primary endpoint is significant $p<0.05$. This is in the CSP in section 9.4.2.1; however, it has been expanded on here.

7 REFERENCES

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Besarab A, Chernyavskaya E, Motylev I, Shutov E, Kumbar LM, Gurevich K, et al. Roxadustat (FG-4592): Correction of anemia in incident dialysis patients. J Am Soc Nephrol 2016; 27: 1225-33.

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Holm, S. A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics 1979: 6 (2): 65–70.

8 APPENDIX

Appendix A: TELVC limits for laboratory variables

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Clinical Chemistry					
Alanine Aminotransferase (ALT)	CV/SI	**U/L**	Female (18-69 years): 6-34 U/L Female (>69 years): 6-32 U/L Male (18-69 years): 6-43 U/L Male (>69 years): 6-35 U/L	CCI	[redacted]
Alkaline Phosphatase (ALP)	CV/SI	**U/L**	Female (18-50 years): 31-106 U/L Female (>50-80 years): 35-123 U/L Female (>80-90 years): 35-135 U/L Male (>18 years): 35≈129 U/L	[redacted]	[redacted]
Aspartate Aminotransferase (AST)	CV/SI	**U/L**	Female: 9-34 U/L Male: 11-36 U/L	[redacted]	[redacted]
Total Bilirubin	CV	**mg/dL**	0.2-1.2 mg/dL	[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
	SI	**umol/L**		CCI	[redacted]
Gamma-Glutamyl Transferase (GGT)	CV/SI	**U/L**	Female (18-59 years): 4-49 U/L Female (≥60 years): 5-50 U/L Male (18-59 years): 10-61 U/L Male (≥60 years): 10-50 U/L	[redacted]	[redacted]
Calcium	CV	**mg/dL**	8.3-10.6 mg/dL	[redacted]	[redacted]
	SI	**mmol/L**	2.07 - 2.64 mmol/L	[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Creatinine (Excluding measurements taken after initiation of dialysis)	CV	**mg/dL**	Female (18-70 years): 0.4-1.1 mg/dL Female (70-80 years): 0.4-1.2 mg/dL Female (>80 years): 0.4-1.4 mg/dL Male (18-50 years): 0.5-1.2 mg/dL Male (50-70 years): 0.5-1.3 mg/dL Male (70-80 years): 0.5-1.5 mg/dL Male (>80 years): 0.5-1.6 mg/dL	CCI [redacted]	[redacted]
	SI	**umol/L**		[redacted]	[redacted]

Potassium	CV	mEq/L	3.4-5.4 mEq/L	CCI [redacted]

	SI	**mmol/L**		CCI [redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Sodium	CV	**mEq/L**	18-59 years: 132-147 mEq/L >59 years: 135-145 mEq/L	CCI	
	SI	**mmol/L**	18-59 years: 132-147 mmol/L >59 years: 135-145 mmol/L		
Total Protein	CV	**g/dL**	18-59 years: 6.1-8.4 g/dL ≥60 years: 6.0-8.0 g/dL		

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
	SI	**g/L**	18-59 years: 61-84 g/L ≥60 years: 60-80 g/L	CCI	[redacted]
Albumin	CV	**g/dL**	18-69 years: 3.3-4.9 g/dL 69-80 years: 3.3-4.6 g/dL >80 years: 3.0-4.6 g/dL	[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
	SI	g/L	18-69 years: 33-49 g/L 69-80 years: 33-46 g/L >80 years: 30-46 g/L	CCI [redacted]	[redacted]
Chloride	CV	**mEq/L**	94-112 mEq/L	[redacted]	[redacted]
	SI	**mmol/L**	94-112 mmol/L	[redacted]	[redacted]
Magnesium	CV	**mg/dL**	18-80 years: 1.5-3.1 mg/dL >80 years: 1.5-2.0 mg/dL	[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
	SI	**mmol/L**	18-80 years: 0.62-1.27 mmol/L >80 years: 0.62-0.82 mmol/L	CCI	[redacted]
Bicarbonate	CV	**mEq/L**	18-70 years: 17.0-30.6 mEq/L >70 years: 17.0-32.0 mEq/L	[redacted]	[redacted]
	SI	**mmol/L**	18-70 years: 17.0-30.6 mmol/L >70 years: 17.0-32.0 mmol/L	[redacted]	[redacted]
Phosphorus	CV	**mg/dL**	2.2-5.1 mg/dL	[redacted]	[redacted]
	SI	**mmol/L**	0.71-1.65 mmol/L	[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Glucose, random	CV	**mg/dL**	70-100 mg/dL	CCI [redacted]	[redacted]
	SI	**mmol/L**	3.9-5.6 mmol/L	[redacted]	[redacted]
Urea (BUN)	CV	**mg/dL**	18-70 years: 4-24 mg/dL 70-80 years: 4-29 mg/dL >80 years: 4-34 mg/dL	[redacted]	[redacted]
	SI	**mmol/L**	0.710-1.65 mmol/L	[redacted]	[redacted]
Lactate dehydrogenase	CV	**U/L**	53-234 U/L	[redacted]	[redacted]
	SI	**ukat/L**	0.884-3.901	[redacted]	[redacted]
Hematology					

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Hemoglobin (Hb)	CV	**g/dL**	Female (12-59 years): 11.6-16.4 g/dL Female (≥60 years): 11.5-15.8 g/dL Male (12-59 years): 12.7-18.1 g/dL Male (≥60 years): 12.5-17.0 g/dL	CCI [redacted]	[redacted]
Hepcidin, Quant	CV/SI	**ng/mL**		[redacted]	[redacted]
Highly sensitive C-Reactive Protein	CV	**mg/dL**		[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Platelet Count	CV/SI	**10^9/L**	12-60 years: 140-400 * 10^9/L >60 years: 130-394 * 10^9/L	CCI [redacted]	[redacted]
White Blood Cell Count (Leukocyte/Leucocyte)	CV/SI	**10^9/L**	3.80-10.70 * 10^9/L	[redacted]	[redacted]
Neutrophils, Particle Concentration	CV/SI	**10^9/L**	1.96-7.23 * 10^9/L	[redacted]	[redacted]
Eosinophils, Particle Concentration	CV/SI	**10^9/L**	0.00-0.57 * 10^9/L	[redacted]	[redacted]
Basophils, Particle Concentration	CV/SI	**10^9/L**	0.00-0.20 * 10^9/L	[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Lymphocytes, Particle Concentration	CV/SI	**10^9/L**	18-59 years: 0.91-4.28 * 10^9/L ≥60 years 0.80-3.00 * 10^9/L	CCI [redacted]	[redacted]
Monocytes, Particle Concentration	CV/SI	**10^9/L**	0.12-0.92 * 10^9/L	[redacted]	[redacted]
Iron Profile					
Iron	CV	**ug/dL**	**Female: 30-160 ug/dL Male: 45-160 ug/dL**	[redacted]	[redacted]
	SI	**umol/L**	**Female: 5.4-28.6 ug/dL Male: 8.1-28.6 ug/dL**	[redacted]	[redacted]
Transferrin (Fe Binding Sites)	CV	**ng/mL**	**210-450 ug/dL**	[redacted]	[redacted]
	SI	**umol/L**	**37.6-80.6 umol/L**	[redacted]	[redacted]
Ferritin	CV	**ng/mL**	**Female: 11.0-306.8 ng/mL Male: 23.9-336.2 ng/mL**	[redacted]	[redacted]
	SI	**ug/L**	**Female: 11.0-306.8 ug/L Male: 23.9-336.2 ug/L**	[redacted]	[redacted]

				AZ Safety Review Limits	
Laboratory Variable	**Unit**	**Unit**	**Range**	**Lower Limit**	**Higher Limit**
Transferrin Saturation	CV	**%**	**Female: 15-50%** **Male: 20-50%**	CCI [redacted]	[redacted]
	SI	**fract TIBC**	**Female: 0.15-0.50** **Male: 0.20-0.50**	[redacted]	[redacted]

LLN: Lower limit of normal, values provided by the laboratory; ULN Upper limit of normal, values provided by the laboratory

Appendix B: TELVC limits for vital signs

Vital Sign Parameter	Unit	Unit	Observed Value	Change from Baseline	AZ Safety Review Limits
Systolic Blood Pressure	mmHg	High	≥170	Increase of ≥20	CCI [redacted]
		Low	≤90	Decrease of ≥20	[redacted]

Vital Sign Parameter	Unit	Unit	Observed Value	Change from Baseline	AZ Safety Review Limits
Diastolic Blood Pressure (mmHg)	mmHg	High	≥110	Increase of ≥15	CCI [redacted]
		Low	≤50	Decrease of ≥15	[redacted]
Pulse Rate	bpm	High	≥120	Increase of ≥20	[redacted]

Vital Sign Parameter	Unit	Unit	Observed Value	Change from Baseline	AZ Safety Review Limits
		Low	≤50	Decrease of ≥20	CCI [redacted]

Appendix C: TELVC limits for ECG

ECG Parameter		Unit	Higher Limit	Change from Baseline	AZ Safety Review Limits
QRS interval		Msec	≥150	≥20	CCI [redacted]
PR interval		Msec	≥250	≥20	[redacted]
QTc interval		Msec	>500 >450	> 30 > 60	[redacted]

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