Clinical Study Protocol	
Drug Substance	Roxadustat
Study Code	D5741C00002
Version	4.0
Date	06 July 2021

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)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 4.0, 06 July 2021 Changes to the protocol are summarized below.
For Inclusion criterion #4, it was clarified that the definition of adequate dialysis includes all values equal to or above those mentioned in the protocol by adding "≥" to these values, ie, patients who have stdKt/V ≥2.1 in HD, and total (renal + PD) weekly Kt/V ≥1.7 in PD, are considered eligible as previously clarified in a protocol clarification letter. For Inclusion criterion #17, it was clarified that COVID-19 tests are allowed to be performed after the first Screening Visit, but before the patient returns for the next study visit, if site procedures cannot be performed on the day of the first Screening Visit. Exclusion criteria #33 and #34 were removed because they were no longer applicable under the amended statistical analysis plan. The definition of dry weight was added in Table 1, footnote j. It was clarified throughout the protocol that COVID-19 tests can be performed after the first Screening Visit, but before the patient returns for the next study visit, if site procedures cannot be performed on the day of the first Screening Visit. The window of tolerance of ±3 minutes for blood sampling timepoints for the ferrokinetic study was clarified throughout the protocol. It was also clarified that the ferrokinetic study on Day 1 must be completed prior to randomization and prior to the hemodialysis procedure on Days 1 and 15, and that patients randomized to the roxadustat group should take the roxadustat at least 6 hours before the ferrokinetic study starts on Day 15. The benefit/risk assessment section was updated based on recent updates in the roxadustat package insert and Investigator Brochure. The number of patients planned to be screened was updated from approximately to a maximum of 104 patients and the number of patients to be randomized was updated from a minimum of 46 to a minimum of 20 patients, which does not impact the assessment of the primary endpoint of the study. The target proportions of DD-HD, DD-PD, NDD-rHuEPO-users and NDD-rHuEPO-naïve patients were modified. Details were added to clarify statistical analysis regarding population and efficacy analysis throughout the protocol.

It was clarified that information on pregnancy has to be provided to FibroGen Drug Safety, instead of AstraZeneca Patient Safety data entry site, within 1 calendar day for all pregnancies.

It was clarified that information on overdose has to be provided to FibroGen Drug Safety instead of AstraZeneca Patient Safety data entry site, and that all relevant information on medication errors has to be completed within 1 calendar day.

Minor editorial changes were made throughout the document, where required.

Version 3.0, 24 Jun 2020
Changes to the protocol are summarized below.

The Run-in Period was removed, and patients will now move directly from the Screening Period to the Treatment Period. After the addition of recombinant human erythropoietin (rHuEPO)-naïve non-dialysis dependent chronic kidney disease (NDD-CKD) patients to the study, the purpose of the Run-in Period was reconsidered. The Run-in Period was removed because the study team concluded that it would neither add scientific nor safety benefit to the study. The day of the end of the Treatment Period was corrected to Day 15. Concerns about any variability in haemoglobin (Hb) values in the patients randomized to rHuEPO for both rHuEPO-user and rHuEPO-naïve patients will be addressed with a Day 8 visit and local Hb test. All the Run-in Period activities will be performed during the Screening Period. Sections 1 (Protocol summary), 4 (Study Design), 5 (Study population), 6.1 (Treatments administered), and 7 (Discontinuation of treatment and patient withdrawal) were updated to clarify this.

To account for a potentially higher screen failure rate due to the patient recruitment measures during the coronavirus disease of 2019 (COVID-19) pandemic, it is anticipated that approximately 104 patients will need to be enrolled in the study. This is to ensure that a minimum of 46 patients (maximum 60) are randomized, with approximately equivalent number of patients in each stratum. The study will have competitive enrollment across all sites and strata. Sections 1.2 (Synopsis) and 4.1 (Overall design) were updated accordingly.

Inclusion criteria were widened to include patients who are non-dialysis-dependent and rHuEPO-naïve. Patients stratification at randomization will be done by dialysis status (dialysis-dependent [DD] versus non-dialysis-dependent [NDD]). Within the NDD strata, patients will be further stratified at randomization by rHuEPO-exposure (rHuEPO-naïve vs rHuEPO-users). Within the DD strata, patients will be stratified at randomization by type of dialysis (hemodialysis [HD] vs peritoneal dialysis [PD]). When rHuEPO-exposure in

NDD, and dialysis type in DD were introduced as stratification factors, high-sensitivity C-reactive protein (hs-CRP) was dropped as a stratification factor since it resulted in more strata than could be accommodated by the planned sample size, with a risk that some strata would remain empty or difficult to fill. The change in stratification further reduces complexity in the analyses. Each stratum is planned to have an equivalent number of patients. Sections 1.2 (Synopsis), 2.1 (Study rationale), 4.1 (Overall design), 6.3 (Measures to minimize bias: randomization and blinding) and 9 (Statistical considerations) were updated to clarify this.

Instruction regarding contraceptive methods to be used by study participants was updated per the roxadustat package insert in Section 5.1 (Inclusion criteria), and exposure to iron-chelating agents within the 6 weeks prior to the Screening Visit was updated in Section 5.2 (Exclusion criteria).

Section 2.3 (Benefit/risk assessment) was updated with roxadustat safety information, and a benefit/risk assessment and risk mitigation plan in view of the coronavirus disease of 2019 (COVID-19) pandemic.

The purpose and schedule of dose adjustments for rHuEPO and roxadustat, and plan for post-study treatments for both, the rHuEPO and roxadustat arms, were clarified in Sections 1.2 (Synopsis), 4.1 (Overall design), and 6.1 (Treatments administered). The permissible methods of administration of rHuEPO were clarified in Sections 6.1.2 (Dose of study treatments) and 6.2 (Preparation/handling/storage/accountability).

Section 8.2.4 (Electrocardiograms) was updated to replace triplicate electrocardiogram (ECG) measurements with single measurements.

The study design, patient population, risk mitigation strategy, statistical considerations, and provisions for patient withdrawal were updated in view of the COVID-19 pandemic in Sections 1.1 (Schedule of activities), 2.3 (Benefit/risk assessment), 4 (Study design), 5.1 (Inclusion criteria), 5.4 (Screen failures), 7.3 (Withdrawal from the study), 8.3 (Collection of adverse events), and 9.4 (Statistical analyses).

Minor editorial changes were made throughout the document, where required.

Version 2.0, 05 July 2019

Changes to the protocol are summarized below.

The dosing for recombinant human erythropoietin (rHuEPO) was changed from 3 times a week (TIW) to allow TIW or 2 times a week (BIW) for the lowest dose of rHuEPO. For

patients on a weekly dose of rHuEPO of 6000 IU, dosing will be BIW (ie, 3000 IU BIW) and for patients on a weekly dose of rHuEPO of >6000 IU, dosing will be TIW. This is due to unavailability of 2000 IU prefilled syringes of rHuEPO. Section 1 (Protocol summary), Section 4 (Study design) and Section 6 (Study treatments) were updated to reflect this change.

Timepoints for dispensation of rHuEPO was clarified in Section 1 (Protocol summary).

The number of patients to be randomized was updated in Section 1 (Protocol summary), Section 4 (Study design) and Section 6 (Study treatments) to reflect a minimum of 46 patients will be randomized, to allow some flexibility in the final number of randomized patients, as it will be difficult to control recruitment to stop at exactly 46 randomized patients.

The primary and secondary assessments text in Section 1 (Protocol summary), Section 8.1 (Efficacy assessments) and Section 9.4 (Statistical analyses) was updated to improve clarity on stratification factors.

Footnote 'a' in the schedule of activities Table (Table 1- Section 1 [Protocol summary]) was updated to clarify that results from the Screening Period for transferrin saturation (TSAT), ferritin, vitamin B12, serum folate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-sensitivity C-reactive protein (hs-CRP) and total bilirubin (TBL) must be available prior to starting the Run-in Period .

It was clarified in Section 1 (Protocol summary), Section 4 (Study design) and Section 6 (Study treatments) that study treatment dosing must occur on the days of the ferrokinetic study (ie, on the days of Visit 4 and 6).

It was clarified in Section 5 (Study population) that inclusion criteria #8 and #9 would be obtained from the Screening Visit (Visit 1).

It was clarified in Section 5 (Study population) that inclusion criteria #12 and #13 referred to Visit 1 (Screening Period) and inclusion criteria #14 referred to both Visit 1 (Screening Period) and Visit 2 (start of Run-in Period).

It was clarified in Section 5 (Study population) for inclusion criteria #14, that ALT or AST and TBL would be obtained from Visit 1, Screening Visit or Visit 2, start of Run-in Period.

It was corrected in Section 5 (Study population) for inclusion criteria #14, that ALT or (not and) AST must be <3 x upper limit of normal (ULN). There was a typographical error in the original protocol – and has been corrected to or.

Section 6.5 was updated to clarify that patients taking iron before the study could not change the dose during the Treatment Period.

New text on malignancy was added to Appendix B (Adverse events definitions and additional safety information) to reflect changes being made to the TransCelerate clinical study protocol template.

Version 1.0, 17 May 2019
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1.1 Schedule of activities (SoA)

The schedule of activities (SoA) for the study is shown in Table 1 below. The study consists of 3 periods: the Screening Period, Treatment Period and Follow-up Period.

Table 1 Schedule of activities

	Screening Period[a,b]	Treatment Period[b]			Discontinuation[b,c]	28-day Follow-up Period[c,d]	Details in CSP or Appendix section
Day	**< -21 > -14 to 0**	**1**	**8 -1/+2 days**	**15 ± 2 days**		**43 ± 3 days**	
Visit	**1, 1a and 1b[e]**	**2**	**3**	**4**		**5**	
Pre-screening telephone contact[f]							Section 4.1.1
Sign written ICF	X						Section 5 and Appendix A 3
Swab test for active COVID-19 infection[g]	X						Section 4.1.1
Eligibility criteria	X	X					Section 5
Demographics, medical and surgical history, and prior medication	X						Section 5
Hematology/hemostasis[h]	X[i]	X	X	X	X		Sections 5 and 8.2.1
HbA1C	X						Section 8.2.1
iPTH	X						Section 8.2.1
Physical examination, dry body weight[j]	X						Sections 5 and 8.2.2
Clinical chemistry[k]	X	X		X	X		Section 8.2.1
Urinalysis[l]	X	X		X	X		Section 8.2.1
Vital signs[m]	X	X	X	X	X		Sections 5 and 8.2.3
12-lead ECG	X						Section 8.2.4
Liver function tests[n]	X	X		X	X		Sections 5 and 8.2.1
Iron profile[o]	X	X		X	X		Sections 5 and 8.1
Hepcidin		X		X	X		Section 8.1
hs-CRP	X	X		X	X		Section 8.1

	Screening Period[a,b]	Treatment Period[b]			Discontinuation[b,c]	28-day Follow-up Period[c,d]	Details in CSP or Appendix section
Day	**< -21 > -14 to 0**	**1**	**8 -1/+2 days**	**15 ± 2 days**		**43 ± 3 days**	
Visit	**1, 1a and 1b[e]**	**2**	**3**	**4**		**5**	
Vitamin B12, folate	X						Sections 5 and 8.2.1
Terminate IV iron + TRIFERIC® in dialysate[p]	X						Section 5
Single dose of oral iron (12.5 mL [100 mg elemental iron]) administration		X[q]		X[q]	X		Section 6.1.3
Ferrokinetic study (T0[r], 1, 2, 3 hours)		X[q,r]		X[q,r]	X		Section 8.1
Concomitant medications	At every visit after Visit 1 and may be conducted by phone if not tied to a visit						Section 6.5
Routine safety measurements							
Adverse events	At every visit after Visit 1 and may be conducted by phone if not tied to a visit						Section 8.3
Serum pregnancy test[s]	X	X					Section 8.2.1
Study treatment administration							
Randomization[t]		X					Section 6.3 and Section 4.1.2
Study treatment dispensed[u]		X	X[v]				Section 6
Study treatment (rHuEPO and roxadustat) compliance			X	X	X		Section 6

[a] 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 Hb tests. To check Hb eligibility criteria, Hb levels must be assessed twice, at least 7 days apart, during the Screening Period; Hb levels may be assessed up to 3 times (Visits 1, 1a and 1b) during the Screening Period. The rHuEPO dose may be adjusted during the Screening Period 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. Results for Screening Period assessments for TSAT, ferritin, vitamin B12, serum folate, ALT, AST, hs-CRP and TBL must be available prior to starting the Treatment Period.

[b] Each patient will be contacted within 24 h before a scheduled visit to confirm that he/she has no symptoms of COVID-19 infection and that he/she has had no contact with a known COVID-19 positive person within the past 14 days. If the patient reports symptoms or contact with a COVID-19-positive patient within the past 14 days, the Investigator may ask the patient to be tested for active COVID-19 infection (swab test to rule out active COVID-19 infection), or withdraw the patient from the study, as is most suitable for the patient's safety, at the Investigator's discretion. The study treatment and assessments may be continued as planned until the swab test results are available, at the discretion of the Investigator. Patients who test positive on the swab test must be withdrawn from the study. A patient who contacts the site at any time during the Treatment Period informing that he/she has symptoms suggestive of COVID-19 may be asked to get tested for active COVID-19 infection, or be withdrawn from the study for safety reasons, at the Investigator's discretion. Patients who test positive (for COVID-19) must be withdrawn from the study. Any study assessments planned on the days of site visits may be completed via a telephone call and/or a visit to the patient's home, as required, and if possible. The handling of patients and their blood or urine samples will be done using sterile techniques and observing precautions for infection control and prevention. Reasons for delayed site visits will be reported as protocol deviations. The actual dates when the visit-related assessments were completed will be recorded in the eCRFs.

[c] Applicable for discontinuation prior to the end of the Treatment Period. Patients who discontinue study treatment early should be asked to return to the study site for the discontinuation visit within 7 days after the study treatment is stopped, and for the Follow-up Visit 28 days later unless consent to participate is withdrawn. Patients who withdraw prior to the end of the Treatment Period due to a positive COVID-19 test result should not attend the Discontinuation Visit or the 28-day Follow-up Visit at the study site. The assessments planned for the Discontinuation and 28-day Follow-up Visit should be completed via a telephone call, as far as possible. See Section 7.1.3 for details.

[d] May be conducted over the phone.

[e] All patients should attend Visits 1 and 1a at the clinical site. All patients will be tested for COVID-19 infection at the first Screening Visit (Visit 1)[g]. Patients may attend Visit 1b at the clinical site, if needed, to assess Hb level (see footnote i).

[f] Each patient will be contacted before the first Screening Visit (Visit 1) to confirm that he/she has no symptoms of COVID-19 and that he/she has had no contact with a known COVID-19 positive person within the past 14 days. Only asymptomatic patients, or those who have had no contact with a known COVID-19 positive person within the last 14 days, will be asked to come to the site for informed consent and eligibility screening procedures.

[g] All patients will be tested for COVID-19 infection at the first Screening Visit, using a swab test to rule out active infection for COVID-19. If according to site procedures the test for COVID-19 infection cannot be performed at the first Screening Visit, the test should be performed as soon as possible thereafter but must be performed before the patient returns for the next study visit. Patients who test positive must be withdrawn from the study. All samples (blood and urine) for eligibility assessment will be collected at Visit 1 during the Screening Period, while the swab test results are awaited. The handling of patients and their blood or urine samples will be done using sterile techniques and observing precautions for infection control and prevention.

[h] Red blood cell, Hb, hematocrit, leukocyte count, leukocyte differential count, platelet count, MCV, reticulocytes. On Days 1 and 15, blood samples for these assessments will be collected **before** time T0 (ie, **before administration of the single dose of oral iron**). 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 re-start 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.

[i] To check Hb eligibility criteria, Hb levels must be assessed in the central laboratory twice, at least 7 days apart, during the Screening Period; Hb levels may be assessed up to 3 times (Visits 1, 1a and 1b) during the Screening Period.

[j] Body weight for HD patients should be the patient's dry weight. Dry weight - also known as optimum postdialysis weight - is the postdialysis weight at which all or most excess body fluid has been removed. Weight for patients on PD should be obtained with a "dry" or empty peritoneal cavity (PD fluid fully drained).

[k] Glucose, calcium, sodium, potassium, bicarbonate, chloride, BUN, creatinine, magnesium, phosphorus.

[l] Urine dipstick glucose, protein and blood performed locally (applicable for non-dialysis-dependent patients, and dialysis-dependent patients who are not anuric).

[m] Vital signs will include tympanic temperature, systolic and diastolic BP, pulse rate and respiratory rate. Blood pressure should be measured prior to the hemodialysis procedure. For patients on PD, BP should be measured in the morning prior to the patient performing the first exchange of the day. Pulse rate and BP should be measured in triplicate after being comfortably at rest in a seated position with the back and feet supported (ie, by chair back and floor or platform, respectively) quietly for at least 5 minutes.

[n] Alanine aminotransferase, AST, ALP, albumin, and TBL.

[o] Serum iron, ferritin, TIBC, TSAT, transferrin, soluble transferrin receptor. On Days 1 and 15, blood samples for these assessments will be collected **before** time T0 (ie, **before administration of the single dose of oral iron**). Note that serum iron and TIBC are included in the ferrokinetic study and should not be taken as part of the iron profile as well on Days 1 and 15. There is no need to collect duplicate sample for serum iron and TIBC. The sample collected before the single dose of oral iron is administered can serve for the iron profile as well.

[p] Intravenous iron and TRIFERIC® in dialysate should be stopped at the Screening Visit (ie, at Visit 1) and should not be taken after stopping, throughout the Screening and Treatment Periods, but can be started again after the Treatment Period.

[q] Must be conducted prior to randomization at Day 1 and prior to the hemodialysis procedures at Days 1 and 15.

[r] The blood samples for the ferrokinetic study (serum iron and TIBC) must be taken immediately **before** the single dose of oral iron is administered (ie, immediately before time T0), and then at T1, T2 and T3 after the single dose of oral iron (sample for serum iron only). The window of allowance for the ferrokinetic study blood sampling will be ±3 minutes.

[s] Collect from female patients of childbearing potential only.

[t] Results for Screening Period assessments for **ALT, AST and TBL must be available before randomization**. Randomization must occur after the ferrokinetic study has completed, ie, after collection of the T3 serum iron sample. Patients will be randomly assigned in 1:1 ratio to either roxadustat or rHuEPO. Study treatment to be administered after randomization at Day 1.

[u] Patients will receive either roxadustat (orally) or rHuEPO (IV or SC) during the Treatment Period. Roxadustat will be administered TIW. For patients on a weekly dose of rHuEPO of 6000 IU, dosing will be BIW (ie, 3000 IU BIW) and for patients on a weekly dose of rHuEPO of >6000 IU, dosing will be TIW. The dose of study treatment administered will be recorded.

[v] For patients randomized to the rHuEPO arm, Hb levels will be tested in the local laboratory on Day 8, and the rHuEPO dose may be adjusted depending on the patient's Hb levels, for safety reasons, as determined by the Investigator. Study treatment dispensation will only occur for patients on the rHuEPO arm, not patients on the roxadustat arm (as only the rHuEPO dose may be adjusted at this visit). The roxadustat dose will not be adjusted during the Treatment Period; therefore, for patients on the roxadustat arm Hb samples will not be collected on Day 8 for testing in the local laboratory.

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BIW=2 times a week; BP=blood pressure; BUN=blood urea nitrogen; eCRF=electronic case report form; COVID-19=coronavirus disease of 2019; CSP=clinical study protocol; ECG=electrocardiogram; Hb=hemoglobin; HbA1C=hemoglobin A1C; HD=hemodialysis; hs-CRP=high-sensitivity C-reactive protein; ICF=informed consent form; iPTH=intact parathyroid hormone; IU=International Unit; IV=intravenous; MCV=mean corpuscular volume; PD=peritoneal dialysis; rHuEPO=recombinant human erythropoietin; SC=subcutaneous; TBL=total bilirubin; TIBC=total iron binding capacity; TIW=3 times a week; T0=time at which single dose of oral iron will be administered at the start of ferrokinetic study; TSAT=transferrin saturation.

1.2 Synopsis

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Protocol title:

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

Short title:

Effect of Roxadustat versus rHuEPO on oral iron absorption in Chinese patients with anemia of CKD.

Rationale:

Advanced stages of chronic kidney disease (CKD) are associated with a hypo-proliferative anemia as well as dysfunctional iron homeostasis. Roxadustat is an orally administered drug for the treatment of anemia caused by CKD in patients who are either on dialysis or not. Roxadustat is currently approved in China for the treatment of anemia in patients with CKD, and is indicated for both, dialysis as well as non-dialysis patients. Roxadustat pharmacologically stimulates erythropoiesis via the hypoxia inducible factor (HIF) pathway and in a manner consistent with the body's normal homeostatic response to hypoxia, but under normoxic conditions. In an open-label, randomized hemoglobin (Hb) correction study in anemic patients incident to hemodialysis (HD) or peritoneal dialysis (PD), roxadustat was well tolerated and corrected anemia in incident HD and PD patients, regardless of baseline iron repletion status or C-reactive protein (CRP) level and with oral or intravenous (IV) iron supplementation; it also reduced serum hepcidin levels (Besarab et al 2016).

This study will evaluate the effect of roxadustat versus recombinant human erythropoietic (rHuEPO) on oral iron absorption in patients with anemia in Stage 4 and Stage 5 CKD and will provide data to meet the medical need to a new standard of care in patients on dialysis and to treat anemia in non-dialysis patients.

Objectives and Endpoints [a]	
Primary objective:	**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 a 3-hour period.
Secondary objectives:	**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 a 3-hour period.
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.
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.

[a] The primary and secondary objectives will be analyzed using the Full Analysis Set (FAS), see Section 9.3 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.

Overall design:

This is a Phase IV, randomized, active-controlled, open-label, parallel design, multicenter prospective study to evaluate the effect of roxadustat versus rHuEPO treatment on the gastrointestinal (GI) iron absorption in patients with anemia of Stage 4 and Stage 5 CKD. This study plans to screen a maximum of 104 patients, and randomize a minimum of 20 patients and a maximum of 60 patients with anemia of CKD, from approximately 7 to 10 sites in China. Patient enrollment will be competitive across all sites and strata.

This study will enroll eligible dialysis and non-dialysis patients ≥ 18 years of age, who have anemia of CKD, and are either dialysis-dependent (DD) and on a stable dose of rHuEPO within 4 weeks prior to screening, or are non-dialysis-dependent (NDD) and are being treated with rHuEPO (ie, on a stable dose of rHuEPO within 4 weeks prior to screening), or are rHuEPO-naïve (ie, no treatment with erythropoietin stimulating agents [ESAs] for > 6 weeks) at the time of screening.

Study period:

Estimated date of first patient enrolled: Q1 2021

Estimated date of last patient completed: Q4 2021

Number of patients:

A maximum of 104 patients are planned to be screened to achieve a minimum of 20 and a maximum of 60 eligible randomized patients with anemia of CKD fulfilling all the inclusion criteria and none of the exclusion criteria.

The minimum sample size required to achieve a 2-sided significance level of 0.05 and power of 90% was calculated based on the assumption of a log scale. A conservative effect due to roxadustat has been assumed of 2.7-times baseline, and accounting for 20% of patients failing to take any study treatment or failing to provide a post-baseline area under the curve (AUC) measurement. A conservative estimate of the standard deviation (SD), based on the estimated range of iron absorption was 0.4 on the log scale. A sample size of 16-20 subjects (8-10 per treatment arm) is considered sufficient to achieve a 2-sided significance level of 0.05, and 90% power, based on the primary endpoint of change from baseline in log(AUC). Patients are to be randomized in a 1:1 ratio. The calculations are based on a 2-sample t-test.

Treatments and treatment duration:

Each patient will be contacted before the first Screening Visit (Visit 1) to confirm that he/she has no symptoms of coronavirus disease of 2019 (COVID-19) and that he/she has had no contact with a known COVID-19 positive person within the past 14 days. Only asymptomatic patients, or those who have had no contact with a known COVID-19 positive person within the last 14 days, will be asked to come to the site for informed consent and eligibility screening procedures.

For each patient, the duration of participation in the study will be approximately 8 to 9 weeks divided into 3 periods:

1. Screening Period: approximately 2-3 weeks. Dialysis and non-dialysis patients with anemia of CKD, fulfilling the eligibility criteria, will be asked to provide informed consent to participate in this study. Patients must provide written informed consent before any screening tests or assessments are performed. All patients will be tested for COVID-19 infection at the first Screening Visit, using a swab test to rule out active COVID-19 infection. If according to site procedures the test for COVID-19 infection cannot be performed at the first Screening Visit, the test should be performed as soon as possible thereafter but must be performed before the patient returns for the next study visit. Patients who test positive (for COVID-19) must be withdrawn from the study. Patients who test negative (for COVID-19) but do not meet the eligibility criteria must be withdrawn from the study. Patients will be assessed for high-

sensitivity CRP (hs-CRP) at the Screening Visit to check whether the measurement is either ≤ the upper limit of normal (ULN), or > the ULN. During the Screening Period, all patients on rHuEPO before entering the study will remain on their current rHuEPO treatment. During the Screening Period, 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 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 Hb tests.

2. Treatment Period: 2 weeks. For patients who are already on rHuEPO, the start of the Treatment Period (Day 1) should be scheduled to fit into the rHuEPO administration regimen (ie, rHuEPO dosing must occur on the day of the Randomization Visit, Visit 2, Day 1). Patients should be instructed not to take their rHuEPO dose in the morning before they attend the study site for the Randomization Visit (Visit 2, Day 1).

At Days 1 and 15, a ferrokinetic study will be done in all patients. 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 liquid elemental iron containing $FeSO_4$ (12.5 mL dose, comprising 100 mg elemental iron). Gastrointestinal iron absorption (serum iron level measured) will then be assessed at 1, 2 and 3 hours **after** the administration of the defined single dose of oral iron (T1, T2 and T3, respectively). The window of allowance for the ferrokinetic study blood sampling will be ±3 minutes.

On Day 1, after the ferrokinetic study has completed (ie, after collection of the T3 serum iron sample), patients will be randomized in a 1:1 ratio to either rHuEPO treatment or to roxadustat treatment. Patients will be centrally randomized by interactive voice response system (IVRS) and stratified by dialysis status (DD versus NDD). Within the NDD stratum, patients will be further stratified by rHuEPO exposure (NDD-rHuEPO-users vs NDD-rHuEPO-naïve). Within the DD stratum, patients will be stratified by type of dialysis (HD vs PD). The study treatment (roxadustat or rHuEPO) will be administered at the study site at Day 1, after randomization. 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). The rHuEPO can be administered either IV or subcutaneously (SC) depending on the route of administration used by the dialysis-dependent patients before the Treatment Period. The rHuEPO will be administered via the SC route for all patients who are NDD. 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. The rHuEPO dose may also be adjusted at any time during the Treatment Period by the Investigator for safety reasons.

Dosing of roxadustat and rHuEPO should be scheduled to occur on Visit 4 (Day 15). On Day 15, patients randomized to the roxadustat group should take the roxadustat in the morning, at least 6 hours before the ferrokinetic study starts. On Day 15, patients randomized to the to the rHuEPO group should take the rHuEPO within 1-2 hours before the ferrokinetic study.

All patients should not ingest any foods containing more than trace amounts of iron such as heme-rich foods, multivitamins with iron etc. for approximately 4 hours before and during the 3 hours of the ferrokinetic study. Patients are allowed limited small snacks with negligible amounts of iron during this 7-hour period. Patients may resume their normal dietary intake following collection of blood at the T3 time point. There is no restriction on drinking water, coffee or tea for the patient before the ferrokinetic study starts and during the ferrokinetic study.

Roxadustat will be administered orally TIW according to the dosage approved in the China Package Insert. The roxadustat dose will not be adjusted during the 2-week Treatment Period, except for safety reasons at the discretion of the Investigator.

In the event of early study discontinuation after the Day 1 visit but prior to the Day 15 visit for a patient, the Investigator will seek to schedule a study discontinuation visit for the patient. Patients who withdraw prior to the end of the Treatment Period due to a positive COVID-19 test result should not attend the Discontinuation Visit or the 28-day Follow-up Visit at the study site. The assessments planned for the Discontinuation and 28-day Follow-up Visits should be completed via a telephone call, as far as possible.

3. Post-Treatment Follow-up Period: 4 weeks. After completing study treatment, all patients will continue for a 4-week Follow-up Period, to monitor safety (all adverse events [AEs] and serious adverse events [SAEs] will be collected during this Period). Patients who discontinue study treatment early will also continue to this 4-week Follow-up Period unless consent to participate is withdrawn. Activities that are planned during this 4-week Follow-up Period may be performed by phone.

Patients who withdraw prior to the end of the Treatment Period due to a positive COVID-19 test result should not attend the Discontinuation Visit or the 28-day Follow-up Visit at the study site. The assessments planned for the Discontinuation and 28-day Follow-up Visits should be completed via a telephone call, as far as possible.

After discontinuation of study treatment, patients who were on rHuEPO before entering the study may either be returned to their previously prescribed rHuEPO treatment, or be prescribed different agent(s) to treat their anemia by the Investigator, based on their local Hb levels and the discretion of the Investigator. For patients who were rHuEPO-naïve before entering the study, Hb levels may be tested in the local laboratory at the discretion of the Investigator, to determine an appropriate course of treatment for anemia in each patient.

Statistical methods:

Population for analyses

Full analysis set (FAS): The FAS will include all randomized patients who have complete baseline (Day 1) measurements for any efficacy analysis, with patients being analyzed as randomized, rather than as treated. The FAS will be used for the primary endpoint and all secondary endpoints.

Per-protocol (PP) analysis set: The 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 major protocol violations. The PP analysis set will be used as a sensitivity analysis population for the primary and secondary endpoints.

Safety analysis set: The safety analysis set will include all randomized patients receiving at least 1 dose of study treatment, with patients being analysed 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.

Primary analyses

The primary endpoint for this study is the GI iron absorption change from baseline (Day 1) to Day 15. This will be assessed via change from baseline (Day 1) to Day 15 in log-transformed AUC of iron absorption from 0-3 hours based on 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. The difference in log (AUC) from baseline (Day 1) to Day 15 will be analyzed using an analysis of covariance (ANCOVA) model, adjusting for study treatment and baseline hs-CRP (≤ ULN, > ULN) level. The result will be back-transformed to the original scale to aid interpretability.

Multiple imputation will be implemented for the primary and secondary analysis to account for missing data. This will be described in more detail in the statistical analysis plan (SAP).

Secondary analyses

The secondary endpoints of interest assess direct treatment and interaction effects in iron absorption and the indices of iron metabolism (serum iron, ferritin, TIBC, transferrin saturation [TSAT], transferrin, soluble transfer receptor) and hepcidin levels are described as follows:

- The relative difference in AUC from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hepcidin value, and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
- The relative difference in AUC from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.
- The relative difference in the indices of iron metabolism from baseline (Day 1) to Day 15, adjusted for study treatment and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.
- The relative difference in the indices of iron metabolism from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hepcidin value, and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
- The relative difference in the indices of iron metabolism from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

The hypotheses for these endpoints can be separated into 2 distinct groups, the relative difference in iron metabolism and the relative difference in AUC. All hypotheses will follow the null hypothesis that there is no difference between AUC or iron metabolism when adjusting for various specified covariates or interactions. The assessments for the secondary endpoints will be performed similar to those for the primary endpoints. All endpoints will be analyzed using ANCOVA models.

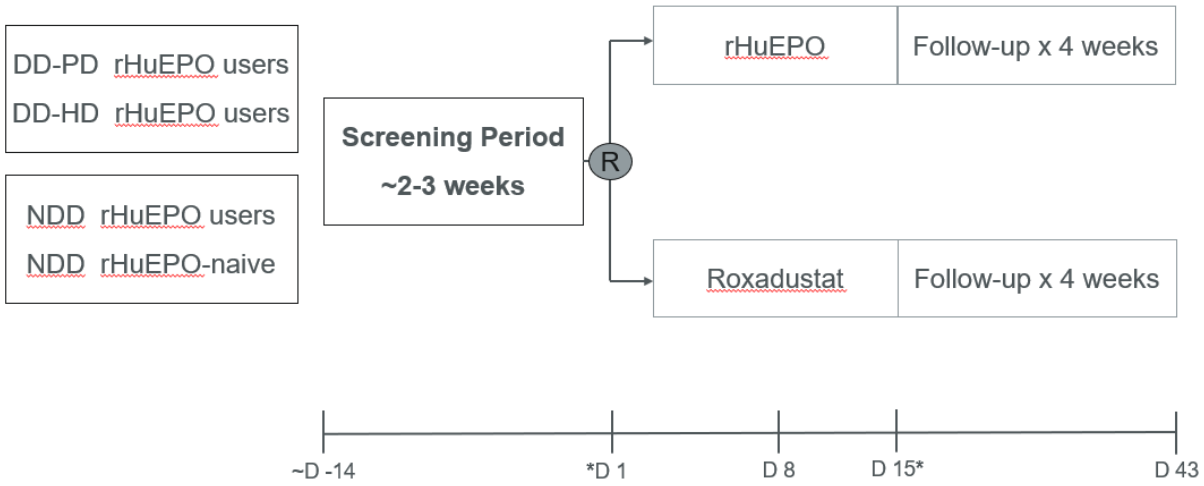
Subgroup analyses

Sample size permitting, subgroup analyses will be performed for the primary and key secondary efficacy endpoints. Summary tables will be produced by strata (HD, PD, NDD) and, if there are sufficient numbers of patients in each strata, all statistical analysis of primary and secondary endpoints will be performed by strata (HD, PD, NDD). If a patient withdraws before Day 15, their discontinuation visit will be used as the postbaseline primary measurement.

1.3 Schema

The general study design is summarized in Figure 1 .

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 and prior to the hemodialysis procedure at Days 1 and 15. 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 window of allowance for the ferrokinetic study blood sampling will be ±3 minutes.

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, Hb=hemoglobin; HD=hemodialysis; NDD=non-dialysis-dependent, PD=peritoneal dialysis; R=randomization; rHuEPO=recombinant human erythropoietin; TIBC=total iron binding capacity.

2 INTRODUCTION

2.1 Study rationale

Advanced stages of chronic kidney disease (CKD) are associated with a hypo-proliferative anemia as well as dysfunctional iron homeostasis. The latter leads to functional iron deficiency, a process that describes multiple abnormalities in iron transport and utilization, including impaired gastrointestinal (GI) iron absorption. The latter appears to be mediated by paucity of hypoxia inducible factor (HIF)-2a, a subunit of HIF which boosts intestinal absorption of iron by upregulating duodenal cytochrome b and divalent metal transporter.

The prevalence of anemia increased as CKD progresses. The prevalence of anemia has been found to increase with the stage of CKD; from 8.4% at Stage 1 to 53.4% at Stage 5 (Stauffer and Fan 2014).

The prevalence of CKD is about 10.8% in China (Zhang et al 2012). According to the 2011 Shanghai Dialysis Registry Report, the prevalence of end-stage renal disease (ESRD) is 759 per million Chinese; the prevalence has almost doubled in the last 4 years when compared to 2007, at which time the prevalence was estimated to be 409.8 per million (http://sh.cnrds.org).

While recombinant human erythropoietin (rHuEPO) has been able to correct anemia in many patients with CKD, it has not been demonstrated to correct underlying iron dysmetabolism associated with CKD. Iron dysmetabolism and impaired GI absorption of iron is a well-recognized clinical phenomenon and is extensively described in the literature (Gupta and Wish 2017). Recombinant human erythropoietin has not been demonstrated to correct this issue (Widness et al 1997).

Phase I and II clinical studies have suggested that the HIF-prolyl hydroxylase inhibitor (HIF-PHI), roxadustat, rectifies many of the abnormalities of iron dysmetabolism in CKD, including GI absorption (Besarab et al 2016). This study is designed to expand evidence supporting enhanced GI iron absorption with roxadustat compared with rHuEPO in patients with anemia of Stage 4 and Stage 5 CKD. In this study, patients with CKD who are either non-dialysis-dependent (NDD), or are dialysis-dependent (DD) and on a stable dose of rHuEPO, are planned to be recruited, with the comparator agent in this RCT being the current standard of care for anemia of CKD, rHuEPO analogues, otherwise known as erythropoiesis stimulating agents (ESAs). Most NDD patients with anemia of CKD are not treated with rHuEPO analogues prior to starting dialysis. Furthermore, the GI absorption of iron may also be different in NDD patients with CKD-related anemia who have had prior exposure to rHuEPO analogues than those who are rHuEPO-naïve. Therefore, this study will recruit both types of NDD patients: those who are rHuEPO-naïve as well as those who are rHuEPO-users, and have been on a stable dose of rHuEPO.

2.2 Background

Roxadustat is an orally administered drug for the treatment of anemia caused by CKD in patients who are either on dialysis or not. Roxadustat is currently approved in China for the treatment of anemia of CKD patients, and is indicated for both dialysis and non-dialysis patients.

Roxadustat is a potent orally active HIF-PHI. Hypoxia inducible factor induces expression not only of erythropoietin (EPO), but also the erythropoietin receptor and proteins that promote iron reabsorption and recycling (Peyssonnaux et al 2008). Thus, roxadustat pharmacologically stimulates erythropoiesis via the HIF pathway and in a manner consistent with the body's normal homeostatic response to hypoxia, but under normoxic conditions. In an open-label, randomized hemoglobin (Hb) correction study in anemic patients on hemodialysis (HD) or peritoneal dialysis (PD), roxadustat corrected anemia in incident HD and PD patients, regardless of baseline iron repletion status or C-reactive protein (CRP) level and with oral or intravenous (IV) iron supplementation and also reduced serum hepcidin levels. Roxadustat was well tolerated in this study (Besarab et al 2016).

A locally available short-acting rHuEPO, approved in China for the treatment of renal anemia for dialysis and non-dialysis patients, will be used as the comparator in this study.

This study will evaluate the effect of roxadustat versus rHuEPO on oral iron absorption in patients with anemia of Stage 4 and Stage 5 CKD and will provide data to meet the medical need to a new standard of care in patients on dialysis and to treat anemia of CKD in non-dialysis patients. The complications associated with ESAs including the need for IV/subcutaneous (SC) administration of ESAs, potential for anti-EPO antibody formation and pure red-cell aplasia, and EPO resistance and potential for transfusion-sparing can be reduced with roxadustat.

The clinical data collected thus far suggest that roxadustat is effective, generally safe and well tolerated in healthy adults, and in dialysis- and non-dialysis CKD patients with anemia.

A description of the chemistry, pharmacology, efficacy, and safety of roxadustat and rHuEPO are provided in the respective China Package Inserts. For additional information regarding roxadustat, please refer to the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

Patients across the continuum of CKD anemia were evaluated in the roxadustat global Phase III clinical development program (IB, Section 5.4.6).

In the NDD clinical program, roxadustat is superior to placebo for the treatment of anemia as measured by mean change in Hb. Compared with placebo, roxadustat effectively raises Hb

levels independently of baseline high sensitivity CRP (hs-CRP) categories or iron repletion status, reduces the need for rescue therapy (red blood cell [RBC] transfusion, IV iron, or ESA), and reduces LDL cholesterol. A key benefit for roxadustat patients is the clinically meaningful reduction in the need for RBC transfusions, currently the primary indication for treatment with ESA in the NDD population.

In the DD clinical program, roxadustat is statistically superior to epoetin alfa, the standard of care, for the treatment of anemia as measured by mean change in Hb. Roxadustat is also as effective as, or more effective than, epoetin alfa in increasing mean Hb levels in patients with elevated hs-CRP, and reducing the requirement for RBC transfusion. In addition, roxadustat demonstrates a clinically meaningful reduction in monthly IV iron supplementation, and reduces LDL cholesterol. Results from the incident dialysis (ID)-DD subpopulation are generally consistent with the overall DD population.

These results support the broad use of roxadustat to increase and maintain Hb levels and manage anemia for patients across the continuum of CKD anemia, including in those patients typically more difficult to treat with ESA. Roxadustat is effective in both the treatment of ESA-naïve patients requiring Hb correction and in patients converting from ESA treatment by maintaining sustained Hb levels.

The safety of roxadustat was evaluated against placebo in NDD CKD studies and against epoetin alfa in DD CKD studies.

For cardiovascular (CV) safety, the dialysis-dependent (DD) patients including incident dialysis (ID) patients (a sub-group of DD patients who have been on dialysis for ≤4 months at the time of randomization) receiving roxadustat have a comparable risk of major adverse cardiovascular events (MACE, defined as stroke, myocardial infarction, all-cause death), MACE+ (events that comprised MACE plus hospitalized unstable angina and congestive heart failure), and all-cause mortality, compared with those who were treated with epoetin alfa. The CV safety of roxadustat has also been established in non-dialysis patients compared to placebo. The risk of MACE, MACE+ or all-cause mortality is similar between the treatment groups (roxadustat compared to placebo).

The overall safety profile of roxadustat was generally comparable to placebo for NDD CKD patients and to epoetin alfa for DD and ID CKD patients for most of the safety issues evaluated. A number of adverse drug reactions (ADRs) were identified, including vascular access thrombosis, deep vein thrombosis, and seizures. Serious infection was considered an important potential risk, but causality was not established. These risks are considered to be manageable with routine risk minimization activities.

The benefit-risk in this study is therefore deemed acceptable, when the study treatments are used in accordance with the rHuEPO and roxadustat China Package Inserts.

2.3.1 Risk assessment and mitigation pertinent to COVID-19 pandemic

Given the circumstances of potentially relapsing pandemic or local epidemic with regard to the spread of coronavirus disease of 2019 (COVID-19), and considering that CKD patients have weakened immune systems, special attention will be paid to protect patients participating in the trial and clinical staff involved in the investigations against infection with COVID-19. Appropriate measures have been implemented into this protocol to detect COVID-19 disease at screening, safely conduct the clinical procedures in the trial, and to confirm the eligibility of study participants who have symptoms suggestive of COVID-19, or with a recent contact with a COVID-19 positive individual.

The Investigator will conduct a risk assessment of each individual participant, as well as an assessment of evolving pandemic conditions. Appropriate risk-mitigation measures will be implemented to prioritize patient safety. All study-level discussions on risk assessment, to preserve data validity, mitigations and decisions will be documented, marked with start/stop dates where applicable on the Study Risk/Issue and Decisions Log and filed in the Trial Master File (TMF). The Institutional Review Board/Independent ethics committee (IRB/IEC) will be consulted or notified, as required. Any urgent safety measures taken by the Investigator/Sponsor will promptly be communicated to the IRB/Health Authority, as required.

Details of study procedures, dose and study design justification are included in Section 4.

3 OBJECTIVES AND ENDPOINTS

Table 2 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 a 3-hour period (see Section 8.1).
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 a 3-hour period (see Section 9.4.2).

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 9.4.2).
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.

[a] The primary and secondary objectives will be analyzed using the Full Analysis Set (FAS), see Section 9.3 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.

4 STUDY DESIGN

4.1 Overall design

This is a Phase IV, randomized, active-controlled, open-label, parallel design, multicenter prospective study to evaluate the effect of roxadustat versus rHuEPO treatment on the GI iron absorption in patients with anemia of Stage 4 and Stage 5 CKD. This study is planned to screen a maximum of 104 patients and randomize a minimum of 20 patients and a maximum of 60 patients with anemia of CKD who are either rHuEPO-naïve or are currently treated with rHuEPO from approximately 7 to 10 sites in China. Patient enrollment will be competitive across all sites and strata.

The study consists of 3 periods; the Screening Period, Treatment Period and Follow-up Period. The enrolled patients will have 5 study visits.

This study will include:

- Dialysis patients, defined as patients who have been on stable renal replacement therapy using HD or PD for >3 months, who have been on a stable dose of rHuEPO within 4 weeks prior to screening.
- Non-dialysis patients, defined as patients with Stage 4 or Stage 5 CKD as defined by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. NDD patients will be either rHuEPO-users (ie, on a stable dose of rHuEPO within 4 weeks prior to screening) or rHuEPO-naïve (ie, no treatment with ESAs for > 6 weeks prior to screening).

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.

For an overview of the study design see Figure 1, Section 1.3. For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

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). The rHuEPO can be administered either IV or SC depending on the route of administration used by the DD patients 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.

4.1.1 Treatment duration and dosing

Each patient will be contacted over telephone before the first Screening Visit (Visit 1) to confirm that he/she has no symptoms of COVID-19 and that he/she has had no contact with a known COVID-19 positive person within the past 14 days. Only asymptomatic patients, or those who have had no contact with a known COVID-19 positive person within the last 14 days, will be asked to come to the site for informed consent and eligibility screening procedures.

For each patient, the duration of participation in the study will be approximately 8 to 9 weeks divided into 3 periods:

1. Screening Period: approximately 2-3 weeks. Dialysis and non-dialysis patients with anemia of CKD, fulfilling the eligibility criteria, will be asked to provide informed consent to participate in this study. All patients will be tested for COVID-19 infection at the first Screening Visit, using a swab test to rule out active COVID-19 infection. If according to site procedures the test for COVID-19 infection cannot be performed at the first Screening Visit, the test should be performed as soon as possible thereafter but must be performed before the patient returns for the next study visit. Patients who test positive (for COVID-19) must be withdrawn from the study. Patients who test negative (for COVID-19) but do not meet the

eligibility criteria must be withdrawn from the study. Patients must provide written informed consent before any screening tests or assessments are performed. Patients will be assessed for hs-CRP at the Screening Visit to check whether the measurement is either ≤ the ULN, or > the ULN. During the Screening Period, all patients 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. To check Hb eligibility criteria, Hb levels must be assessed twice, at least 7 days apart, during the Screening Period; Hb levels may be assessed up to 3 times (Visits 1, 1a and 1b) during the Screening Period. 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 Hb tests. Screening procedures will be performed according to the schedule of activities (SoA), Table 1.

2. Treatment Period: 2 weeks. Treatment Period procedures will be performed according to the SoA, Table 1 in all randomized patients. For patients who are already on rHuEPO, the start of the Treatment Period (Day 1) should be scheduled to fit into the rHuEPO administration regimen (ie, rHuEPO dosing must occur on the day of the Randomization Visit, Visit 2, Day 1). Patients should be instructed not to take their rHuEPO dose in the morning before they attend the study site for the randomization visit (Visit 2, Day 1).

At Days 1 and 15, a ferrokinetic study will be done in all patients. Immediately **before** time T0 of the ferrokinetic study, a blood sample will be collected to measure baseline serum iron level and TIBC, immediately followed by administration of a defined single dose of oral liquid elemental iron containing $FeSO_4$ (12.5 mL dose, comprising 100 mg elemental iron). Gastrointestinal iron absorption (serum iron level measured) will then be assessed at 1, 2 and 3 hours **after** the administration of the defined single dose of oral iron (T1, T2 and T3, respectively). The window of allowance for the ferrokinetic study blood sampling will be ±3 minutes. Patients on HD will have their HD when the ferrokinetic study is completed ie, after the T3 timepoint. For patients on PD, there are no timing restrictions for their PD in relation to the timing of the ferrokinetic study.

On Day 1, after the ferrokinetic study has completed (ie, after collection of the T3 serum iron sample), patients will be randomized in a 1:1 ratio to either rHuEPO treatment or roxadustat treatment. Patients will be centrally randomized by interactive voice response system (IVRS) and stratified by dialysis status (DD versus NDD) and by the following strata: NDD (rHuEPO-users vs rHuEPO-naïve) and DD (PD vs HD). The study treatment (roxadustat or rHuEPO) will be administered at the study site on Day 1, after randomization. On Day 1, patients on HD, or PD can take their study treatment after randomization at any time before, during or after dialysis.

Dosing of roxadustat and rHuEPO should be scheduled to occur on Visit 4 (Day 15). On Day 15, patients randomized to the roxadustat group should take the roxadustat in the morning, at least 6 hours before the ferrokinetic study starts. On Day 15, patients randomized to the rHuEPO group should take the rHuEPO within 1-2 hours before the ferrokinetic study.

All patients should not ingest any foods containing more than trace amounts of iron such as heme-rich foods, multivitamins with iron etc. for approximately 4 hours before and during the 3 hours of the ferrokinetic study. Patients are allowed limited small snacks with negligible amounts of iron during this 7-hour period. Patients may resume their normal dietary intake following collection of blood at the T3 time point. There is no restriction on drinking water, coffee or tea for the patient before the ferrokinetic study starts and during the ferrokinetic study.

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 BIW and for patients on a weekly dose of rHuEPO of > 6000 IU, dosing will be TIW. The rHuEPO can be administered either IV or SC depending on the route of administration used by the DD patients before the Treatment Period. The rHuEPO will be administered via the SC route for all patients who are NDD. For patients randomized to the rHuEPO arm, Hb levels will be tested in the local laboratory on Day 8, and the rHuEPO dose may be adjusted depending on the patient's Hb levels, for safety reasons, as determined by the Investigator. The rHuEPO dose may also be adjusted at any time during the Treatment Period by the Investigator for safety reasons.

Roxadustat will be administered orally TIW according to the dosage approved in the China Package Insert. The roxadustat dose will not be adjusted during the Treatment Period; therefore, for patients on the roxadustat arm Hb samples will not be collected on Day 8 for testing in the local laboratory. The roxadustat dose may only be adjusted during the 2-week Treatment Period for safety reasons, as determined by the Investigator (see Section 6.6 for details). Hemodialysis or PD patients can take roxadustat at any time before, during or after dialysis treatment.

Each patient will be contacted within 24 h before a scheduled visit to confirm that he/she has no symptoms of COVID-19 and that he/she has had no contact with a known COVID-19-positive person within the past 14 days. If the patient reports symptoms or contact with a COVID-19-positive patient, the Investigator may ask the patient to be tested for COVID-19 infection (swab test to rule out active COVID-19 infection), or withdraw the patient from the study, as is most suitable for the patient's safety, at the Investigator's

discretion. The study treatment and assessments may be continued as planned until the swab test results are available, at the discretion of the Investigator. Patients who test positive on the swab test must be withdrawn from the study. A patient who contacts the site at any time during the Treatment Period informing that he/she has symptoms suggestive of COVID-19 may be asked to get tested for active COVID-19 infection, or be withdrawn from the study for safety reasons, at the Investigator's discretion. Patients who test positive (for COVID-19) must be withdrawn from the study.

Any study assessments planned on the days of site visits may be completed via a telephone call and/or a visit to the patient's home, as required, and if possible. The handling of patients and their blood or urine samples will be done using sterile techniques and observing precautions for infection control and prevention. Reasons for delayed site visits will be reported as protocol deviations. The actual dates when the visit-related assessments were completed will be recorded in the electronic case report form (eCRFs).

In the event of early study discontinuation after baseline but prior to the Day 15 visit for a patient, the Investigator will seek to schedule a study discontinuation visit for the patient, including measurement of the primary efficacy assessments and other assessments according to the SoA, Table 1.

3. Post-Treatment Follow-up Period: 4 weeks. Post-Treatment Follow-up Period procedures to monitor safety will be performed according to the SoA, Table 1. After completing study treatment, all patients will continue for a 4-week Follow-up Period, to monitor safety (all AEs and SAEs will be collected during this Period). Patients who discontinue study treatment early will also continue to this 4-week Follow-up Period unless consent to participate is withdrawn.

Activities that are planned during this 4-week Follow-up Period may be performed by phone. Patients who withdraw prior to the end of the Treatment Period due to a positive COVID-19 test result should not attend the Discontinuation Visit or the 28-day Follow-up Visit at the study site. The assessments planned for the Discontinuation and 28-day Follow-up Visits should be completed via a telephone call, as far as possible.

After discontinuation of study treatment, patients who were on rHuEPO before entering the study may either be returned to their previously prescribed rHuEPO treatment, or be prescribed different agent(s) to treat their anemia by the Investigator, based on their local Hb levels and the discretion of the Investigator. For patients who were rHuEPO-naïve before entering the study, Hb levels may be tested in the local laboratory at the discretion of the Investigator, to determine an appropriate course of treatment for anemia in each patient.

4.1.2 Randomization

A maximum of 104 patients are planned to be screened to achieve a minimum of 20 and a maximum of 60 eligible randomized patients with anemia of CKD fulfilling all the inclusion criteria and none of the exclusion criteria. Enrolled patients will be centrally randomized via an IVRS in a 1:1 ratio to receive either roxadustat or rHuEPO treatment. At randomization, patients will be stratified by NDD (NDD-rHuEPO-users, NDD-rHuEPO-naïve), DD-PD, and DD-HD patients.

4.1.3 Dose of study treatments

For details on treatments given during the study, see Section 6.1 Treatments Administered. Roxadustat will be administered orally TIW. For patients on dialysis: dose of 100 mg for patients with body weight 45 to < 60 kg, or 120 mg for patients with body weight ≥ 60 kg; for non-dialysis patients: dose of 70 mg for patients with body weight 40 to < 60 kg, or 100 mg for patients with body weight ≥ 60 kg. The roxadustat dose will not be adjusted during the 2-week Treatment Period, except for safety reasons as judged by the Investigator. The rHuEPO will be BIW or TIW as an IV or SC dose. The rHuEPO can be administered either IV or SC depending on the route of administration used by the DD patients before the Treatment Period. The rHuEPO will be administered via the SC route for all patients who are NDD.

For patients randomized to the rHuEPO arm, Hb levels will be tested in the local laboratory on Day 8, and the rHuEPO dose may be adjusted depending on the patient's Hb levels, for safety reasons, as determined by the Investigator. The roxadustat dose will not be adjusted depending on the patient's Hb levels during the treatment period, therefore for patients on the roxadustat arm Hb samples will not be collected on Day 8 for testing in the local laboratory (also see Section 6.6).

4.2 Scientific rationale for study design

This study is designed to investigate the effect of roxadustat versus rHuEPO treatment on the GI iron absorption in patients with anemia of CKD, on dialysis or non-dialysis-dependent at Stage 4 and 5.

This study is a randomized, parallel design with 2 treatment groups; roxadustat or rHuEPO and includes dialysis and non-dialysis patients. Performing a parallel design study instead of a crossover design will obviate the risk of "carry-over effects" from either study treatment, in this case roxadustat as rHuEPO has minimal influence on GI iron absorption. The control group will receive rHuEPO, which allows a direct comparison of the effect of roxadustat on GI iron absorption.

The study population consists of patients with anemia associated with CKD; the target population for roxadustat.

In this study, the first dose of study treatment will be given at Day 1. Gastrointestinal iron absorption will be assessed before the first dose of study treatment and will then be re-assessed again in both groups after 2 weeks of study treatment exposure. Data on file on FG-2216, sister compound to roxadustat, has shown significant changes in GI iron absorption following oral dosing of iron in a population with anemia associated with CKD occurring 2 weeks after initiation of FG-2216.

This is an open-label randomized study. Any potential bias will be reduced by central randomization of the patients. The endpoints are measuring levels rather than more subjective patient reported outcomes and will not be influenced by patient or Investigator knowledge of the study treatment.

4.3 Justification for dose

The roxadustat and rHuEPO doses used in this study are according to approved prescribing information available in the respective China Package Inserts.

Details on dose modifications are included in Section 6.6.

4.4 End of study definition

The end-of-study (EOS) is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled procedure shown in the SoA, Table 1.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of CSP deviations to recruitment and enrollment criteria, also known as CSP waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study treatment. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures (Section 5.4). Rescreening of patients is allowed as detailed in Section 5.4.

In this CSP, “enrolled” patients are defined as those who sign informed consent. “Screened” patients are defined as those who fulfil the inclusion/exclusion criteria and have not yet entered the Treatment Period. “Randomized” patients are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Provision of signed and dated, written informed consent form (ICF) prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

Age

2 Patient must be ≥18 years of age, at the time of signing the ICF.

Type of patient and disease characteristics

At Visit 1 prior to screening

Dialysis patients:

3 Patients receiving HD or PD for treatment of ESRD for at least 12 weeks. Patients treated with HD must have access consisting of an arteriovenous (AV) fistula, AV graft, or tunneled (permanent) catheter. Patients on PD must have a functioning PD catheter in place.

4 Hemodialysis patients should be on 3x/week dialysis with evidence of achievement of adequate dialysis as defined by stdKt/V ≥2.1 in HD, and total (renal + PD) weekly Kt/V ≥1.7 in PD documented twice during the 16 weeks preceding screening for the study.

5 Patients should be on a stable rHuEPO dose as defined by change in rHuEPO dose, not exceeding 20% within 4 weeks prior to screening.

Non-dialysis patients:

6 Patients with estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2, (calculated by central laboratory) corresponding to Stage 4 or Stage 5 CKD according to the Kidney Disease Outcomes Quality Initiative (KDOQI), and not receiving dialysis (Levey et al 2006).

7 Patients should either be on a stable dose of rHuEPO for 4 weeks before screening (defined as not exceeding 20% within 4 weeks prior to screening) or be rHuEPO-naïve (no ESA treatment for > 6 weeks before screening).

Dialysis and non-dialysis patients:

8 Patients agree not to take any new traditional Chinese medicine (TCM) and not to change, dose, schedule or brand of any TCM from beginning of the Screening Period through the end of the Follow-up Period.

At Visit 1 (screening)

9 Ferritin ≥50 ng/mL and transferrin saturation (TSAT) ≥15% in non-dialysis patients (obtained from Visit 1, Screening Visit).

10 Ferritin ≥100 ng/mL and TSAT ≥20% in dialysis patients (obtained from Visit 1, Screening Visit).

Weight

11 At Visit 1 (screening), dry body weight 45 to 100 kg (inclusive).

During the Screening Period

12 Dialysis patients must have a mean Hb level of ≥ 9 to ≤ 12 g/dL based on the mean of the 2 most recent central laboratory Hb values within 0.50 g/dL on 2 assays taken at least 7 days apart during the Screening Period.

13 Non-dialysis patients must have a mean Hb level of ≥ 9 to ≤ 12 g/dL for rHuEPO-user patients and ≥ 7 and ≤ 10 g/dL for rHuEPO-naïve patients, based on the mean of the 2 most recent central laboratory Hb values within 0.50 g/dL on 2 assays taken at least 7 days apart during the Screening Period.

At Visit 1 Screening

14 Serum folate level ≥ lower limit of normal (LLN) (obtained from Visit 1, Screening Visit).

15 Serum vitamin B12 level ≥ LLN (obtained from Visit 1, Screening Visit).

16 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 3 x ULN and total bilirubin (TBL) ≤ 1.5 x ULN (obtained from Visit 1, Screening Visit).

17 Negative test results on the swab test to rule out active COVID-19 infection at the Screening Visit. If according to site procedures the test for COVID-19 infection cannot be performed at the first Screening Visit, the test should be performed as soon as possible thereafter but must be performed before the patient returns for the next study visit. Any participant who has had confirmed COVID-19 infection in the past, has fully recovered from symptoms at least 14 days prior to Screening, and has a negative swab test result for COVID-19 infection at Screening, may be included in the study.

Reproduction

18 At the start of the Screening Period, negative serum pregnancy test for female patients of childbearing potential.

19 Female patients of childbearing potential and male patients (non-surgically sterile ie, vasectomy) with a female partner of childbearing potential must, if not practicing complete sexual abstinence, agree to practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depot progesterone or intrauterine device; and (2) a barrier method (condom or diaphragm).

Contraceptive methods must be practiced upon being randomized to the study and until at least 7 days after the last dose of study treatment. Male patients must not donate or bank sperm during this same time period.

5.2 Exclusion criteria

Medical conditions

1 New York Heart Association Class III or IV congestive heart failure (CHF) at screening.

2 Acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event (eg, deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.

3 History of severe, chronic, end-stage, or uncontrolled autoimmune liver disease with ALT > 3 x ULN, or AST > 3 × ULN, or total bilirubin > 1.5 × ULN.

4 Known hereditary hematologic disease such as thalassemia, sickle cell anemia, a history of pure red-cell aplasia or other known causes for anemia other than CKD.

5 Known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis).

6 Systolic blood pressure (BP) ≥ 160 mm Hg or diastolic BP ≥ 95 mm Hg (confirmed by repeated measurement), within 2 weeks prior to randomization. Patients may be rescreened once BP is controlled.

7 History of prostate cancer, breast cancer, renal cell carcinoma or any other malignancy, except the following: cancers determined to be cured or in remission for ≥ 5 years; curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps.

8 Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), ankylosing spondylitis, psoriatic arthritis or active inflammatory bowel disease that is determined to be the principal cause of anemia.

9 Known hemosiderosis, hemochromatosis or hypercoagulable condition.

10 Any prior organ transplant or a scheduled organ transplantation date.

11 Any current condition leading to active significant blood loss.

12 Known allergy to the study treatment or any of its ingredients.

13 Any medical condition, including active, clinically significant infection, that in the opinion of the Investigator or Sponsor may pose a safety risk to a patient in this study, which may confound safety or efficacy assessment or may interfere with study participation.

14 Intolerance of oral iron in the past as defined by stomach upset, nausea, vomiting, or diarrhea.

15 Active GI bleed.

16 Hospitalizations within the 12 weeks preceding study randomization for GI bleeding or CHF.

17 Life expectancy <6 months.

18 Patients who are likely to be initiated on dialysis within the next 3 months per Investigator's assessment at the time of screening.

19 Previous bowel resection.

20 Coeliac disease.

21 Gastroenteritis in the 4 weeks prior to randomization.

22 Cognitive disabilities, physical or psychiatric disease that in the opinion of the Investigator/clinician influence the patient's adherence and successful completion of the study.

Prior/concomitant therapy

23 Any treatment with roxadustat or a HIF-PHI.

24 Any RBC transfusion within 6 weeks prior to the first Screening Visit, or during the Screening Period.

25 Has received another new chemical entity (defined as a compound which has not been approved for marketing) within the 12 weeks prior to Screening Visit.

26 Exposure to IV iron or use of TRIFERIC® in dialysate during the Screening Period (ie, 2 weeks before randomization [Day 1]).

27 Exposure to iron-chelating agent (eg, deferoxamine/desferrioxamine, deferiprone or deferaxirox therapy) within the 6 weeks prior to the first Screening Visit.

Prior/concurrent clinical study experience

28 Participation in any other clinical study that included drug treatment within at least 4 weeks of screening. (Note: patients consented and screened, but not randomized in this study or a previous study are not excluded).

Other exclusions

29 Involvement in the planning and/or conduct of the study (applies to AstraZeneca and FibroGen staff and/or staff at the study site).

30 Patient non-adherence to medications or missing > 1 dialysis treatments/month per the Investigator's knowledge.

31 Previous randomization in the present study.

32 History of alcohol or drug abuse within 2 years prior to randomization.

5.3 Lifestyle restrictions

No restrictions are required.

5.4 Screen failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently entered in the Treatment Period. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Patients who failed to meet 1 or more of the following eligibility criteria for participation in this study (screen failure) on initial evaluation may be rescreened once only, at the Investigator's discretion:

Inclusion criteria for rescreening

- Patients receiving or initiating HD or PD for treatment of ESRD for at least 12 weeks. Patients treated with HD must have access consisting of an AV fistula, AV graft, or tunneled (permanent) catheter. Patients on PD must have a functioning PD catheter in place.
- Patients (dialysis and non-dialysis, rHuEPO-users) must have a mean Hb level of ≥ 9 to ≤ 12 g/dL based on the mean of the 2 most recent central laboratory Hb values within 0.50 g/dL on 2 assays taken at least 7 days apart during the Screening Period. Non-dialysis rHuEPO-naïve patients must have a mean Hb level of ≥ 7 and ≤ 10 g/dL based on the mean of the 2 most recent central laboratory Hb values within 0.50 g/dL on 2 assays taken at least 7 days apart during the Screening Period.
- Hemodialysis patients should be on 3x/week dialysis with evidence of achievement of adequate dialysis as defined by stdKt/V ≥2.1 in HD, and total (renal + PD) weekly Kt/V ≥1.7 in PD documented twice during the 3 months preceding evaluation for the study.
- Negative swab test result to rule out active COVID-19 infection at the Screening Visit. If according to site procedures the test for COVID-19 infection cannot be performed at the first Screening Visit, the test should be performed as soon as possible thereafter but must be performed before the patient returns for the next study visit. Any participant who has had confirmed COVID-19 infection in the past, has fully recovered from symptoms at

least 14 days prior to Screening, and has a negative swab test result for COVID-19 infection at Screening may be included in the study.

Exclusion criteria for rescreening

- Systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg (confirmed by repeated measurement), within 2 weeks prior to randomization.
- Any RBC transfusion during the Screening Period.
- Hospitalizations within the 12 weeks preceding study randomization for GI bleeding or CHF.
- Exposure to IV iron or use of TRIFERIC® in dialysate during the Screening Period (ie, 2 weeks before randomization [Day 1]).
- Exposure to iron-chelating agent (eg, deferoxamine/desferrioxamine, deferiprone or deferaxirox therapy) within the 6 weeks prior to the first Screening Visit.
- Gastroenteritis in the 4 weeks prior to randomization.

Rescreening is not allowed for any other criteria apart from those listed above.

Rescreened patients will be assigned a new patient number. An extra file will be included in the eCRF to record the original enrollment code (ECode). Rescreening will be documented so that its effect on study results, if any, can be assessed.

These patients should have the reason for study withdrawal recorded in the eCRF.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the CSP. Study treatment in this study refers to roxadustat and rHuEPO.

6.1 Treatments administered

6.1.1 Investigational products

During the randomized Treatment Period, patients will be randomly assigned in 1:1 ratio to receive either roxadustat or rHuEPO for 2 weeks.

Patients will be provided roxadustat and rHuEPO and both treatments will be used according to their approved indication and dosage during the study. Refer to roxadustat and rHuEPO China Package Inserts for further details on these study treatments. For additional information regarding roxadustat, please refer to the IB.

6.1.2 Dose of study treatments

The starting dose of roxadustat will be calculated as per the China Package Insert. The recommended starting dose of roxadustat will depend on the body weight of the patient: 100 mg (45 to < 60 kg) or 120 mg (≥ 60 kg) in patients on dialysis (weight should be patient's empty weight prior to instillation of dialysate); 70 mg (40 to < 60 kg) or 100 mg (≥ 60 kg) in non-dialysis patients.

Roxadustat doses must be administered at least 2 days apart but no more than 4 days apart (eg, Monday, Wednesday, Friday). Dosing of roxadustat should be scheduled to occur on the day of Visit 4 (Day 15). Patients can take roxadustat at any time before or after dialysis treatment. On Day 1, roxadustat should be taken after the ferrokinetic study has completed. On Day 15 roxadustat should be taken at least 6 hours before the ferrokinetic study starts. The dose of roxadustat will not be adjusted during the study except for safety reasons as judged by the Investigator.

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 BIW and for patients on a weekly dose of rHuEPO of > 6000 IU, dosing will be TIW. The rHuEPO can be administered either IV or SC depending on the route of administration used by the DD patients before the Treatment Period. The rHuEPO will be administered via the SC route for all patients who are NDD.

For patients who were rHuEPO-users before Screening, the initial dose selection of rHuEPO will be based on the patient's Hb levels, and average prescribed rHuEPO dose during the 4 weeks prior to the Screening Visit. For patients who are rHuEPO-naïve at study entry, the initial start dose of the study rHuEPO will be based on the patient's Hb levels and will be in accordance with the rHuEPO China Package Insert. Previously rHuEPO-naïve patients randomized to the rHuEPO arm may be trained by the site staff to self-administer SC injection on the day of randomization, if required. The rHuEPO may also be administered by a qualified person at the study site or at another hospital.

For patients who are already receiving the uniform brand of rHuEPO that will be used for the study, the initial rHuEPO dosing regimen in the study (starting from Visit 2) should be equivalent to their prior rHuEPO dosing regimen, unless a dose adjustment is needed per the Investigator's judgment.

For patients on any other short-acting rHuEPOs, a conversion ratio of 1:1 (equivalent dose) to the study rHuEPO should be used unless a dose adjustment is needed per the Investigator's judgment.

For patients on long-acting rHuEPOs, the initial dose of the study rHuEPO will be determined using the conversion table (see Table 3), unless a dose adjustment is needed per the Investigator's judgment.

The study rHuEPO dose can be adjusted on Day 8 during the 2-week Treatment Period, depending on the patient's Hb levels. The rHuEPO dose may also be adjusted at any time during the Treatment Period by the Investigator for safety reasons, if judged necessary (see Section 6.6 for details).

For patients already on rHuEPO, dosing of rHuEPO should be scheduled to occur on the day of Visit 2 (Day 1). Patients should be instructed not to take their rHuEPO dose in the morning before they attend for the randomization visit (Visit 2, Day 1). On Day 1, patients randomized to rHuEPO should have rHuEPO administered after the ferrokinetic study has completed. For patients randomized to rHuEPO, dosing of rHuEPO should be scheduled to occur on the day of Visit 4 (Day 15). On Day 15, patients randomized to rHuEPO should have rHuEPO administered within 1-2 hours before the ferrokinetic study starts.

Table 3 Initial dosing of rHuEPO for patients treated with an erythropoietic analogue at study entry

	Conversion ratio	**Examples of converted initial epoetin alfa dose (IU/week) [c]**
Darbepoetin alfa (µg/week) [a]	x 200	40 µg/week x 200 = 8,000 IU/week
Mircera® (µg/month) [a]	x 70 to 80	100 µg/month x 70 = 7,000 IU/week
	(Lower conversion ratio can be used for lower Mircera® dose)[b]	200 µg/month x 80 = 16,000 IU/week

[a] Mean weekly monthly dose prior to Screening Visit 1.
[b] Per discretion of Investigator.
[c] May be rounded if deemed necessary.

rHuEPO=recombinant human erythropoietin; IU=international unit.

Recombinant human erythropoietin must not be mixed with other drugs for injection.

If a patient misses a dose of study treatment (roxadustat or rHuEPO), the patient should make a note of this and inform the study site staff at their next study visit. They should continue with the next scheduled dose.

Details on dose modifications are in Section 6.6.

6.1.3 Additional treatments

All patients will receive the same brand of liquid oral iron containing $FeSO_4$ to be administered as a single oral (liquid) dose of 12.5 mL (100 mg elemental iron) at Days 1 and 15 for the ferrokinetic study.

6.2 Preparation/handling/storage/accountability

Recombinant human erythropoietin can be administered either IV or SC. Administration of rHuEPO will be performed by the Investigator or a qualified member of the site staff in HD patients. In PD or NDD patients with CKD, rHuEPO can be self-administered SC by the patient or a caregiver after adequate training by site staff , unless the Investigator is of the opinion that the patient or caregiver is already adequately self-administering an rHuEPO analogue prior to the study. Previously rHuEPO-naïve patients randomized to the rHuEPO arm may be trained by the site staff to self-administer SC injection on the day of randomization. The rHuEPO may also be administered by a qualified person at the study site or at another hospital.

On Day 15, patients randomized to the roxadustat group should take the roxadustat in the morning, at least 6 hours before the ferrokinetic study starts. On Day 15, patients randomized to the rHuEPO group should take the rHuEPO within 1-2 hours before the ferrokinetic study starts. The time a patient takes the roxadustat and rHuEPO should be recorded in the eCRF.

Details on food restrictions on Days 1 and 15 are in Sections 4.1.1 and 8.1.1.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Investigator Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label study in which a minimum of 20 patients and a maximum of 60 patients will be randomized in a 1:1 ratio to either roxadustat or rHuEPO. Results for Screening Period assessments for serum folate, vitamin B12, ALT, AST and TBL **must** be available before randomization. Randomization to treatment will be performed centrally using PAREXEL MATCH, an IVRS, in sequence and stratified by the following strata: NDD (rHuEPOuser, rHuEPO-naïve), DD-PD, and DD-HD patients.

The use of a central randomization will be implemented to avoid selection bias. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each study site.

If a patient withdraws from the study, then his/her enrollment/randomization ECode cannot be reused. Withdrawn patients will not be replaced.

Tables ran prior to database lock will be presented using a dummy treatment list to ensure decision bias is minimized.

6.4 Treatment adherence

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the study treatment from receipt by the study site until the destruction or return of all unused study treatment. The Investigator(s) is responsible for ensuring that the patient has returned all unused study treatment. Patients who withdraw prior to the end of the Treatment Period due to a positive COVID-19 test result will be instructed to send any remaining study treatment to the study site by mail, when it is safe to do so.

6.5 Concomitant therapy

Concomitant medications are any prescription or over-the-counter preparations, including herbal products, TCM and “natural remedies”, used by a patient while participating in this clinical study. Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal products and “natural remedies” that the patient is receiving at the time of screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Patients should not take any new TCM and should not change the dose, schedule or brand of any TCM from beginning the of the Screening Period through the end of the Follow-up Period.

Patients taking oral iron before the study can continue taking this during the study. The dose of the oral iron should not be changed during the Treatment Period. The oral iron should not be taken in the morning on the day of ferrokinetic procedures and on this day, patients will be given a defined single dose of oral liquid elemental iron containing $FeSO_4$ used for the study.

For details of medications for which care should be taken when concomitantly administered with roxadustat or rHuEPO, refer to the respective China Package Inserts.

6.5.1 Prohibited medications/therapy

The following medications/therapies are prohibited during the study:

- Any other investigational drug: from randomization until EOS
- Any rHuEPO treatment during the Treatment Period, except for study treatment
- Iron-chelating agents (eg, deferoxamine/desferrioxamine, deferiprone or deferaxirox therapy): from 6 weeks prior to the first Screening Visit until the end of the Treatment Period
- Intravenous iron and TRIFERIC® in dialysate need to be stopped during the Screening Period (ie, 2 weeks before randomization [Day 1]), and should not be taken throughout the remaining Screening Period and the Treatment Period, but can be started again after the Treatment Period
- Any vitamin C formulation: from randomization until EOS.

For details of prohibited medications, refer to the respective China Package Inserts.

6.5.2 Other concomitant treatment

Medication other than that described above is discouraged but may be given at the discretion of the Investigator if considered necessary for the patient's safety and well-being. All concomitant medications are to be recorded in the appropriate sections of the eCRF.

6.5.3 Rescue guidelines

If a patient's medical condition requires rescue therapy, the patient should be treated at the Investigator's discretion. Rescue therapy should be recorded in the eCRF.

6.6 Dose modification

The dose for roxadustat will not be adjusted during this study due to its short duration, except for safety reasons as judged by the Investigator.

Change in rHuEPO dosing will be allowed both during Screening and Treatment Periods at the discretion of the Investigator for the patient's safety and to maintain the patient's Hb levels within the CSP defined range. Ideally, dosage changes would not occur or would be minimal during the week leading up to and during the 2-week Treatment Period. However, appropriate adjustments should occur as required to ensure patient safety.

6.7 Treatment after the end of the study

After discontinuation of study treatment, patients who were on rHuEPO before entering the study may either be returned to their previously prescribed rHuEPO treatment, or be prescribed a different agent(s) to treat their anemia by the Investigator, based on their local Hb levels and the discretion of the Investigator. For patients who were rHuEPO-naïve before entering the study, Hb levels may be tested in the local laboratory at the discretion of the Investigator, to determine an appropriate course of treatment for anemia in each patient.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study. See the SoA, Table 1, for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation from study treatment

For patients needing treatment with prohibited concomitant medications, study treatment must be discontinued or interrupted temporarily.

For decisions around discontinuation, Parexel Medical can be consulted as appropriate.

7.1.2 Permanent discontinuation from study treatment

- Patient decision: The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Investigator's decision, including but not limited to these examples:
  - Incorrectly randomized patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
  - Adverse event for which the Investigator thinks continued study treatment may put the patient at undue risk
  - Severe non-compliance with CSP
  - Pregnancy

Each permanent discontinuation from study treatment should be communicated to the study team. For decisions around permanent discontinuation, Parexel Medical can be consulted as appropriate. Study assessments or follow-up should be continued in all cases if possible (see SoA, Table 1).

If a patient discontinues prematurely, the contraceptive method must be practiced until at least 7 days following final administration of study treatment.

7.1.3 Procedures for discontinuation of study treatment

The Investigator should instruct the patient to contact the study site before or at the time if study treatment is stopped.

A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of study treatment, for any reason, does not impact on the patient´s participation in the study. At the time that the patient discontinues study treatment, the patient should be asked to return to attend the discontinuation visit (to perform all assessments that would have been performed at Visit 4), within 7 days after the study treatment is stopped. The patient will also attend the 28-day Follow-up Visit (28 ±3 days after the study treatment is stopped). If the patient does not agree to attend these study visits in-person, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study. The patient should return all study treatment to the study site.

If a patient discontinues prematurely, the contraceptive method must be practiced until at least 7 days following final administration of study treatment.

Patients who withdraw prior to the end of the Treatment Period due to a positive COVID-19 test result should not attend the Discontinuation Visit or the 28-day Follow-up Visit at the study site. The assessments planned for the Discontinuation and 28-day Follow-up Visits should be completed via a telephone call, as far as possible. These patients will be instructed to send any remaining study treatment to the study site by mail, when it is safe to do so.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the study site for a required study visit:

- The study site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by eg, repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the EOS. Should the patient be unreachable at the EOS, the patient should be considered to be lost to follow-up with unknown vital status at EOS and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (study treatment **and** assessments) at his/her own request, without prejudice to further treatment.

A patient may be withdrawn from the study at any time at the discretion of the Investigator or Sponsor for safety reasons.

If the patient reports symptoms on a pre-visit telephone call, reports contact with a COVID-19 positive patient within the past 14 days, the Investigator may ask the patient to be tested for COVID-19 infection (swab test to rule out active COVID-19 infection), or withdraw the patient from the study, as is most suitable for the patient's safety, at the Investigator's discretion. The study treatment and assessments may be continued as planned until the swab test results are available, at the discretion of the Investigator. Patients who test positive on the swab test must be withdrawn from the study. A patient who contacts the site at any time during the Treatment Period informing that he/she has symptoms suggestive of COVID-19 may be asked to get tested for COVID-19 infection, or be withdrawn from the study for safety reasons, at the Investigator's discretion. Patients who test positive (for COVID-19) must be withdrawn from the study. The assessments planned for the Discontinuation and 28-day Follow-up Visits should be completed via a telephone call, as far as possible. Patients who withdraw prior to the end of the Treatment Period visit due to a positive COVID-19 test result will be instructed to send any remaining study treatment to the study site by mail, when it is safe to do so.

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow-up patients as medically indicated.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the EOS from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

See SoA, Table 1, for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA, Table 1.

The Investigator will ensure that data are recorded on the eCRF. The Web-Based Data Capture (WBDC) system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with Parexel Medical immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, Table 1 is essential and required for study conduct.

All Screening Period evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record

details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the CSP-specified criteria and were performed within the time frame defined in the SoA, Table 1.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will be included in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Ferrokinetic study and ferrokinetic measurements (serum iron, ferritin, TIBC, TSAT, transferrin, and soluble transferrin receptor), hs-CRP and hepcidin levels will be assessed during the Treatment Period at the timepoints included in the SoA, Table 1.

All ferrokinetic assessments will be obtained during the hours preceding the mid-week HD treatment for patients on HD to provide some degree of ideal weight achievement and avoid blood volume changes and associated interference with biochemical assays that might occur during the dialysis procedure itself. On Days 1 and 15, blood samples for the ferrokinetic study (for serum iron and TIBC) will be taken immediately before the single dose of oral iron (12.5 mL [100 mg elemental iron) is administered, and then after 1, 2 and 3 hours (each ±3 minutes) after the single dose of oral iron (for serum iron only).

A central laboratory will perform the laboratory assessments required for efficacy assessments. A central laboratory manual will be provided to all participating study sites with instructions on specimen collection, processing, storing and shipping to the central laboratory.

A local laboratory will be used to measure Hb levels to assess if dose adjustment of rHuEPO is needed (see Section 6.6).

8.1.1 Primary efficacy assessments

The primary endpoint 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 immediately 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 (each ±3 minutes) 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.

The primary endpoint is the relative difference in AUC for serum iron from baseline (Day 1) to Day 15 adjusted for study treatment and baseline hs-CRP level (≤ ULN, > ULN). The model is described in Section 9.4.1.

The time the patient takes the single dose of oral iron and the collection time for each of the ferrokinetic study samples should be recorded in the eCRF.

On Day 1, after the ferrokinetic study has completed, the study treatment (roxadustat or rHuEPO) will be administered at the study site after randomization.

On Day 15, patients randomized to the roxadustat group should take the roxadustat in the morning, at least 6 hours before the ferrokinetic study. On Day 15 patients randomized to the rHuEPO group should take the rHuEPO within 1-2 hours before the ferrokinetic study. The time a patient takes the roxadustat and rHuEPO should be recorded in the eCRF.

All patients should not ingest any foods containing more than trace amounts of iron such as heme-rich foods, multivitamins with iron etc. for approximately 4 hours before and during the 3 hours of the ferrokinetic study. Patients are allowed limited small snacks with negligible amounts of iron during this 7-hour period. Patients may resume their normal dietary intake following collection of blood at the T3 time point. There is no restriction on drinking water, coffee or tea for the patient before the ferrokinetic study starts and during the ferrokinetic study.

Patients on HD will have their HD when the ferrokinetic study is completed (ie, after the T3 timepoint). For patients on PD, there are no timing restrictions for their PD in relation to the timing of the ferrokinetic study.

8.1.2 Secondary efficacy assessments

The secondary endpoints of interest assess direct treatment and interaction effects in iron absorption and the indices of iron metabolism (serum iron, ferritin, TIBC, TSAT, transferrin, soluble transfer receptor) and hepcidin levels are described as follows*:

- The relative difference in AUC from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hepcidin value, and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
- The relative difference in AUC from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hs-CRP value, and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.
- The relative difference in the indices of iron metabolism from baseline (Day 1) to Day 15, adjusted for study treatment and baseline hs-CRP level (≤ ULN, > ULN). Treatment effect to be assessed.

- The relative difference in the indices of iron metabolism from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hepcidin, and treatment interaction with baseline hepcidin value. Treatment and interaction effects to be assessed.
- The relative difference in the indices of iron metabolism from baseline (Day 1) to Day 15, adjusted for study treatment, baseline hs-CRP value and treatment interaction with baseline hs-CRP value. Treatment and interaction effects to be assessed.

The assessments for the secondary endpoints will be performed similar to those for the primary endpoints (see Section 8.1.1).

8.2 Safety assessments

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 EOS visit. See Sections 8.3 and 8.4 for details on AE and SAE reporting.

Safety will be assessed through:

- Adverse events
- Laboratory parameters
- Vital signs (tympanic temperature, BP, pulse and respiratory rate)

Planned timepoints for all safety assessments are provided in the SoA, Table 1.

8.2.1 Clinical safety laboratory assessments

See Table 4 for the list of clinical safety laboratory tests to be performed and refer to the SoA, Table 1 for the timing and frequency. All CSP-required laboratory assessments, as defined in Table 4 must be conducted in accordance with the central laboratory manual and the SoA, Table 1.

The Investigator should make an assessment of the available laboratory results with regard to clinically relevant abnormalities and should determine if any of the laboratory values are clinically significant. The laboratory results should be signed and dated and retained at study site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The clinical chemistry and hematology will be performed at a central laboratory. The central laboratory will provide the site with the necessary material and instructions for the sampling. In exceptional circumstances and upon discussion with the Sponsor, local laboratory assessments may have to be undertaken to collect key information supporting an AE or SAE.

On Days 1 and 8, and 15 Hb 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 re-start 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. (see Section 6.6). If there are local requirements for any local laboratory testing of safety laboratory parameters, these will be performed at the local laboratory, but will be deemed to be outside the requirements of the study and the results will not be collected as part of the study. In such cases these samples will also be sent to the central laboratory for testing, as part of the study requirements.

The following laboratory variables will be measured (blood, serum or plasma will be specified in the laboratory manual):

Table 4 Laboratory variables

Hematology/Hemostasis	**Clinical Chemistry**
Hemoglobin (Hb)	Creatinine
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	Alkaline phosphatase (ALP)
Platelet count	Aspartate transaminase (AST)
Red blood cell (RBC)	Alanine aminotransferase (ALT)
Hematocrit	Albumin
Mean corpuscular volume (MCV)	Potassium
Reticulocytes	Calcium, total
Glycated hemoglobin (HbA1C)	Sodium
	Glucose
Urinalysis (Urine dipstick) *	Bicarbonate
Blood	Chloride
Protein	Blood urea nitrogen (BUN)
Glucose	Magnesium
	Phosphorus
Additional Laboratory Analytes	
Vitamin B12	**Iron Profile**
Folate	Serum iron
Intact parathyroid hormone (iPTH)	Ferritin
high sensitivity C-reactive protein (hs-CRP)	Total iron binding capacity (TIBC)
Hepcidin	Transferrin saturation (TSAT)
Test to Rule out COVID-19 infection	Transferrin
Swab test	
Pregnancy tests	Soluble transferrin receptor
Serum human chorionic gonadotropin (hCG)	

* Urine dipstick glucose, protein and blood performed locally (applicable only for non-dialysis-dependent patients, and dialysis-dependent patients who are not anuric).

Note. In case a patient shows an AST **or** ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

If the patient reports symptoms or contact with a COVID-19 positive patient, the Investigator may ask the patient to be tested for COVID-19 infection (swab test to rule out active COVID-19 infection), or withdraw the patient from the study, as is most suitable for the patient's safety, at the Investigator's discretion. The study treatment and assessments may be continued as planned until the swab test results are available, at the discretion of the

Investigator. Patients who test positive on the swab test must be withdrawn from the study. A patient who contacts the site at any time during the Treatment Period informing that he/she has symptoms suggestive of COVID-19 may be asked to get tested for active COVID-19 infection, or be withdrawn from the study for safety reasons, at the Investigator's discretion. Patients who test positive (for COVID-19) must be withdrawn from the study.

Additional laboratory assessments performed for purposes other than general safety evaluation are also listed in Table 4.

8.2.2 Physical examinations

A complete physical examination will be performed at screening (Visit 1) and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Body weight will be measured at Screening Visit. Patients should be in light indoor clothes without shoes. Weight for patients on PD should be obtained with a "dry" or empty peritoneal cavity (PD fluid fully drained).

Physical examination will be performed at timepoints as specified in the SoA, Table 1, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details. Additional physical examinations can be performed at the discretion of the Investigator or as indicated by development of any new or changing patient symptoms and recorded in the eCRF.

8.2.3 Vital signs

The vital signs include tympanic temperature, systolic and diastolic BP, pulse rate and respiratory rate and will be assessed as outlined in the SoA, Table 1.

Blood pressure should be measured before the HD procedure when applicable. For patients on PD, BP should be measured in the morning prior to the patient performing the first exchange of the day. Blood pressure and pulse rate should be measured with a completely automated device in triplicate with at least 1-minute intervals between measurements after being comfortably at rest in a seated position with the back and feet supported (ie, by chair back and floor or platform, respectively) quietly for at least 5 minutes. Manual techniques will be used only if an automated device is not available. The position of the patient should be comfortable with the arm where the BP is recorded to be within the level of heart (the middle of the cuff on the upper arm is at the level of the right atrium [the midpoint of the sternum]). The patient will be instructed to relax as much as possible and to not talk during the measurement procedure. The same device should preferably be used for the patient during the course of the study and in the same arm. The first reading of the BP and pulse rate should be

rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

8.2.4 Electrocardiograms

A 12-lead electrocardiogram (ECG) measurement will be obtained at screening as outlined in the SoA, Table 1, using an ECG machine that automatically calculates the pulse rate and measures PR, QRS, QT, and QTc intervals.

8.3 Collection of adverse events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3.

8.3.1 Method of detecting adverse events and serious adverse events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.1.1 Reporting of AEs/SAEs in relation to COVID-19

All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP.

For patients experiencing signs and symptoms indicating an infection, an attempt will be made to determine whether the COVID-19 virus is the infectious organism and the AE will be recorded accordingly. If a patient presents with clinical signs and symptoms suggestive of COVID-19, a test will be requested where possible:

- If the test is positive, record "COVID-19 positive" in the Adverse Event Field.
- If the test is negative, record "COVID-19 negative" in the Adverse Event Field, along with the AE/SAE signs and symptoms and/or other diagnosis.

If a test has not been performed or result is not available and signs and symptoms, as judged by the Investigator, are suggestive of COVID-19 infection, record "COVID-19 suspected" in

the Adverse Event Field. If the Investigator has other concurrent diagnoses for the patient's signs and symptoms (eg, pneumonia), these will be recorded as separate AEs.

8.3.2 Time period and frequency for collecting adverse event and serious adverse event information

All AEs and SAEs will be collected from the time of signature of informed consent throughout the Treatment Period and including the Follow-up Period.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

All roxadustat Adverse Drug Reactions (ie, AEs that the Investigator considers that there is a reasonable possibility that the AE may have been caused by roxadustat) will be reported to the Sponsor or designee within 24 hours.

Investigators are not obligated to actively seek AE or SAE information in study patients who are no longer on the study. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator should notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the Follow-up Visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the EOS, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- Adverse event (verbatim)
- The date when the AE started and stopped
- Maximum intensity grade per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade version ≥5.0
- Whether the AE is serious or not

- Investigator causality rating against the study treatment (yes or no)
- Action taken with regard to study treatment
- Adverse event caused by patient's withdrawal from study
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of AE

8.3.5 Causality collection

The Investigator will assess causal relationship between study treatment and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'* or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR).

The Investigator should make an assessment of the available laboratory results with regard to clinically relevant abnormalities and should determine if any of the laboratory values are clinically significant. The laboratory results should be signed and dated and retained at study site as source data for laboratory variables.

Any protocol-mandated laboratory values or vital signs from the baseline visit that the Investigator assesses to be clinically significant, should be reported in the medical history. Deterioration as compared to baseline of any protocol-mandated laboratory values or vital signs that the Investigator assesses to be clinically significant should be reported as AEs. If deterioration of a laboratory value or vital sign meets the seriousness criteria, it should be reported as an SAE. If the reason for discontinuation of study treatment is due to deterioration of a laboratory value or vital sign compared to baseline (whether or not considered clinically significant), this should be reported as an AE. If a laboratory value or vital sign is outside the normal range, and the Investigator has assessed it as not clinically significant and study treatment has not been discontinued as a result of the laboratory value or vital sign, this does not need to be reported as an AE.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease-under study (DUS), see Sections 8.3.9 and 8.3.10.

8.3.8 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3x ULN together with TBL ≥ 2x ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

8.3.9 Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of CKD or procedures to diagnose or treat the CKD. Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study treatment.

8.3.10 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. Worsening of anemia should not be considered an AE unless the worsening of anemia is associated with a cause other than the patient's CKD. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study treatment, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1-day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the FibroGen Drug Safety **within 1 calendar day** of initial receipt for all SAEs. FibroGen Drug Safety will be responsible for processing all SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The Investigator is obliged to report SAE to the appropriate local regulatory authorities, Ethics Committees and AstraZeneca representative within 24 hours of SAE awareness.

Safety information (SAEs, serious adverse drug reactions [SADRs], adverse drug reactions [ADRs] and suspected unexpected serious adverse reactions [SUSARS]) are to be reported by

Sponsor or Sponsor Representative to the appropriate local regulatory authorities within legally binding timelines.

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the AstraZeneca representative except for:

- If the pregnancy is discovered before the study patient has received any study treatment.

If a pregnancy is reported, the Investigator should inform the Sponsor representative within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to FibroGen Drug Safety within 1 calendar day.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT form is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until at least 7 days after the last dose of roxadustat and as indicated by previous studies (pre-clinical and clinical) should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed and followed up as described in Section 8.4.2. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information.

8.4.3 Overdose

Refer to the respective China Package Insert for roxadustat and rHuEPO for information on the management of study treatment overdose.

AstraZeneca does not recommend specific treatment for an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study treatment occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the FibroGen Drug Safety within 1 calendar day.

8.4.4 Medication error

Medication errors with AstraZeneca study treatment are collected in all studies where medication error is possible.

If a medication error occurs in the course of the study, then the Investigator or other site personnel initially reports to the appropriate AstraZeneca representatives within 1-day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative will then work with the Investigator to ensure that all relevant information is completed within 1 calendar day.

The definition of a medication error can be found in Appendix B.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

This section highlights statistical considerations for this CSP.

Individual data will be presented in patient listings. All patient data listings will be sorted by treatment, site, dialysis status and patient.

9.1 Statistical hypotheses

Statistical testing will be conducted at a 2-sided significance level of 5%. A multiple testing strategy will be used as described in Section 9.4.2.1. 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.

9.1.1 Primary endpoint

The primary endpoint for this study is described in Section 8.1.1. This will be assessed via change from baseline (Day 1) at 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. 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.

$$\bar{d}_{rHuEPO} = \bar{d}_{roxa}$$

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

$$\bar{d}_{rHuEPO} \neq \bar{d}_{roxa}$$

Where $\bar{d}_{rHuEPO}$ is the average change from baseline for the rHuEPO treatment group and $\bar{d}_{roxa}$ is the average change from baseline for the roxadustat treatment group.

9.1.2 Secondary endpoints

The secondary endpoints of interest are described fully in Section 8.1.2. The hypotheses for these endpoints can be separated into 2 distinct groups, the relative difference in iron metabolism and the relative difference in AUC. All hypotheses will follow the null hypothesis that there is no difference between AUC or iron metabolism when adjusting for various specified covariates or interactions.

9.2 Sample size determination

CCI

[redacted]

CCI [redacted]

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
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.
Full analysis set	The full analysis set (FAS), the primary efficacy analysis set, will include all randomized patients who have who have complete baseline (Day 1) measurements for any efficacy analysis. 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.
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 major protocol violations. Details for PP analysis set exclusion will be specified in the statistical analysis plan (SAP). The PP analysis set will be used as a sensitivity analysis population for the primary and secondary endpoints.
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.

9.4 Statistical analyses

Analyses will be performed by Parexel. A comprehensive statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. A stable SAP will be produced prior to first patient-in. This section is a summary of the planned statistical analyses of the primary, secondary and safety endpoints. Any deviations from this plan or the SAP will be reported in the CSR.

All efficacy and safety variables will be summarized by study treatment groups using descriptive statistics (n, mean, SD, median, minimum and maximum for continuous data and n, frequencies and percentages for categorical data, including proportion of missingness). Data will be summarized by visit, randomization strata and site as applicable.

Treatment and interaction effects will be evaluated via analysis of covariance (ANCOVA). All analyses will involve the difference of log-transformed AUC and indices of iron metabolism. Results can be presented on the untransformed scale for interpretability.

Multiple imputations 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. This will be described in further detail in the SAP.

The statistical methods and how the variables are presented will be further detailed in the SAP.

9.4.1 Primary efficacy analyses

The primary efficacy endpoint is described in (Section 8.1.1). It 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.

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

$$AUC_{X,i} = \sum_{j=0}^{2} \left(\frac{P_{j+1} + P_j}{2} - P_0 \right)$$

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

$$d_i = \log(AUC)_{\ Day\ 15,i} - \log(AUC)_{\ Baseline,i}$$

The difference in log (AUC) from baseline (Day 1) to Day 15 will be analyzed using an ANCOVA model, adjusting for study treatment and baseline hs-CRP level (≤ ULN, > ULN).

If a patient withdraws before Day 15, their discontinuation visit will be used as the post-baseline primary measurement.

9.4.2 Secondary efficacy analyses

The secondary efficacy endpoints for this study are outlined in Section 8.1.2.

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 are described in Table 5. All endpoints will be analyzed using ANCOVA models.

Table 5 Summary of secondary endpoints to be analyzed

Outcome of interest	Adjusted for	Variable(s) to be assessed
Relative difference in AUC [a]	Study treatment Baseline hepcidin value	Treatment effect Treatment-hepcidin interaction
Relative difference in AUC [a]	Study treatment Baseline hs-CRP value	Treatment effect Treatment-hs-CRP interaction
Relative difference in indices of iron metabolism [b]	Study treatment Baseline hs-CRP level (≤ ULN, > ULN)	Treatment effect
Relative difference in indices of iron metabolism [b]	Study treatment Baseline hepcidin value	Treatment effect Treatment-hepcidin interaction
Relative difference in indices of iron metabolism [b]	Study treatment Baseline hs-CRP value	Treatment effect Treatment-hs-CRP interaction

[a] The absorption of iron over a 3-hour period, measured just prior to T0 and at T1, T2, T3.

[b] Indices of iron metabolism (ie, serum iron, ferritin, TIBC, TSAT, transferrin, soluble transferrin receptor, and hepcidin levels). These will be laboratory serum measurements.

AUC=area under the curve; hs-CRP=high sensitivity C-reactive protein; TIBC=total iron binding capacity; TSAT=transferrin saturation, ULN=upper limit of normal.

These secondary endpoints will be analyzed using ANCOVA models, similar to that described in Table 5. 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 log-transformed baseline hs-CRP are to be used as covariates. The results will be back transformed to the original scale to aid interpretability.

9.4.2.1 Multiple testing

Let P_1, P_2,…P_n be the p-values for each of the *n* separate hypotheses tests. The Holm-Bonferroni (Holm 1979) 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 corresponded 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 familywise error rate (FWER) ≤α.

9.4.3 Subgroup analyses

A subgroup analysis may be performed for the primary and key secondary endpoints. Summary tables will be produced by strata (HD, PD, NDD) and, if there are sufficient

numbers of patients in each strata, all statistical analysis of primary and secondary endpoints will be performed by strata (HD, PD, NDD). The subgroup analysis will be performed using the same analysis methods as described in Sections 9.4.1 and 9.4.2. Further details will be provided in the SAP.

9.4.4 Safety analyses

All safety analyses will be performed on the safety analysis set and will be analyzed descriptively.

Adverse events (and also separately SAEs) will be summarized by study treatment group by incidence summaries by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

Laboratory data for hematology, clinical chemistry and liver function test will be summarized by visit and study treatment group.

Vital signs will be summarized by visit and study treatment group.

9.5 Interim analyses

No interim analysis will be conducted for this study. 9.4.1

9.5.1 Data monitoring committee

No data monitoring committee (DMC) will be utilized for this study.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the Clinical Study Protocol (CSP) and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The CSP, CSP amendments, informed consent form (ICF), Investigator's Brochure (IB) if applicable, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the CSP will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators

are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

If a patient's partner becomes pregnant in the period from the date of the first dose until at least 7 days after the last dose of roxadustat, then the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study patients" and provide information about the pregnancy accordingly.

Patients who are rescreened are required to sign a new ICF.

A 4 Data protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical study will be available on *http://astrazenecaclinicaltrials.com* as will the summary of the main study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on electronic case report form (eCRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the source data agreement and computerized data check list for electronic source data.

A 9 Study and site closure

The Sponsor designee reserves the right to close the study sites or terminate the study at any time for any reason at the sole discretion of the Sponsor. The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study treatment
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of study treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patient's interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the CSP, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator

- Discontinuation of further study treatment development

A 10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

The Sponsor publishes clinical study and other medically important research results, whether positive, negative or inconclusive, while protecting patient confidentiality.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram [ECG]). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, screening, run-in, treatment, follow-up) and fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Adverse Events for malignant tumours reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a non-serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

B 3 Definition of adverse drug reactions

An adverse drug reaction (ADR) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

B 4 Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 5 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 6 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 7 Intensity rating scale:

The Investigator should use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version ≥5.0. For terms not specified as part of NCI-CTCAE, the following guidelines should be used to determine grade:

- **Grade 1, Mild:** Asymptomatic or mild symptoms that the patient finds easily tolerated. The event is of little concern to the patient and/or of little-or-no clinical significance; clinical or diagnostic observations only; intervention not indicated
- **Grade 2, Moderate:** The patient has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or non-invasive intervention indicated
- **Grade 3, Severe:** The patient is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the patient and/or poses substantial risk to the patient's health or well-being; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization
- **Grade 4, Life-threatening:** The patient was at immediate risk of death from the event as it occurred
- **Grade 5, Death:** Related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 8 A guide to interpreting the causality question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease-under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 9 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study treatment that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient

- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding interactive voice response system [IVRS] errors)
- Wrong drug administered to patient (excluding IVRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS – including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused study treatment or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following United Nations (UN) number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

Exempt – all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (**http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm**)
- **Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content**
- International Airline Transportation Association compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report potential Hy's law (PHL cases and Hy's Law (HL) cases). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine aminotransferase (ALT) from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the study treatment.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting serious AEs (SAEs) and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** TBL ≥ 2×ULN at any point during the study following the start of study treatment irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
Aspartate aminotransferase or ALT ≥ 3× ULN **together with** TBL ≥ 2×ULN, where no other reason, other than the study treatment, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

D 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

When a patient meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory electronic case report form (eCRF) module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol (CSP).

D 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central study team.

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For patients that met PHL criteria prior to starting study treatment, the Investigator is not required to submit a PHL SAE unless there is a significant change in the patient's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

D 5 Review and assessment of Potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study treatment, to ensure timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study treatment:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to study treatment and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions required for repeat episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease-under study (eg, chronic or progressing malignant disease, severe infection or liver disease),

If **No**: Follow the process described in Appendix D 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.

- If there is a significant change, follow the process described in Appendix D 4.2 for reporting PHL as an SAE.

  Note: A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

D 7 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgement. If required, additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

Table 6 Hy's Law laboratory kit for central laboratories

Additional standard chemistry and coagulation tests	gamma-glutamyl transferase (GGT) Lactate dehydrogenase (LDH) Prothrombin time International normalized ratio (INR)
Viral hepatitis	Immunoglobulin M (IgM) anti-hepatitis A virus (HAV) IgM and immunoglobulin G (IgG) anti-hepatitis B core antibody (HBc) Hepatitis B surface antigen (HbsAg) Hepatitis V virus deoxyribonucleic acid (HBV DNA) IgG anti-hepatitis C virus (HCV) Hepatitis C virus ribonucleic acid (HCV RNA) [a] IgM anti-hepatitis E virus (HEV) HEV RNA
Other viral infections	IgM and IgG anti-cytomegalovirus (CMV) IgM and IgG anti-herpes simplex virus (HSV) IgM and IgG anti-Epstein-Barr virus (EBV)
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [b]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a] HCV RNA is only tested when IgG anti-HCV is positive or inconclusive.

[b] Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly.

REFERENCES

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H et al: Case definition and phenotype standardization in drug-induced liver injury. Clinical Pharmacology and Therapeutics 2011; 89(6):806-15.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix E Abbreviations

Abbreviation	Explanation
ADR	Adverse drug reactions
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Arteriovenous
BIW	2 times a week
BP	Blood pressure
CHF	Congestive heart failure
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CRP	C-reactive protein
CSR	Clinical study report
CSP	Clinical study protocol
CV	cardiovascular
DD	Dialysis-dependent
DILI	Drug-induced liver injury
DMC	Data monitoring committee
DUS	Disease-under study
ECG	Electrocardiogram
ECode	Enrollment code
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EDC	Electronic data capture
EOS	End of study
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
ESRD	End-stage renal disease
FAS	Full analysis set
FWER	Familywise error rate

Abbreviation	Explanation
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
HD	Hemodialysis
HIF	Hypoxia inducible factor
HL	Hy's Law
hs-CRP	High-sensitivity C-reactive protein
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Incident dialysis
IEC	Independent ethics committee
IRB	Institutional review board
IU	International Unit
IV	Intravenous
IVRS	Interactive voice response system
KDOQI	Kidney Disease Outcomes Quality Initiative
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
LLN	Lower limit of normal
NDD	Non-dialysis dependent
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	Peritoneal dialysis
PHI	Prolyl hydroxylase inhibitor
PHL	Potential Hy's law
PP	Per-protocol
PT	Preferred Term
QT	Interval between the Q and T waves of an electrocardiogram
RBC	Red blood cell
rHuEPO	Recombinant human erythropoietin
SADRs	Serious adverse drug reactions
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous

Abbreviation	Explanation
SD	Standard deviation
SoA	Schedule of activities
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reactions
TIBC	Total iron binding capacity
TBL	Total bilirubin
TCM	Traditional Chinese medicine
TIW	3 times a week
TMF	Trial Master File
TSAT	Transferrin saturation
ULN	Upper limit of normal
UN	United Nations
WBDC	Web-Based Data Capture

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