A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis

ISN/Protocol 1517-CL-0613

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Sponsor: Astellas Pharma Europe B.V. (APEB)

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A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis

Protocol for Phase 3 Study of Roxadustat (ASP1517/FG-4592)[a]

ISN/Protocol 1517-CL-0613

Version 3.0

Incorporating Substantial Amendment 2 [See Attachment 1]

30 May 2017

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Sponsor:

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***Investigator**:* Investigator information is on file at Astellas

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[a] The INN of the compound is roxadustat. FG-4592 is the code name used by FibroGen Inc. to describe the investigational product. The development partner Astellas uses the code ASP1517. Both codes refer to the same product as the INN.

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g. Protocol authors, sponsor's reviewers and contributors, etc.) are located in Section 14. Sponsor's Signatures; e-signatures (when applicable) are located at the end of this document.

2. COORDINATING INVESTIGATOR'S SIGNATURE

A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis

ISN/Protocol 1517-CL-0613

Version 3.0 / Incorporating Substantial Amendment 2

30 May 2017

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: ---------- ----------
Date (DD Mmm YYYY)

Printed Name: ----------

Address: ----------

----

3. INVESTIGATOR'S SIGNATURE

A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis

ISN/Protocol 1517-CL-0613

Version 3.0 / Incorporating Substantial Amendment 2

30 May 2017

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ----------

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Astellas Contact for Serious Adverse Events (SAEs) See Section 5.5.5	**Astellas Pharma Europe B.V.** **Product Safety & Pharmacovigilance** **Fax : +31 71 545 5208** **Email: safety-eu@astellas.com**
Medical Monitor:	[redacted]
Clinical Research Contact:	[redacted]

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
α1-AGP	Alpha 1-Acid Glycoprotein
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
anti-HCV Ab	Anti-hepatitis C Virus antibody
APD	Automated peritoneal dialysis
APEB	Astellas Pharma Europe BV
ASP1517	=FG-4592; codename of investigational product roxadustat
AST	Aspartate Aminotransferase
BIW	twice weekly
BL	Baseline
BL Hb	Baseline Hemoglobin (please refer to key definitions for information)
CAPD	Continuous ambulatory peritoneal dialysis
CHMP	Committee for Medicinal Products for Human Use
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CI	Confidence interval
CKD	Chronic Kidney Disease
C_{max}	Maximum concentration
CRO	Contract Research Organization
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EPO	Erythropoietin
EQ-5D 5L	European Quality of Life 5 Domain 5 Level
ESA	Erythropoiesis Stimulating Agent
ESRD	End Stage Renal Disease
EU	European Union
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	Food and Drug Administration
FAS	Full Analysis Set
FG-4592	=ASP1517; codename of investigational product roxadustat
GCP	Good Clinical Practice
Hb	Hemoglobin
HbA1c	Hemoglobin A1c; Glycated hemoglobin
HBsAG	Hepatitis B Surface Antigen
HD	Hemodialysis
HDF	Hemodiafiltration
HDL	High-density Lipoprotein
HIF	Hypoxia-inducible Factor

Abbreviations	Description of abbreviations
HIF-PH	HIF Prolyl Hydroxylase
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
hs-CRP	High Sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
IRS	Interactive Response System
IUD	Intra Uterine Device
IUS	Intra Uterine System
ISN	International Study Number
ITT	Intention to Treat Set
IV	Intravenous(ly)
k_a	First order absorption rate constant
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	Kilogram
LDL	Low-density Lipoprotein
LA-CRF	Liver Abnormality Case Report Form
LFT	Liver Function Tests
LOCF	Last Observation Carried Forward
MACE	Major cardiovascular adverse events: myocardial infarction, stroke, death from all causes
MACE+	Myocardial infarction, stroke, death from all causes, chronic heart failure requiring hospitalization, unstable angina requiring hospitalization
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliters
MMRM	Mixed Model of Repeated Measures
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
OATP1B1	Organic anion transporting polypeptide 1B1
PD	Peritoneal Dialysis
PF	Physical Functioning
PGIC	Patients' Global Impression of Change
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
QoL	Quality of Life
QTc	QT Interval corrected for heart rate
QW	Once weekly
RBC	Red Blood Cell
r-HuEPO	Recombinant Human Erythropoietin
SAE	Serious Adverse Event
SAF	Safety Analysis Set

Abbreviations	Description of abbreviations
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Subcutaneous(ly)
SI	International System of Units
SF-36	Short Form 36
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TIBC	Total Iron Binding Capacity
TIW	Three times weekly
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	Transferrin Saturation
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USRDS	United States Renal Data System
VAS	Visual Analogue Scale
VT	Vitality
WBC	White Blood Cell Count
Wk(s)	Week(s)

List of Key Study Terms

Terms	Definition of terms
Adverse Event	An adverse event (AE) is any untoward medical occurrence in a subject administered study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. AE collection starts after obtaining signed informed consent and continues until the End of Study (EOS) visit. Serious adverse events (SAEs) and cardiovascular and thromboembolic AEs will be collected during the poststudy follow-up period. AEs will not be collected during the period between first screen where subject has failed screening and first rescreening visit.
Baseline	1) Observed values/findings, which are regarded, as calibrated zero status in the present study; 2) Time when 'Baseline' is observed.
Baseline Hemoglobin (Hb) value	Mean of 4 Hb values: the 3 Screening Hb values and the Hb value at the day of randomization, all assessed by the central laboratory.
Discontinuation	The act of concluding participation in either the study treatment or the study, prior to completion of all protocol-required elements, in a study by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: active discontinuation by a subject (also a noun referring to such a discontinued subject); b) investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard.
Enroll	To register or enter into a clinical study; transitive and intransitive. Informed consent precedes enrollment, which precedes randomization.
Hb Response	Mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL.
Post study follow-up	Period of time from the actual EOS visit to the projected EOS visit or until consent withdrawn. This period is only applicable to subjects who prematurely discontinued treatment. These subjects will be followed up at a 6-monthly frequency for vital status, SAEs and cardiovascular and thromboembolic AEs.
Randomization	The process of assigning study subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. (after randomization subjects receive either roxadustat or ESA [epoetin alfa or darbepoetin alfa] from day 1 until End Of Treatment [EOT]).
Re-screening	Process of repeating screening. If subject fails screening they may be re-screened once if deemed appropriate; all screening procedures will be repeated. Renal ultrasound only to be repeated if not within 12 weeks prior to randomization.
Screening	A process of active consideration of potential subjects for enrollment in a study.

Terms	Definition of terms
Screening Hb value	Mean of subject's 3 most recent screening Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart. The last Hb value must be within 10 days prior to the randomization visit (day 1).
Screen / Re-screen failure	Potential subject who did not meet one or more criteria required for participation in a study during screening or re-screening.
Serious Adverse Event	An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: results in death, is life threatening, results in persistent or significant disability / incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly, or birth defect, requires in-subject hospitalization or leads to prolongation of hospitalization, or a medically important event.
Study period	Period of time from first subject screened to end of the last scheduled visit of the last subject randomized.
Subject	An individual who participates in a clinical study.
Treatment period	It is the period of time - between first dose of the study drug and EOT visit where major interests of protocol objectives are observed, and where roxadustat (test drug), epoetin alfa or darbepoetin alfa (comparative drugs) is given to a subject.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	30 May 2017, Version 3.0
Sponsor: Astellas Pharma Europe BV (APEB)	**Protocol Number:** 1517-CL-0613
Name of Study Drug: Roxadustat	**Phase of Development:** Phase 3
Title of Study: A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis	
Planned Study Period: From 4Q2014 to 3Q2018	
Study Objective(s): The primary objective of this study is to evaluate the efficacy of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in End Stage Renal Disease (ESRD) subjects on stable dialysis. The secondary objectives of this study are to: ● Evaluate the safety of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in ESRD subjects on stable dialysis. ● Evaluate the effects on health-related quality of life of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in ESRD subjects on stable dialysis.	
Planned Total Number of Study Centers and Locations: Approximately 150 centers Global	
Study Population: The study population consists of adult subjects with ESRD who are on stable hemodialysis (HD) or peritoneal dialysis (PD) and on stable treatment with epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa for anemia. Subjects on polyethylene glycol-epoetin beta (Mircera®) are not to be included. Subjects on hemodiafiltration are also allowed to participate in the study and will follow the same study procedures and requirements as HD subjects.	
Number of Subjects to be Randomized: ● 750 ● Approximately 400 subjects pretreated with epoetin and approximately 350 subjects pretreated with darbepoetin alfa.	
Study Design Overview: This is a phase 3, multicenter, randomized, open-label, active-controlled study. The study will consist of 3 study periods: ● Screening Period: up to 6 weeks ● Treatment Period: For all subjects in the study the minimum treatment duration will be 52 weeks and the maximum treatment duration will be 104 weeks. The study end date will be declared when the targeted number of MACE* and MACE+** events have been reported across the roxadustat phase 3 development program and consequently the treatment will end for all subjects who have completed 52 weeks at that point. Subjects who have not completed 52 weeks when	

the target has been declared will continue until they reach 52 weeks and at that point their treatment will end.

- Follow-up Period: 4 weeks

  * MACE: Major cardiovascular adverse events: myocardial infarction, stroke, death from all causes

  ** MACE+: Myocardial infarction, stroke, death from all causes, chronic heart failure requiring hospitalization, unstable angina requiring hospitalization

During the course of the study, visits and assessments will be performed as defined in the Schedule of Assessments.

Screening Period

During the screening period of up to 42 days eligibility assessments will be performed. Subjects in screening will continue treatment with epoetin or darbepoetin alfa per local standard of care.

Treatment Period

Subjects are randomized to 1 of 2 treatment arms as illustrated in Table 1 below.

- Treatment arm 1: subjects will be switched from epoetin or darbepoetin alfa treatment to roxadustat treatment (see Table 2 for doses).
- Treatment arm 2: subjects will continue erythropoiesis stimulating agent (ESA) treatment, i.e. epoetin alfa if pretreated with any epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) and darbepoetin alfa if pretreated with darbepoetin alfa, at approximately the same average weekly dose the subject was on prior to randomization. It is not allowed to switch from epoetin alfa to darbepoetin alfa or vice versa, during the treatment period. Subjects on polyethylene glycol-epoetin beta (Mircera®) are not to be included.

The randomization will result in an overall 1:1 ratio of subjects receiving roxadustat administered orally, or epoetin alfa or darbepoetin alfa administered as subcutaneous (SC) or intravenous (IV) injection. Study treatment administration is implemented in an open-label manner.

Randomization to treatment arms will occur through an Interactive Response System.

Table 1: Treatment Arms, Dosing Frequency and Subject Numbers

Treatment Arms	Study Treatment	Dosing Frequency	N
1	roxadustat	TIW	375
2	ESA	Dosing per SmPC	375

TIW = 3 times weekly; ESA = Erythropoiesis Stimulating Agent (epoetin alfa or darbepoetin alfa)
SmPC = Summary of Product Characteristics

During the treatment period, subjects will attend weekly study visits from day 1 to week 8, followed by every other week study visits from week 10 to 36. Following week 36, study visits will occur every 4 weeks until the End of Treatment (EOT).

Randomization and administration of the first dose of study treatment (roxadustat or ESA) is to occur on day 1, which should correspond to a day when their next dose of epoetin or darbepoetin alfa would have been administered.

On day 1, all study procedures and assessments will be completed prior to the first study treatment administration.

During the treatment period, the aim is to maintain the hemoglobin (Hb) levels between 10.0 g/dL and 12.0 g/dL. All subjects receiving roxadustat will initiate and continue roxadustat dosing at a dosing frequency of 3 times weekly (TIW) throughout the entire period and dose adjustment is to follow prespecified dose adjustment rules (see Table 3). Intake should occur at approximately the same time of day and, if possible, dosing days should remain consistent throughout the study. For HD subjects it is recommended that roxadustat is administered any time after completion of dialysis if dosing is

scheduled on a dialysis day to avoid potential bias on certain study assessments. Specific rules apply on the dialysis day(s) at which pharmacokinetic (PK) sampling is scheduled.

During the treatment period, the active comparator drugs epoetin alfa (Eprex®) and darbepoetin alfa (Aranesp®) will be provided by the sponsor. Dosing, dosing frequencies and dose adjustments should be in accordance with the UK Summary of Product Characteristics (SmPC) for Eprex® and EU SmPC for Aranesp®. The protocol-specified frequencies are once weekly, twice weekly or TIW for epoetin alfa; and once weekly or once every other week for darbepoetin alfa. In addition, the protocol allows for administration of epoetin alfa once every other week and darbepoetin alfa once every 4 weeks. These frequencies are only to be used in subjects on low ESA doses that do not fit into the normal frequencies of administration and if deemed clinically appropriate. For PD subjects, darbepoetin dosing every 4 weeks is allowed.

For both treatment arms dose adjustments are to be made based on Hb values using HemoCue®, a point-of-care device.

Subjects will receive study treatment (roxadustat or ESA) for a minimum of 52 weeks and a maximum of 104 weeks.

Follow-up Period

After EOT period subjects will proceed to the 4-week follow-up period. The choice of anemia treatment during the follow-up period is at the discretion of the investigator.

Poststudy Follow-up *(for premature treatment discontinued subjects only)*

Subjects that have prematurely discontinued study treatment will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and End of Study (EOS) visit. Thereafter, these subjects (only if they have taken at least 1 dose of study drug) will continue to be followed up at a 6-monthly frequency for vital status, serious adverse events (SAEs) and cardiovascular and thromboembolic adverse events (AEs) until their projected date of completion of the follow-up period (i.e. projected EOS visit) or until consent withdrawn.

Data Safety Monitoring Board/Independent Event Review Committee

A Data Safety Monitoring Board (DSMB) will review prespecified safety data periodically in collaboration with the sponsor to ensure subject safety. Details will be specified in a DSMB charter.

An Independent Event Review Committee will adjudicate all relevant cardiovascular and cerebrovascular events in a blinded manner to ensure consistent safety assessment. Details will be specified in an Independent Event Review Committee charter.

Optional Genotyping Sample

Optional genotyping sampling for subjects randomized to the roxadustat arm will be included in this study. If a separate (optional) informed consent is signed by the subject, a 5 mL whole blood sample for genotyping will be collected after randomization, preferably on day 1.

Selection Criteria:

Inclusion

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations has been obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject age is ≥18 years.

3. Subject is on stable HD, HDF or PD treatment with the same mode of dialysis for ≥4 months prior to randomization.
4. For subject receiving HD or HDF, the vascular access must be via native arteriovenous (AV) fistula or graft, or permanent, tunneled catheter.
5. Subject is on IV or SC epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or IV or SC darbepoetin alfa treatment for ≥8 weeks prior to randomization with stable weekly doses (≤ 30% change from the maximum prescribed average weekly dose, i.e. ([max-min]/max≤ 0.3) during 4 weeks prior to randomization. Subjects on polyethylene glycol-epoetin beta (Mircera®) are not to be included.
6. Mean of the subject's 3 most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart, must be ≥9.5 g/dL and ≤12.0 g/dL with an absolute difference ≤1.3 g/dL between the highest and the lowest value. The last Hb value must be within 10 days prior to the randomization visit (Day 1).
7. Subject has a ferritin level ≥100 ng/mL (≥220 pmol/L) at screening.
8. Subject has a transferrin saturation (TSAT) level ≥20% at screening.
9. Subject has a serum folate level ≥ lower limit of normal (LLN) at screening.
10. Subject has a serum vitamin B_{12} level ≥ LLN at screening.
11. Subject's alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are ≤3 x upper limit of normal (ULN), and total bilirubin (TBL) is ≤1.5 x ULN.
12. Subject's body weight (postdialysis weight) is 45.0 kg to a maximum of 160.0 kg.
13. Female subject is either:

    Of non-childbearing potential:
    - postmenopausal (defined as at least 1 year without any menses) prior to screening, or
    - documented surgically sterile

    Or if of childbearing potential:
    - agree not to try to become pregnant during the study and for 28 days after the final study drug administration.
    - must have a negative serum pregnancy test at screening, and
    - if heterosexually active, agree to consistently use a highly effective form of birth control* starting at screening and throughout the study period, and continue to do so for 28 days after the last study treatment administration. If required by local law, 2 highly effective methods of birth control must be used, 1 of which must be a barrier method.
14. Female subject must agree not to breastfeed starting at screening or during the study period, and continue to do so for 28 days after the final study treatment administration.
15. Female subject must not donate ova starting at screening and throughout the study period and continue to do so for 28 days after final study treatment administration.
16. Male subject and their female spouse/partner(s) who are of childbearing potential must be using a highly effective form of birth control starting at screening and continue to do so throughout the study period, and for 12 weeks after final study treatment administration. If required by local law, 2 highly effective methods of birth control must be used, 1 of which must be a barrier method.
17. Male subject must not donate sperm starting from screening, throughout the study period and up to 12 weeks after final study drug administration.

18. Subject agrees not to participate in another interventional study from the time of signing informed consent until the EOS visit.

    * Highly effective forms of birth control include:
    - Consistent and correct usage of established oral contraception.
    - Injected or implanted hormonal methods of contraception.
    - Established intrauterine device (IUD) or intrauterine system (IUS).
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (if allowed by local regulations).
    - Any male partner that has undergone effective surgical sterilization.
    - Any female partner that has undergone effective surgical sterilization, if applicable.

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion:

Subject will be excluded from participation if any of the following apply:

1. Subject has received a Red Blood Cell (RBC) transfusion within 8 weeks prior to randomization.
2. Subject has a known history of myelodysplastic syndrome or multiple myeloma.
3. Subject has a known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia, or other known causes for anemia other than Chronic Kidney Disease (CKD).
4. Subject has a known hemosiderosis, hemochromatosis, coagulation disorder, or hyper-coagulable condition.
5. Subject has a known chronic inflammatory disease that could impact erythropoiesis (e.g., systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission.
6. Subject is anticipated to undergo elective surgery that is expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization.
7. Subject has active or chronic gastrointestinal bleeding.
8. Subject has received any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor.
9. Subject has been treated with iron-chelating agents within 4 weeks prior to randomization.
10. Subject has a history of chronic liver disease (e.g. cirrhosis or fibrosis of the liver).
11. Subject has known New York Heart Association Class III or IV congestive heart failure.
12. Subject has had a myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thrombo-embolic event (e.g., deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.
13. Subject has had uncontrolled hypertension, in the opinion of the investigator, within two weeks prior to randomization
14. Subject has known hypersensitivity to epoetin alfa (Eprex®), darbepoetin alfa (Aranesp®) or any of their excipients.
15. Subject has a diagnosis or suspicion (e.g., complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma as shown on renal ultrasound, or another appropriate imaging method, within 12 weeks prior to randomization.
16. Subject has a history of malignancy, except for 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.

17. Subject is positive for any of the following:
    - human immunodeficiency virus (HIV)
    - hepatitis B surface antigen (HBsAg), or
    - anti-hepatitis C virus antibodies (anti-HCV Ab)
18. Subject has an active clinically significant infection manifested by White Blood Count (WBC) > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection within 1 week prior to randomization.
19. Subject has a known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion.
20. Subject has had any prior organ transplant (that has not been explanted), or subject is scheduled for organ transplantation.
21. Subject has participated in any interventional clinical study or has been treated with any investigational drugs within 30 days or 5 half lives or limit set by national law, whichever is longer, prior to the initiation of screening.
22. Subject has an anticipated use of dapsone in any dose amount or anticipated chronic use of acetaminophen/paracetamol >2.0 g/day during the treatment or follow-up period of the study.
23. Subject has a history of alcohol or drug abuse within 2 years prior to randomization.
24. Subject has any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation.

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Products:
Roxadustat

- Tablets
- Strengths of 20 mg, 50 mg and 100 mg

Mode of Administration:
Oral

Doses:
The initial study drug (roxadustat) dose is based on the dosing scheme shown in Table 2 and is determined by the subject's average prescribed weekly dose of epoetin or darbepoetin alfa within 4 weeks prior to randomization.

Table 2: Initial Dose of Roxadustat

epoetin† (IU/week)	**darbepoetin alfa†** (µg/week)	**roxadustat** (mg/dose) TIW
<8,000	<40	100
8,000 to 16,000	40-80	150‡
>16,000	>80	200§

TIW: 3 times weekly
† Average prescribed weekly dose in the last 4 weeks prior to randomization.
‡ If the initial dose of 150 mg exceeds the maximum dose of 3.0 mg/kg, then 100 mg is to be used as the starting dose.
§ If the initial dose of 200 mg exceeds the maximum dose of 3.0 mg/kg, then 150 mg is to be used as the starting dose.

After randomization, roxadustat will be dosed TIW for the entire duration of the treatment period. The dose of roxadustat will remain constant during the first 4 weeks of the treatment period. After week 4, dose adjustments are permitted on a 4-weekly interval and will be aimed at keeping subjects' Hb levels between 10.0 to 12.0 g/dL. Dose adjustments will be based upon current Hb and change in Hb over the preceding 4 weeks as illustrated in Table 3 (deviation from the 4-week period is allowed anytime during the study in case of excessive hematopoiesis or Hb ≥13.0 g/dL).

Table 3: Dose Adjustment Rules for Roxadustat

Change in Hb Over Past 4 Weeks (g/dL)[a]	**Hb (g/dL)**		
	<10.5	**10.5 to <12.0**	**12.0 to <13.0**
< -1.0	↑	↑	No change
-1.0 to 1.0	↑	No change	↓
> 1.0	No change	↓	↓

Hb: hemoglobin
[a] Subtract first Hb value from last value Hb to calculate the change

- All dose adjustments are made based on Hb values using HemoCue®, a point-of-care device.
- Dose increases by 1 dose step (↑) and reductions by 1 dose step (↓) are pre-set
- If the dose adjustment is 'No change' per the above table, the dose remains unchanged and the next dose adjustment review is 4 weeks after that visit.
- The dose steps for roxadustat are as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.
- The maximum dose is the dose step corresponding to 3.0 mg/kg (based on postdialysis weight in HD subjects and in PD subjects weight minus abdominal fluid based on last filling) per administration or 400 mg, whichever is lower. At study visits where weight is collected the default weight and maximum allowed dose step for a subject will be adjusted if the weight change is ≥ 5% compared to the previous default weight collected in the study. Initial default weight is weight at randomization visit.
- If there is a safety concern, investigators may deviate from the dose adjustment rules for roxadustat. This should be discussed with the medical monitor and documented in the source documentation.
- Contact the medical monitor if dose adjustments would lead to doses outside the limits of the dose step range; i.e. lower than 20 mg or higher than 400 mg.

In the following cases dose adjustment may be made at any time outside the 4-weekly interval:

- Dose reduction in case of excessive hematopoiesis
- Dose increase by 1 step in case subject Hb < 9.0 g/dL (HemoCue®) and no dose adjustment occurred in the preceding 4 weeks.

<u>At any time when Hb ≥13.0 g/dL</u>

- Stop dosing.
- Resume dosing when Hb <12.0 g/dL at a dose that is reduced by 2 steps.
- Next dose adjustment review is 4 weeks after dose resumption and in 4-weekly intervals thereafter.

<u>Dose Adjustment for Excessive Hematopoiesis</u>

At any time during the Treatment Period:

- If Hb increases by >2.0 g/dL within 4 weeks, the dose should be reduced by 1 dose step

<u>Note: Only 1 dose reduction for excessive hematopoiesis is recommended within a period of 4 weeks. If a blood transfusion has been performed or a course of ESA rescue therapy has been administered within 2 weeks of meeting the criteria for excessive hematopoiesis, it is recommended not to perform a dose reduction for excessive hematopoiesis.</u>

After a dose adjustment due to excessive hematopoiesis, the subject's next dose adjustment review will occur 4 weeks later, and in 4-weekly intervals thereafter.

If the dose adjustment interval falls on a non-visit study week, the dose adjustment review should be performed at the next scheduled study visit.

Comparative Drug:
ESA: epoetin alfa or darbepoetin alfa

Subjects pretreated with epoetin:	Subjects pretreated with darbepoetin alfa:
Epoetin alfa (Eprex®)	Darbepoetin alfa (Aranesp®)

Mode of Administration:
IV or SC injection (both ESAs).

All administrations will be performed by the investigator or a qualified member of the site staff, by the subject themselves or caregiver, e.g. relative, if well trained and willing to self-administer.

Dose(s):
Subjects that are randomized to the ESA arm will receive their ESA at approximately the same average weekly dose the subject was on prior to randomization using the same mode of application (intravenous [IV] or subcutaneous [SC] injection).
During the treatment period, the active comparator drugs epoetin alfa (Eprex®) and darbepoetin alfa (Aranesp®) will be provided by the sponsor. Dosing, dosing frequencies and dose adjustments should be in accordance with the UK SmPC for Eprex® and EU SmPC for Aranesp®. The protocol-specified frequencies are once weekly, twice weekly or TIW for epoetin alfa; and once weekly or once every other week for darbepoetin alfa. In addition, the protocol allows for administration of epoetin alfa once every other week and darbepoetin alfa once every 4 weeks. These frequencies are only to be used in subjects on low ESA doses that do not fit into the normal frequencies of administration and if deemed clinically appropriate. For PD subjects, darbepoetin dosing every 4 weeks is allowed. For both ESAs the target of treatment is maintaining Hb in the range of 10.0 to 12.0 g/dL. Contact the medical monitor if dose adjustments would lead to doses lower than 1000 IU epoetin once every other week or 10 µg darbepoetin once every 4 weeks.

Initial dose:

The initial ESA dose and frequency of administration are at the investigator's discretion provided the average weekly dose remains approximately the same as prior to randomization. All subjects randomized to the ESA arm must receive their ESA dose according to the protocol-specified frequencies irrespective of their frequency of administration prior to randomization.

All dose adjustments are made based on Hb values using HemoCue®, a point-of-care device.

Rescue Therapy:
Rescue therapy guidelines are provided to optimize standardization of rescue therapy by investigators and to ensure safety of the individual study subjects.

1. RBC Transfusion (for all subjects)

RBC transfusion is allowed if rapid correction of anemia is required to stabilize the patient's condition or the investigator is of the opinion that the blood transfusion is a medical necessity. Study treatment may continue during or after transfusion administration.

2. ESA (only for subjects treated with roxadustat)

One course of rescue ESA is allowed. If the investigator considers administration of ESA as a medical necessity, 1 course of rescue ESA may be initiated if the following criteria are met:

- the Hb level has not responded adequately despite two or more roxadustat dose increases in the previous 8 weeks or the roxadustat dose has reached the maximum dose limit, and

- the subject's Hb level is < 9.0 g/dL (HemoCue®) as confirmed at 2 consecutive study visits, and
- reducing the risk of alloimmunization in transplant eligible subjects and/or reduction of other RBC transfusion-related risks is a goal.

Prior to the initiation of rescue ESA (epoetin alfa for subjects treated with any epoetin prior to randomization; and darbepoetin alfa for subjects treated with darbepoetin alfa prior to randomization), the subject's Hb response, as well as factors influencing the Hb response, such as iron status, inflammatory status, hemolysis, blood loss or other potential reasons for Hb decrease should be considered and, where applicable, be addressed by the investigator. Prior to initiating ESA rescue therapy iron deficiency should be corrected (i.e. 100 ng/mL [220 pmol/L] ferritin and 20% TSAT).

The subject may continue on study, however, the subject is not allowed to be administered both rescue ESA and roxadustat during the same time period. The course of rescue ESA (i.e. the amount that may be administered) will be limited by duration of therapy and effect on Hb, including that 1 course of treatment with rescue ESA will not exceed 4 weeks in duration, and that ESA rescue will be stopped as soon as Hb ≥9.0 g/dL as measured by HemoCue. Treatment with roxadustat may be resumed as soon as possible after the following intervals:

- At least 2 days after stop of epoetin alfa
- At least 1 week after stop of darbepoetin alfa

If a subject requires a second course of rescue with ESAs, the subject must be discontinued from study treatment. The subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit, and will continue to be followed up at a 6-monthly frequency for vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion or until consent withdrawn.

Doses:
The doses of rescue therapies are at investigator's discretion.

Emergency Procedure:
Therapeutic Phlebotomy
If there are clinical concerns for a subject's high Hb level, the investigator may decide to perform a therapeutic phlebotomy instead of, or in addition to, a study treatment dose hold – this should be documented in the electronic Case Report Form and source documents, and discussed with the study medical monitor.

Concomitant Medication Restrictions and/or Requirements:

Supplemental Iron

1. Subjects receiving roxadustat

a. Oral iron

For subjects receiving roxadustat, oral iron is recommended for supplementation to support erythropoiesis and as first-line treatment for iron deficiency, unless the subject is intolerant to this treatment. The recommended daily dose is 200 mg of elemental iron. Subjects should be advised to take roxadustat at least 1 h before or 1 h after oral iron.

b. Intravenous iron

For subjects receiving roxadustat, IV iron supplementation is allowed if all of the following criteria are met:

- The subject's Hb level has not responded adequately to roxadustat following two consecutive dose increases or reached the maximum dose limit, **and**
- The subject's ferritin is <100 ng/mL (<220 pmol/L) **or** TSAT < 20%, or the subject is intolerant of oral iron therapy.

Treatment with roxadustat should continue during IV iron administration. Discontinuation of IV iron administration is recommended once ferritin levels are ≥100 ng/mL (≥220 pmol/L) and TSAT ≥20%. Serum ferritin and TSAT can be measured at any time after IV iron delivery at the discretion of the investigator.

2. *Subjects receiving epoetin alfa or darbepoetin alfa*

For subjects treated with epoetin alfa or darbepoetin alfa, IV iron supplementation will be given according to standard of care.

Antihypertensive and Lipid-lowering Medication

To avoid confounding effects on study endpoints, changes to antihypertensive and lipid lowering medications should be minimized as much as possible, and made only if deemed medically necessary by the investigator.

Prohibited Medication

The following medications are prohibited during the period identified:

- Any investigational drug: within 30 days or 5 half lives or limit set by national law (whichever is longer), prior to the initiation of screening until EOS.
- Roxadustat or another hypoxia-inducible factor prolyl hydroxylase inhibitor: at any time prior to randomization. After randomization any hypoxia-inducible factor prolyl hydroxylase inhibitor other than roxadustat, as allocated by randomization, until EOS.
- Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy): from 4 weeks prior to randomization until EOS.
- Androgens: From randomization onwards until EOS.
- Dapsone in any dose amount, or chronic doses of acetaminophen/paracetamol >2.0 g/day, from randomization until EOS.

Use of herbal medicines is discouraged during the course of the study.

Duration of Treatment:
52 weeks to 104 weeks

Formal Stopping Rules
Subjects should be **prematurely discontinued from study treatment** for any of the following reasons:

- Physician decision that it is in the best interest of the subject to be discontinued from study treatment.
- Significant noncompliance with study procedures, as determined by principal investigator and/or sponsor.
- Pregnancy in a study subject.
- Subject no longer consents to participate in treatment phase of the study.
- Subject receives an organ transplant
- Subject randomized to roxadustat who requires a second course of ESA rescue therapy

If subjects have prematurely discontinued study treatment (and have taken at least 1 dose of study drug), they will continue to be followed up at a 6-monthly frequency for the subject's vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of follow-up period (i.e. projected EOS visit) or until consent withdrawn.

Subjects should be **withdrawn from the study** for any of the following reasons:

- Subject no longer consents to participate in the study.
- Subject is lost to follow-up despite reasonable efforts by the investigator to contact the subject.

The sponsor may decide to prematurely stop the entire study, e.g. for safety considerations.

Endpoints for Evaluation:

Primary

There are 2 separate regionally based primary efficacy endpoints in this study, depending upon whether the data are being filed to support submission to the US FDA or to Ex-US health authorities, such as the EMA.

- The EU (EMA) primary efficacy endpoint is change in Hb from baseline (BL) to the average level during the evaluation period (defined as week 28 until week 36), without having received rescue therapy (i.e. RBC transfusion for all subjects or ESA for subjects treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period.
- The US (FDA) primary efficacy endpoint is change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 52), regardless of rescue therapy.

Key Secondary

- Hb response defined as mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
- Change from BL in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol of weeks 12 to 28.
- Mean monthly IV iron use (mg) during day 1 to week 36 (monthly defined as a period of 4 weeks).
- Change from BL in Short Form 36 (SF-36) Physical Functioning (PF) sub-score to the average PF sub-score of weeks 12 to 28.
- Change from BL in SF-36 Vitality (VT) sub-score to the average VT sub-score of weeks 12 to 28.
- Blood pressure effect
    - Change from BL in mean arterial pressure (MAP) to the average MAP value of weeks 20 to 28.
    - Time to an increase in blood pressure: An increase from BL of ≥ 20 mm Hg systolic blood pressure (SBP) and SBP ≥ 170 mmHg or an increase from baseline of ≥15 mmHg diastolic blood pressure (DBP) and DBP ≥ 100 mmHg during weeks 1 to 36.

Additional Secondary

Hb maintenance:

- Hb response during weeks 28 and 36 regardless of use of rescue therapy. Hb response defined as mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL.
- Hb change from BL to each postdosing time point.
- Hb level averaged over weeks 28 to 36, 44 to 52, and 96 to 104 without use of rescue therapy within 6 weeks prior to and during these 8-week evaluation periods.
- Hb change from BL to the average Hb value of weeks 28 to 36, 44 to 52, and 96 to 104 regardless of the use of rescue therapy.
- Proportion of Hb values within 10.0 to 12.0 g/dL in weeks 28 to 36, 44 to 52, and 96 to 104 without use of rescue therapy within 6 weeks prior to and during these 8-week evaluation periods.

Hospitalizations:

- Occurrence (number) of hospitalizations (HD days - including overnight - are not counted as hospitalizations)
- Number of days of hospitalization

Rescue therapy use:

- Having received rescue therapy (composite of RBC transfusions (all subjects) and rescue ESA (roxadustat treated subjects only])
- Having received RBC transfusions
- Number of RBC packs per subject
- Volume of RBC transfused per subject

Iron use:

- Having required IV iron supplementation
- Mean monthly IV iron (mg) per subject during weeks 37-52 and weeks 53-104 (monthly defined as a period of 4 weeks)
- Having required oral iron supplementation
- Mean monthly oral iron (mg) use per subject during day 1 to week 36, weeks 37 to 52, and weeks 53-104 (monthly defined as a period of 4 weeks)

Changes in cholesterol levels, apolipoproteins:

- Change from BL to each postdosing study visit in
  - Total cholesterol
  - LDL/High-density Lipoprotein (HDL) ratio
  - Non-HDL cholesterol
  - Apolipoproteins A1 and B
  - ApoB/ApoA1 ratio
- Occurrence of mean LDL cholesterol <100 mg/dL calculated over weeks 12 to 28

Blood pressure effect:

- Occurrence of achieved antihypertensive treatment goal in CKD subjects (SBP <140 mmHg and DBP <90 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28

Health-related Quality of Life and European Quality of Life 5 Domain 5 Level:

- Change from BL to the average value of weeks 12 to 28 in
  - SF-36 Physical Component Score
  - Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia Score
  - Total Functional Assessment of Cancer Therapy-Anemia Score
  - European Quality of Life 5 Domain 5 Level visual analogue scale Score
- Patients' Global Impression of Change (qualitative assessment)

Hepcidin, Iron status, glycated hemoglobin:

- Changes from BL to each study visit (when measured) in:
  - Serum hepcidin
  - Serum ferritin
  - TSAT
  - Glycated hemoglobin (HbA1c) level

<u>Safety</u>

Safety will be assessed by evaluating the following:

- Occurrence of AEs, SAEs, treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs) and clinically significant changes in laboratory values from BL
- Changes from BL in vital signs, electrocardiogram (ECG) findings and clinical laboratory values
- Occurrence, and time to occurrence, of prespecified adjudicated cardiovascular and cerebrovascular events (will be reported separately). Various region-specific pooled analyses of

prespecified adjudicated cardiovascular and cerebrovascular events (such as major cardiovascular AEs [MACE, MACE+] and other events) will be conducted; these analyses will be detailed in region-specific pooled safety analysis plans.

Statistical Methods:

Sample Size Justification:

The study is sufficiently powered for both regionally-based primary efficacy endpoints. Approximately 750 subjects will be randomized to receive roxadustat or ESA in an open-label fashion in a 1:1 ratio. Randomization will be stratified by the following five factors:

- Previous ESA treatment (epoetin versus darbepoetin alfa)
- Region (region A versus region B*)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No)
- Average prescribed weekly ESA dose in last 4 weeks prior to randomization (≤200 IU/kg epoetin or ≤ 1 μg/kg darbepoetin alfa versus >200 IU/kg epoetin or > 1 μg/kg darbepoetin alfa)
- Screening Hb value (≤11.0 g/dL versus >11.0 g/dL)

* Country assignment to region A and B will be determined based on health care system comparability.

EU (EMA)

Results from simulations of the EU primary efficacy endpoint in stable dialysis subjects suggest that dosing levels of ESA prior to randomization may impact Hb response. Therefore, the EU primary analysis of this study will be tested both in the overall population and in the subgroup of patients defined as subjects with an average prescribed weekly epoetin or darbepoetin dose within the last 4 weeks prior to randomization ≤ 200 IU/kg or ≤ 1 μg/kg respectively, following a parametric chain procedure (Millen et al., 2011; Spiessens et al, 2010). The information fraction will be calculated at the time of database hard lock; it is defined as the number of subjects in the subgroup with respect to the number of subjects in the total study population.

Assuming that the Per Protocol Set (PPS) analysis will consist of 80% of the randomized subjects, 750 randomized subjects will yield approximately 600 subjects in the PPS. The overall 1-sided significance level (alpha) is fixed at 0.025 and the non-inferiority margin for the EU primary endpoint is set to 0.75 g/dL. The overall alpha will be equally allocated to each of the 2 test populations. If we assume an information fraction of 0.80, this rule will lead to a significance level of 0.0174.

In this setting, 300 subjects for the roxadustat treatment group and 300 subjects for the ESA treatment group will provide 97% power to statistically demonstrate noninferiority of roxadustat versus ESA in the EU primary endpoint in both the total study population and the planned subgroup analysis, assuming a difference (roxadustat minus ESA) of -0.25 g/dL in the Hb change from BL and a standard deviation of 1.5 g/dL. In the case that these assumptions do not hold across the overall population, the planned procedure can still allow for a successful conclusion for the subgroup.

US (FDA)

With 750 randomized subjects (Intention To Treat Set [ITT]), the study will provide at least 99% power to demonstrate statistical noninferiority of roxadustat vs ESA in the primary endpoint for US submission.

Analysis Sets:

The following analysis sets are defined and will be used for the statistical analysis:

- ITT: randomized subjects
- Full Analysis Set (FAS): randomized subjects who received at least 1 dose of study drug and have at least 1 postdose Hb assessment
- PPS: FAS subjects who received at least 12 weeks of study treatment with at least 1 postdose Hb assessment and without any criteria for PPS exclusion
- Safety Analysis Set (SAF): subjects that received at least 1 dose of study drug

Pharmacokinetic Analysis Set: SAF subjects with at least 1 quantifiable plasma concentration of roxadustat with dosing and sampling history recorded

Efficacy:

EU (EMA)

Primary Hypothesis

The Hb change from BL to the average Hb of weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period will be analyzed using a Mixed Model of Repeated Measurements (MMRM) with an unstructured covariance matrix. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment arm and other stratification factors. For subjects who require rescue therapy, the reported values after the initiation of rescue therapy will be set to missing for 6 weeks; the MMRM model will implicitly impute missing data via the within-patient correlation structure.

The primary analysis of this EU primary efficacy endpoint will be tested both in the overall population and in the subgroup of patients defined as subjects with an average prescribed weekly epoetin or darbepoetin alfa dose within the last 4 weeks prior to randomization ≤ 200 IU/kg or ≤ 1 µg/kg, respectively, following a parametric chain procedure.

The 2 null hypotheses to be tested are:

- H_{A0}: Hb change from baseline in the roxadustat arm ≤ Hb change from baseline in the ESA arm minus 0.75 g/dL in the overall study population
- H_{B0}: Hb change from baseline in the roxadustat arm ≤ Hb change from baseline in the ESA arm minus 0.75 g/dL in the subgroup

The alternative hypotheses HA1 and HB1 are defined as the negation of the null hypotheses HA0 and HB0 respectively. The information fraction will be calculated at the time of database hardlock as the number of subjects in the subgroup with respect to the number of subjects in the total study population. The overall 1-sided significance level (alpha) is fixed as 0.025. The overall alpha will be equally allocated to each of the 2 null hypotheses defined above. In case of an information fraction of 0.80, this rule will lead to significance level of 0.0174. Following the parametric chain procedure, if at least 1 of both hypotheses is rejected at the significance level of 0.0174, the other 1 can be tested at a significance level of 0.025 while still strongly controlling the overall type I error. The study will be successful for the EU primary efficacy endpoint if either of the null hypotheses is rejected.
The EU primary analysis will be tested on the PPS. The analysis will be repeated on the FAS and ITT as secondary analyses.

US (FDA)

The Hb change from BL to the average Hb of weeks 28 to 52, regardless of rescue therapy, will be analyzed using a MMRM model with an unstructured covariance matrix. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment arm, and other stratification factors.

The null hypothesis to be tested for the US primary efficacy analysis is:

- H_0: Hb change from baseline in the roxadustat arm ≤ Hb change from baseline in the ESA arm minus 0.75 g/dL

The alternative hypothesis H1 is defined as the negation of the null hypothesis H0. The overall 1-sided significance level (alpha) is fixed as 0.025. The study will be successful for the US primary endpoint if the null hypothesis is rejected.
The US primary analysis will be tested on the ITT. The analysis will be repeated on the FAS and PPS as secondary analyses.

Secondary Hypotheses

Once a primary hypothesis has been rejected for the EU primary efficacy endpoint, the secondary endpoints will be tested as described below using a fixed sequence testing procedure. These tests will

be performed only for the overall population in the case that the primary hypothesis was rejected for the overall study population. If the EU primary analysis was not successful for the overall population, but only for the subgroup, then the tests will be performed only for the subgroup.

1. Proportion of Hb responders in the average of weeks 28 to 36 (noninferiority of roxadustat versus ESA) without having received rescue therapy. The non-inferiority margin for the difference between groups is 15%.
2. LDL cholesterol change from BL to the average of weeks 12 to 28 (superiority of roxadustat versus ESA)
3. Monthly IV iron (mg) use per subject during weeks 1 to 36 (superiority of roxadustat vs ESA).
4. SF-36 PF sub-score change from BL to the average of weeks 12 to 28 (noninferiority of roxadustat versus ESA). The noninferiority margin is fixed as a difference of 3 points.
5. SF-36 VT sub-score change from BL to the average of weeks 12 to 28 (noninferiority of roxadustat versus ESA). The noninferiority margin is fixed as a difference of 3 points.
6. MAP change from BL to the average MAP of weeks 20 to 28 (non-inferiority of roxadustat versus ESA). The noninferiority margin for the difference between groups is 1 mmHg.
7. Time to an increase in blood pressure during weeks 1 to 36 (non-inferiority of roxadustat versus ESA). The noninferiority margin is fixed as a hazard ratio of 1.3.
8. MAP change from BL to the average MAP of weeks 20 to 28 (superiority of roxadustat versus ESA).
9. Time to an increase in blood pressure during weeks 1 to 36 (superiority of roxadustat versus ESA).

The EU primary analysis will be tested on the PPS for the noninferiority tests and the FAS for the superiority tests.

The analysis will be repeated using (a) the FAS and ITT for noninferiority tests and (b) the PPS and ITT for superiority tests as secondary analyses

Pharmacokinetics:
PK assessments will only be performed in subjects treated with roxadustat.

All details of the population PK (PPK) analysis will be described in a separate analysis plan, and a separate PPK modeling report will be written

Pharmacodynamics:
Pharmacodynamic data may be submitted to population pharmacodynamic or population pharmacokinetic/pharmacodynamic modeling. When deemed necessary, data from this study may be combined with data from other studies. Results will be reported in a separate population pharmacokinetic/pharmacodynamic modeling report.

Safety:

- Safety analyses will be performed using the SAF. Safety parameters include AEs, SAEs, laboratory parameters, vital signs, and ECG parameters.
- The number and percentage of subjects reporting (treatment-emergent) AEs and (treatment-emergent) SAEs in each treatment group will be tabulated. Descriptive statistics will be presented for laboratory, vital signs values and ECG parameters by visit and for the changes from BL to each visit.
- The statistical methods for analysis of adjudicated safety data will be detailed in a separate Statistical Analysis Plan. The analysis of adjudicated safety data will be provided in a separate report.
- Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be conducted by an independent DSMB.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

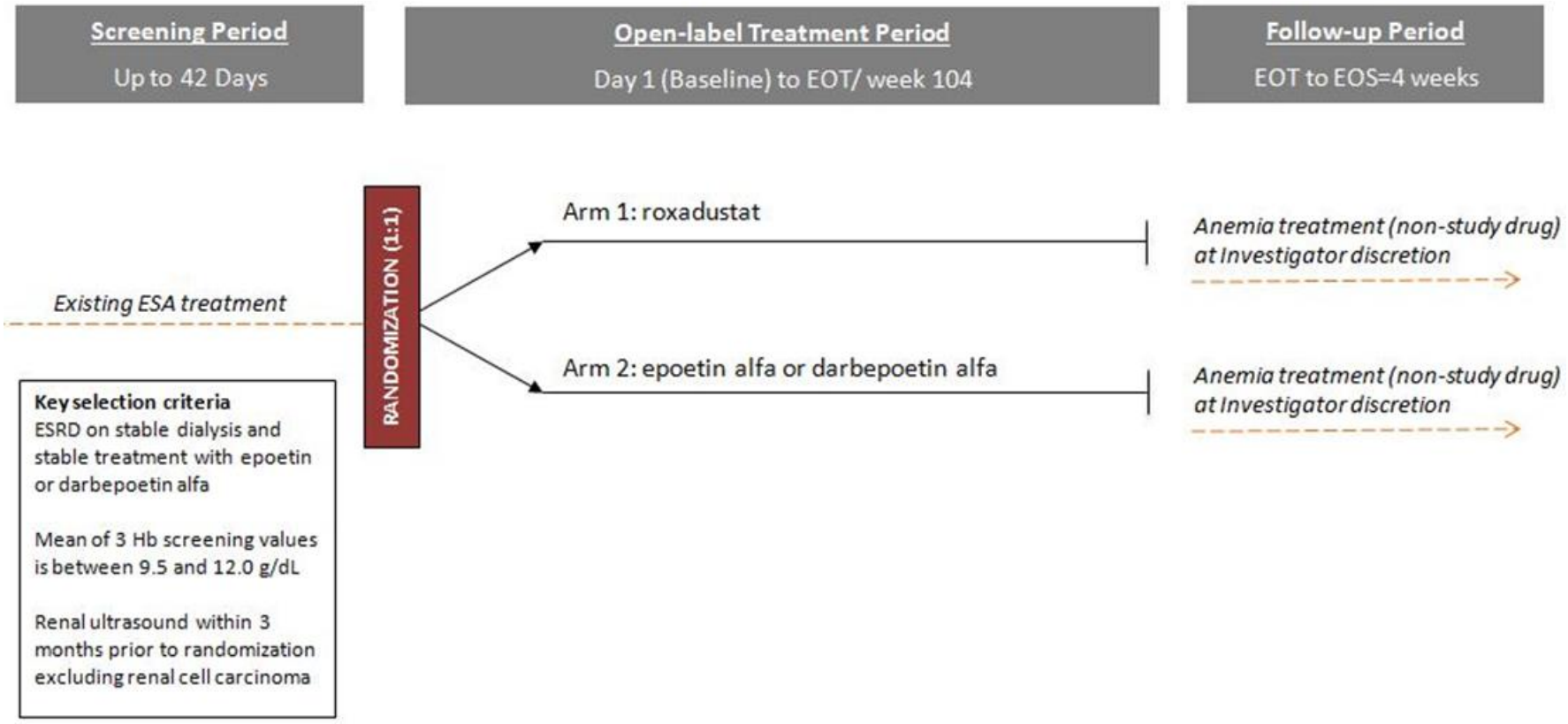


Table 1 Schedule of Assessments

Study Period:	**Screening Period**			**Treatment Period**					**Follow-up Period**		**Unscheduled Visits**	Poststudy Follow-up[c]
Visit/Week:	**2-6 Weeks[a]**			**Day 1[b]**	Weekly (Wks 1 to 8) ± 2 days	Every 2 Weeks (Wks 10 to 36) ± 2 days	Every 4 Weeks (Wks 40 to 100) ± 3 days	EOT[c] (Week 104) ± 3 days	EOT + 2 wks ± 3 days	EOS[c] (EOT + 4 wks) ± 3 days		Every 6 months until projected EOS
	S1	**S2**	**S3**									
Dialysis procedure	◄										►	
ESA pretreatment	◄											
Written informed consent	X											
Randomization				X								
Eligibility Criteria	X			X								
Demographics	X											
Height, weight [d]	X	X	X	X		Wks 12, 24, 36	Wks 52, 76	X		X	O	
Medical History	X											
Physical Examination	X			X		Wks 12[e], 24[e], 36[e]	Wks, 52[e], 76[e]	X		X[e]	O	
Blood pressure[f], heart rate[f], respiratory rate[g]	X	X	X	X	X	X	X	X		X	O	
CBC with WBC diff, red cell indices and platelets	X			X	Wks 1, 2, 3, 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
Hemoglobin[h,i]		X	X		X	X	X		X		O	
HemoCue Assessment[i]				X	X	X	X				O	
Reticulocyte count and Hb in reticulocytes (CHr)	X			X	Wks 1, 2, 4, 6, 8	Wks 12, 16, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
12-lead ECG	X			X		Wks 12, 24, 36	52, 76	X			O	
Serum Chemistry[j]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X	X	X	O	
Renal Ultrasound [k]		X									O	
Liver Function Tests (LFTs) [l]					Wks 2, 6	Wk 16					O	

Table continued on next page

Study Period:	**Screening Period**			**Treatment Period**					**Follow-up Period**		**Unscheduled Visits**	Poststudy Follow-up[c]
Visit/Week:	**2-6 Weeks[a]**			**Day 1[b]**	Weekly (Wks 1 to 8) ± 2 days	Every 2 Weeks (Wks 10 to 36) ± 2 days	Every 4 Weeks (Wks 40 to 100) ± 3 days	EOT[c] (Week 104) ± 3 days	EOT + 2 wks ± 3 days	EOS[c] (EOT + 4 wks) ± 3 days		Every 6 months until projected EOS
	S1	**S2**	**S3**									
Serum Lipid Panel[m]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wks 44, 52, 68, 84	X		X	O	
Serum iron, ferritin, TIBC, TSAT[n]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
HbA1c	X			X		Wk 12, 28, 36	Wks 44, 52, 60, 84	X		X	O	
Vitamin B_{12}, folate	X										O	
HIV, HBsAg, anti-HCV Antibody	X										O	
Serum Pregnancy Test (HCG)[o]	X					Wks 12, 24, 36	Wks 48, 60, 72, 84, 96	X			O	
high sensitivity C-reactive protein (hs-CRP), hepcidin				X	Wk 4	Wks 12, 20, 36	Wk 52	X		X		
Archival Serum Samples for Biomarkers				X	Wk 4	Wks 12, 20	Wks 52, 76	X		X		
Blood Sample for PK[p]					Wks 2 to 8							
QoL Questionnaires[q]				X	Wk 8	Wks 12, 28, 36	Wks 52, 76	X				
Dialysate[r]					Wks 2 to 8							
Optional genotyping[s]				O								
Study Treatment: roxadustat dispensing OR ESA administration[t]				←	—	—	→				O	
Dose Adjustment Review[u]					X	X	X				O	
AE and Concomitant Medication Recording	←	—	→									
Procedure and non-drug Therapy Recording	←	—	→									

Table continued on next page

Study Period:	**Screening Period**			**Treatment Period**					**Follow-up Period**		**Unscheduled Visits**	Poststudy Follow-up[c]
Visit/Week:	**2-6 Weeks[a]**			**Day 1[b]**	Weekly (Wks 1 to 8) ± 2 days	Every 2 Weeks (Wks 10 to 36) ± 2 days	Every 4 Weeks (Wks 40 to 100) ± 3 days	EOT[c] (Week 104) ± 3 days	EOT + 2 wks ± 3 days	EOS[c] (EOT + 4 wks) ± 3 days		Every 6 months until projected EOS
	S1	**S2**	**S3**									
Vital status, SAEs, cardiovascular and thromboembolic AEs												X

S1/S2/S3=Screening visit 1, 2 and 3; EOT = End of Treatment; EOS = End of Study; Wk(s) = Week(s); X = mandatory test/assessment; O = optional test/assessment. In HD subjects all lab sampling is to be performed prior to or at initiation of the dialysis session.

Note: Instructions for roxadustat-treated subjects moving from Protocol v1.0 to Protocol v2.0 in terms of dosing are provided in Appendix 12.3

[a] Due to the requirement of 4-day separation between the screening Hb values, the screening period will last a minimum of 2 weeks approximately, but is allowed to be a maximum of 6 weeks. Sites are recommended to schedule the 3 screening visits in the shortest time span possible.

[b] Randomization and administration of the first dose of study drug (roxadustat or ESA) are to occur on day 1, which should correspond to a day when the subjects' next dose of epoetin or darbepoetin alfa would have been administered. In HD subjects only, postdialysis weight and postdialysis vital signs do not have to be completed prior to randomization and first study drug administration.

[c] In case of premature treatment discontinuation, the subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit. Thereafter subjects who have taken at least 1 dose of study drug will continue to be followed up at a 6-monthly frequency for vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of the follow-up period (i.e. projected EOS date) or until consent withdrawn. No additional study visits will be required during the poststudy follow-up.

[d] Height at first screening visit only; Weight is postdialysis weight in HD subjects. For day 1 visit the postdialysis weight on the third screening visit is to be recorded in the Interactive Response System (IRS) for HD subjects. Weight for PD subjects is the weight measured at site minus the abdominal fluid based on last filling. For drug dispensing purposes (at visits after randomization), weight from the previous dialysis session may be used.

[e] Targeted physical examination (e.g., respiratory and cardiovascular).

[f] Blood pressure and heart rate measured singly during the screening period, and in triplicate at all other visits; in HD subjects both pre- and postdialysis.

[g] Respiratory rate measured singly during screening period and all other visits; in HD subjects both pre- and postdialysis.

[h] Separate Hb should be collected at all the visits where Complete Blood Count (CBC) is not collected; i.e. Hb at weeks 5, 6, 7, 10 until the end of the study. It is recommended that the Hb assessments be performed on the same day of the patient's dialysis schedule throughout the study.

[i] If during an unscheduled visit hemoglobin needs to be assessed, this should always be done with the HemoCue AND a central laboratory hemoglobin assessment.

[j] Serum chemistry includes LFTs.

[k] Renal ultrasound examination can be performed at any time during the screening period. Not required if results of a previous renal ultrasound (or other renal imaging modality such as CT scan or MRI providing a conclusive report on the kidney) within 12 weeks prior to randomization is available and ruling out renal cell carcinoma.

Footnotes continued on next page

[l] LFTs to be collected at further visits where serum chemistry is not collected.

[m] Fasting, whenever possible.

[n] TSAT = [FeSat (Ferro Saturation = % Iron Saturation) measured by central lab and derived from iron and TIBC].

[o] Human chorionic gonadotropin (HCG); to be collected from female subjects of childbearing potential only.

[p] Only for subjects randomized to roxadustat at 6 time points over 1 to 3 visits. At each PK visit, an additional sample will be collected for albumin and alpha-acidglycoprotein determination.

[q] Includes Short Form 36 (SF-36), Functional Assessment of Cancer Therapy-Anemia (FACT-An), European Quality of Life 5 Domain 5 Level (EQ-5D 5L) and Patients' Global Impression of Change (PGIC). PGIC will not be performed on day 1. In HD subjects, the quality of life questionnaires are to be completed by the subject prior to any other assessment or at the latest at the start of dialysis session. It is important that the physician does not discuss the status of the subject prior to completion of the questionnaires. In PD subjects the questionnaires are to be completed prior to any study assessment.

[r] Only for continuous ambulatory peritoneal dialysis (CAPD) subjects randomized to roxadustat. Sample to be withdrawn from the drainage bag after draining complete volume at the site and at the same visit as the PK blood samples (see footnote o).

[s] Optional assessment and only for subjects randomized to roxadustat. If a separate (optional) informed consent form is signed by the subject, a sample can be collected after randomization, preferably on day 1.

[t] Dosing of epoetin alfa and darbepoetin alfa according to approved SmPC (Eprex® United Kingdom SmPC; Aranesp® European Union SmPC). It is recommended that roxadustat is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day).

[u] Subjects randomized to roxadustat: dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (deviation from the 4-week period is allowed anytime during the study in case of excessive hematopoiesis or Hb ≥13.0 g/dL). If next dose adjustment interval falls on a non-visit study week, the dose adjustment review should be performed at the next scheduled study visit. ESA dose adjustments should follow the SmPC.

1 INTRODUCTION

1.1 Background

1.1.1 Epidemiology of Chronic Kidney Disease and End Stage Renal Disease

Chronic kidney disease (CKD) is a condition characterized by progressive loss of kidney function that is associated with increased risk for severe complications such as cardiovascular disease and premature death. Importantly, all-cause mortality increases exponentially as CKD stages advance [Tonelli et al, 2006]. The average expected remaining lifetime of a dialysis patient in the US is 5.9 years, compared to 16.4 years for a patient who received a kidney transplant, and 25.2 years for aged-matched controls in the general population [USRDS, 2009].

The number of patients worldwide affected by CKD is growing continuously. Approximately 13% of the US adult population, or 29 million individuals, are affected by CKD [Coresh et al, 2007]. The unadjusted CKD prevalence in Europe is estimated to 5-11% [Zoccali et al, 2010].

Epidemiological surveys corroborate that the number of CKD patients who develop end-stage renal disease (ESRD) and warrant renal replacement therapy (kidney transplantation or dialysis) is increasing as well. The US has 1 of the highest ESRD rates in the world with a reported ESRD prevalence that exceeded 1700 subjects per million in 2010, corresponding to a 23% increase during the last ten-year period [USRDS, 2011]. In Europe, prevalence of renal replacement therapy increased from 480 to 807 patients per million during 1992–2005, [Zoccali et al, 2010].

The most frequent causes of ESRD are diabetic kidney disease, hypertension, glomerulo-nephritis and polycystic kidney disease. Age and ethnicity are other, non-modifiable, risk factors for ESRD. Notably, individuals older than 75 years represent the most common age group in ESRD (1735 per million in the US in 2007). The influence of ethnicity and risk for ESRD is illustrated by substantial differences in ESRD incidence rates across ethnical origins: 998 per million for African Americans, whereas substantially lower for Asians/Pacific Islanders and Whites (396 and 273 per million, respectively) [USRDS, 2009]. The increased prevalence of type 2 diabetes combined with a steady rise in the expected average life span predict that the number of ESRD patients in the US will increase to 774,000 [USRDS, 2009] in 2020.

Treatment of ESRD varies widely across geographical regions and depends on available medical resources. In the US there are approximately 570,000 ESRD patients, of whom 370,000 are treated with hemodialysis (HD), 27,000 with peritoneal dialysis (PD), and 173,000 had a functioning kidney transplant [USRDS, 2011]. Of note, more than 50% of the global dialysis patient population is treated in only five countries – the US, Japan, China, Brazil and Germany. The large variability in ESRD prevalence in these countries, ranging from as little as 150 patients per million in China to 2370 patients per million in Japan, exemplifies a marked geographical difference in terms of dialysis practice pattern.

1.1.2 Anemia Associated with CKD

Anemia is a frequently occurring complication in CKD with multiple etiologies. The principal cause of renal anemia is insufficient production of erythropoietin (EPO), a hormone

mainly produced in the kidneys that stimulates the synthesis of red blood cells. In addition, CKD-related anemia develops due to impaired ability to absorb iron from the gastrointestinal tract as well as to utilize existing iron pools to generate new red blood cells.

Anemia may arise at an early stage of CKD, and its prevalence increases as CKD progresses. Anemia is present in 17% of patients with late Stage 3 CKD; this increases to 25% in patients with Stage 4 CKD, and 49% in patients with Stage 5 CKD who have not yet progressed to dialysis [Coresh et al, 2007; Go et al, 2004]. Over 90% of patients undergoing dialysis are anemic. Quantitatively, 50.1% of incident dialysis patients had hemoglobin (Hb) levels below 10 g/dL and approximately 28% had Hb levels below 9 g/dL [USRDS, 2003].

European surveys on anemia prevalence in CKD corroborate with USRDS data. A prospective study of 403 predialysis patients indicated that 60% of patients with a creatinine clearance of < 20 mL/min/1.73 m^2 were anemic (Hb <11 g/dL) [Jungers et al, 2002]. In another large retrospective anemia care study of 6271 incident dialysis patients, the average predialysis Hb level was 10.3 g/dL whereas 63.6% of the patients had a Hb value lower than 11 g/dL [Thilly et al, 2008].

The clinical consequences of anemia in patients with CKD have been studied extensively. Because the main consequence of anemia on organ function is reduced tissue delivery of oxygen, it affects almost every organ system.

Anemia contributes to the excess morbidity and mortality in CKD, and the severity of anemia correlates directly with the risk of hospitalization and cardiovascular disease in this population [Collins et al, 1998]. Patients with the lowest Hb levels have the poorest outcomes, as was emphasized in the *post-hoc* analysis of mortality by Hb quintiles for the Normal Hematocrit and Correction of Hemoglobin (NHCH) and Outcomes in Renal Insufficiency (CHOIR) studies in the Food and Drug Administration (FDA) briefing document for the October 2007 Cardiovascular and Renal Advisory Committee [Unger, 2007]. These results are consistent with USRDS registry data which demonstrated that all-cause mortality between 1993-1996 stratified by Hb level showed significantly higher first-year death rates in patients with Hb levels <9 g/dL and 9 to <10 g/dL, compared to 11 to <12 g/dL. The relative risk for patients with Hb <9 g/dL compared to with Hb >12 g/dL are more than 2-fold for all-cause mortality [USRDS, 2002] and 1.26 for cardiovascular hospitalization [USRDS, 2001].

Multiple studies have shown that treatment of anemia reduces the need for blood transfusions and improves health-related quality of life (HRQoL) [National Kidney Foundation KDOQI, 2007].

1.1.3 Treatment of Anemia

Erythropoiesis-stimulating agents (ESAs) in combination with iron supplementation is a widely accepted approach for treatment of anemia in CKD patients who are not resistant to ESAs and in whom iron monotherapy is insufficient to maintain Hb levels within the recommended target range. For this purpose, parenteral administration of exogenous recombinant human EPO (epoetin alfa or beta) or pegylated analogues is an established practice pattern [Eschbach et al, 1987; Winearls et al, 1986; US Recombinant Human

Erythropoietin Predialysis Study Group, 1991], despite the documented safety risks such as hypertension, thrombosis and cerebrovascular events. These risks have been partially linked to supraphysiologic plasma EPO levels resulting from recombinant ESA therapy.

Anemia treatment in CKD and ESRD improves quality of life (QoL), functional well-being and physical performance, yet several studies in these populations have shown higher mortality, or trends in that direction, in the higher-dosed ESA-treated cohorts when the protocol objective was to treat to high target Hb levels [Besarab et al, 1998; Drüeke et al, 2006; Singh et al, 2006]. An ESA dose relationship to mortality has been reported in a review of the USRDS database (Zhang et al. 866-76) of ESRD patients who received higher ESA doses. Additionally, ESA therapy for anemia in ESRD patients on HD usually requires concomitant intravenous (IV) iron supplementation, while IV iron use is not free of risk in such patients.

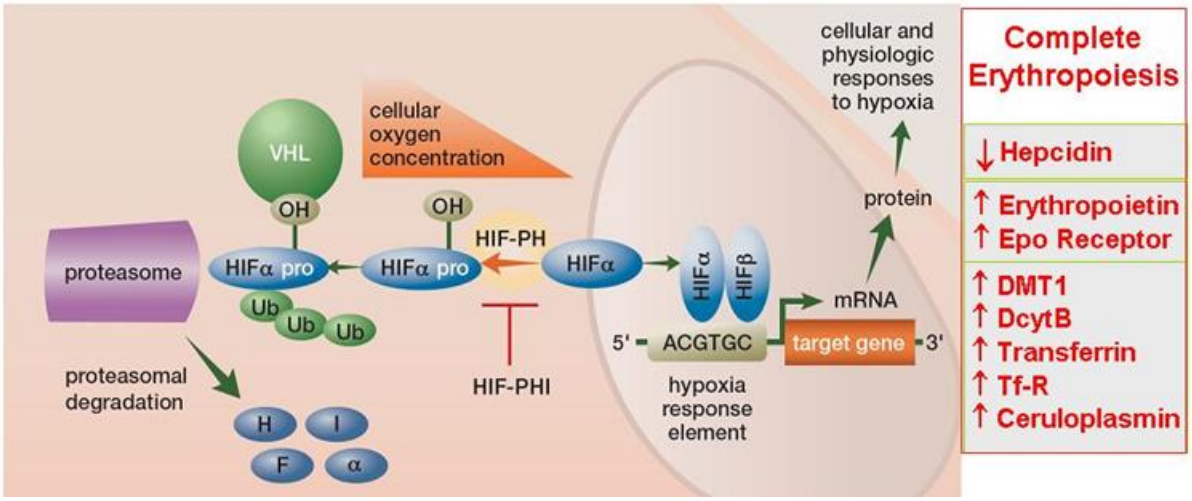
There is currently an unmet medical need for an oral treatment that will correct anemia in CKD nondialysis and dialysis patients to a target Hb level that is safe and well tolerated without a supraphysiological rise in serum EPO concentrations. Roxadustat is an oral medication with a new mechanism of action distinct from ESA that could potentially address all these requirements and which may translate into an improved safety profile.

1.2 Nonclinical and Clinical Data

1.2.1 Mechanism of Action of Roxadustat

Virtually all tissues depend on a sufficient supply of oxygen for survival. Lack of oxygen associated with hypoxic, ischemic, and anemic conditions triggers a series of homeostatic responses (Figure 1). Hypoxia-inducible factor (HIF) is a transcription factor that is believed to be the key element in the body's oxygen sensing mechanism [Semenza, 2000]. HIF regulates expression of genes that modulate both the acute and chronic response to hypoxia, and HIF-responsive genes regulate processes as diverse as erythropoiesis, iron metabolism, oxidation, cellular metabolism, glycolysis, vasculogenesis, cell cycle progression, and apoptosis. Chronic hypoxia and intermittent hypoxia induce different sets of genes associated with HIF transcriptional activity [Fan et al, 2005]. HIF is a heterodimeric transcription factor family comprising 3 oxygen-sensitive isoforms (HIF-1α, HIF-2α and HIF-3α), and a constitutively expressed HIF-1β subunit, with each heterodimeric isoform responsible for the induction of specific sets of genes [Greijer et al, 2005; Hu et al, 2003]. For example, HIF-1α has been shown to regulate vascular endothelial growth factor expression [Gray et al, 2005; Büchler et al, 2003], while HIF-2α is critical for the induction of the EPO gene and erythropoiesis [Warnecke et al, 2004; Scortegagna et al, 2005].

Figure 1 HIF-PHI Mechanism of Action



Source: Epstein, et al. Cell, 2001.

HIF target genes are expressed when the active heterodimer binds to a conserved deoxyribonucleic acid motif found within all HIF target genes, termed the hypoxia response element, and in cooperation with other co-activators initiates de novo transcription. One of the most sensitive and well-studied HIF-responsive genes is the EPO gene. Increased transcription of the EPO gene leads to increased circulating levels of EPO, which acts at sites of erythropoiesis to enhance the differentiation and proliferation of red blood cell (RBC) precursors.

Although HIF-α isoforms are constitutively produced, their accumulation under normoxic conditions is prevented by recruitment and binding by the Von Hippel-Lindau protein, which targets HIF-α isoforms for degradation through the ubiquitin-proteasome pathway. The molecular mechanism for oxygen-dependent degradation of HIF-α is based on the hydroxylation of specific proline residues, as catalyzed by a family of HIF prolyl hydroxylases (HIF-PH) that utilize molecular oxygen as the substrate for hydroxylation. Thus, HIF-PH constitutes the body's main oxygen sensor by regulating the prevalence and activity of nuclear HIF protein. Under hypoxic conditions, HIF-PHs are inactive and lead to initiation of the HIF-responsive transcriptional cascade [Wang et al, 1995; Semenza, 1998].

Roxadustat (code names FG4592 or ASP1517) is a potent and reversible HIF-PH inhibitor that transiently induces HIF stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure to intermittent hypoxia. HIF induces expression of EPO, as well as the EPO receptor and proteins that promote iron absorption 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 anemia, but under normoxic conditions.

Roxadustat also has the potential to effectively treat anemias caused by inflammation-induced functional iron deficiency, which are typically hyporesponsive to ESAs. In these conditions, iron availability for erythropoiesis is reduced due to a number of inflammatory

mediators. Because HIF-PH inhibitors such as roxadustat alter expression not only of the EPO gene but also of genes regulating iron metabolism, it is postulated that roxadustat may be effective in treating these anemias as well [Langsetmo et al, 2005].

Chronic hypoxia and intermittent hypoxia induce different sets of genes associated with HIF transcriptional activity, presumably because intermittent stimulation allows the restoration of HIF degradation, turnover, and inactivation. Transient activation of HIF thereby precludes sustained gene expression and the induction of genes that are expressed late after HIF activation, as well as expression of additional genes that are secondary to activation of HIF-dependent genes. Both nonclinical and clinical studies of roxadustat have successfully used the intermittent dosing paradigm to induce selective erythropoiesis and to optimize the Hb dose response. Furthermore, roxadustat was selected for development over other HIF-PH-inhibiting candidate molecules based on an optimal biodistribution profile that enhances its selective actions. The specific tissues where roxadustat enters the cytoplasm and triggers gene expression reside in the main target organs for erythropoiesis: the kidney (EPO production), the bone marrow (increase in EPO receptors), the duodenum (transepithelial iron transport) and the liver (EPO production and down-regulation of hepcidin production); roxadustat distributes preferentially to these organs.

These characteristics result in several potential advantages over ESAs beyond the convenience of oral therapy. These potential advantages include:

- Increase in the number of EPO receptors in the bone marrow
- Improved iron metabolism and bioavailability
- Effective erythropoiesis at non-supraphysiologic plasma EPO levels (10- to 20-fold lower than with parenteral ESA therapy)
- Absence of hypertensive effect
- Effective erythropoiesis in the presence of inflammation
- Mitigation of thromboembolic risk
- Improvement in lipid profile

1.2.2 Clinical Experience with Roxadustat

Roxadustat is currently being studied in dialysis and nondialysis CKD subjects with anemia. Numerous Phase 1 and 2 clinical studies have been completed, in the US, Europe and Asia. Information from these studies is provided in the most recent version of the Investigator's Brochure (IB). As of 07 Sep 2014, an estimated total of 1485 subjects have been exposed to roxadustat in the clinical development program, comprising 571 healthy subjects and an estimated 483 subjects with nondialysis CKD and 431 subjects with dialysis CKD. In completed studies, subjects with CKD have received up to 24 weeks of roxadustat, in doses of up to 3.0 mg/kg. In completed Phase 1 studies, healthy subjects received single doses of roxadustat up to 4.0 mg/kg and repeat doses up to 3.75 mg/kg 3 times a week for 4 weeks. In a completed thorough QT study in healthy subjects, single doses up to 5 mg/kg were administered, without evidence of QT prolongation.

The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in healthy adult subjects, and in dialysis and nondialysis CKD subjects with anemia who have been treated in the completed and ongoing studies.

1.2.2.1 Pharmacokinetics and Pharmacodynamics

The pharmacokinetics (PK) and pharmacodynamics of roxadustat were characterized in studies in healthy subjects and in dialysis and nondialysis CKD subjects. Roxadustat showed generally dose proportional PK (except at the lowest dose of 0.3 mg/kg); $t_{1/2}$ was 12 to 14 h in healthy subjects, and 15 to 19 h in dialysis subjects (after single doses of 1 and 2 mg/kg). The exposure was higher in dialysis subjects compared to healthy subjects. Roxadustat can be administered before or after dialysis, since the PK of roxadustat was not significantly altered when administered prior to the start of dialysis compared with after dialysis [Study FGCL-4592-039].

A relative bioavailability study was conducted in 24 healthy subjects comparing the capsule formulation, which was used in phase 1 and phase 2, with the tablet formulation which was developed for phase 3. PK parameters were comparable between the 2 formulations.

With an intermittent dose regimen of once weekly (QW), twice weekly (BIW) or 3 times weekly (TIW), no or limited accumulation in mean area under the plasma concentration curve (AUC) or maximum concentration (C_{max}) was observed. Furthermore no evidence was found for time-dependent PK (no auto-induction or inhibition). Roxadustat is highly protein bound and the PK of roxadustat is not affected by dialysis. Metabolites found in urine suggested phase 2 metabolism as the major metabolic pathway. In plasma, parent roxadustat is the main component. The inhibitory potential of roxadustat on cytochrome P450 (CYP) enzymes, based on *in vitro* studies is limited, and the lowest inhibition constant value was observed for CYP 2C8 (16 μM). In a clinical drug-drug interaction study with rosiglitazone, a probe drug for CYP 2C8, roxadustat did not show any inhibitory potential on CYP 2C8 *in vivo*.

Additional drug-drug interaction studies were performed with statins and phosphate binders. Roxadustat increases the AUC_{inf} of simvastatin 1.9-fold; of rosuvastatin 2.9-fold; and of atorvastatin 2.0-fold. The AUC_{inf} of roxadustat is decreased 2.9-fold and 1.8-fold, respectively, by simultaneous administration with the phosphate-binders sevelamer carbonate and calcium acetate. Administration of roxadustat at least 1 h before or 1 h after the phosphate binder minimized the interactions.

In healthy adult male subjects (Study FGCL-SM4592-016), roxadustat administered orally as a single dose up to 4.0 mg/kg, and QW, BIW, or TIW for 4 weeks at doses up to 3.75 mg/kg, was pharmacodynamically active as evidenced by dose-dependent transient increases in endogenous EPO level (starting from single doses of 0.3 mg/kg), increases in reticulocytes (starting from doses of 2 mg/kg), and Hb responses (starting at 3 mg/kg). The mean peak level of plasma EPO following the day 26 dose of 2.0 mg/kg TIW (the high therapeutic dose studied) was 326.3 ± 197.0 mIU/mL.

In pharmacodynamic studies conducted with roxadustat in CKD subjects not on dialysis (Study FGCL-4592-017), the mean maximum EPO increase from baseline (BL) ranged from

82-443 mIU/mL and 492-554 mIU/mL after a single 1 and 2 mg/kg dose, respectively. In dialysis subjects (Study FGCL-4592-039), comparable dose-dependent increases in EPO levels were observed, both predialysis and postdialysis. These increases in endogenous EPO were transient and the effect disappeared within approximately 48 h.

In contrast, EPO levels associated with therapeutic ESA dosing range from 1,500 to over 10000 mIU/mL [Besarab et al, 2009]. In a clinical study with dialysis subjects, the reported mean administered individual ESA dose was 8000 IU, which would correspond to plasma EPO C_{max} levels exceeding 3000 mIU/mL [Fishbane & Besarab, 2007]. This is approximately 10-fold higher than the physiologic range.

1.2.2.2 Efficacy

Data from a 4-week treatment study in anemic CKD subjects not on dialysis (Study FGCL-SM4592-017) showed that roxadustat promoted erythropoiesis at lower doses in CKD subjects than in healthy subjects. In contrast to the classical paradigm suggesting that anemia in CKD subjects is caused by the inability of these subjects to produce EPO, the results of this study suggest that the EPO production in this patient population is sufficient to achieve a robust erythropoiesis. With roxadustat 0.7 mg/kg TIW dosing, mean maximum Hb increased by 1.0 g/dL over a 6-week period in anemic CKD subjects who completed 4 weeks of dosing; more robust mean Hb increases of 2.0 to 2.3 g/dL occurred at roxadustat doses of 1.5 and 2.0 mg/kg TIW, respectively. Hemoglobin responder (Hb increase of ≥1.0 g/dL) rates were 62%, 60%, 91%, and 100% in the roxadustat 0.7, 1.0, 1.5, and 2.0 mg/kg TIW cohorts, respectively. The Hb responses were also robust at the higher roxadustat doses (1.5 to 2.0 mg/kg) in the BIW dosing groups. With the additional criterion that Hb achieves a level of ≥11.0 g/dL as well as increasing by ≥1.0 g/dL from baseline, the Hb responder rate with roxadustat 2.0 mg/kg was 89% and 91% in BIW and TIW dosing, respectively. The rapid rates of rise in Hb with roxadustat treatment were not accompanied by elevations in blood pressure, as has been reported with ESA treatment [Eschbach et al, 1989].

Data from a completed 16- to 24-week treatment study in CKD subjects not on dialysis (Study FGCL-4592-041) showed absolute and weight-based doses of roxadustat, administered TIW and BIW, effectively corrected Hb levels in these subjects. Corrected Hb levels were maintained within target range for the 16- or 24-week treatment period at TIW and BIW dosing and were generally maintained even with conversion to once weekly dosing. The median time to Hb response was 28 days for subjects who received adequate weight-based or absolute starting doses of roxadustat and longer for those who received a lower absolute starting dose. Treatment with roxadustat in these anemic CKD patients led to positive changes or trends for positive changes from baseline in subscales of the Short Form 36 (SF-36) QoL questionnaire (Vitality, Mental Component, and Social Functioning). Dose-response trends suggested that starting doses of 1.0−1.6 mg/kg roxadustat administered TIW are appropriate to correct Hb levels during 4 weeks of treatment in nondialysis CKD subjects. Dosing frequency reduction, once Hb correction is achieved, appears to be feasible to maintain Hb in the target range.

A total of 197 ESRD patients undergoing dialysis have received either single or multiple roxadustat doses for up to 19 weeks. Data from a 6- and 19-week treatment study in ESRD subjects on dialysis showed the feasibility of converting subjects from a stable ESA dose to roxadustat (Study FGCL-4592-040). I n the 6-week dose range portion of this conversion study (during which roxadustat doses were mostly fixed upon switching from stable doses of epoetin alfa), dose response was observed. The 1.0 mg/kg roxadustat dose was comparable to the epoetin alfa control, which resulted in a small decline in Hb levels from BL and a lower percent Hb responder rate compared to the higher doses of roxadustat. The 1.5 and 2.0 mg/kg roxadustat dose arms resulted in a Hb increase of about 1 g/dL from BL and an 89% response rate, more than double that of the epoetin alfa arm, despite the absence of IV iron supplementation; no restriction was made in the study protocol for the use of oral iron. Regression slope analyses of Hb values over time showed that the estimated rate of Hb rise was positive and statistically significant for the 1.5 and 2.0 mg/kg dose cohorts, with a Hb increase of 0.22 g/dL (p=0.0040) and 0.18 g/dL (p=0.0146) per week, respectively. In the 19-week portion of the study, during which dose-titration was allowed, Hb maintenance was demonstrated in roxadustat treatment arms (combined) over a 19-week period. The roxadustat dose requirement for Hb maintenance was mostly between 0.7 mg/kg to 2.0 mg/kg in normoresponder subjects, with occasional subjects requiring doses up to 3.0 mg/kg TIW. In contrast, the Hb levels in the epoetin alfa control group appeared to decline gradually over time despite steady epoetin alfa doses, as IV iron supplementation was not permitted. In the present study, in which IV iron supplementation is prohibited, roxadustat treatment resulted in increased levels of serum iron at the end of treatment compared with baseline in the 6-week treatment arms, whereas serum iron levels decreased from BL in subjects treated with epoetin alfa reticulocyte Hb content was better maintained in the pooled roxadustat treatment arm than in the pooled epoetin alfa arm, suggesting that functional iron deficiency does not occur when treating with roxadustat unaccompanied by IV iron. This finding is consistent with the different mechanism(s) of action of roxadustat and epoetin alfa.

For subjects treated for 19 weeks, the mean corpuscular volume (MCV) level with roxadustat treatment was slightly elevated at 2 weeks and was maintained during the study, whereas MCV levels for epoetin alfa-treated subjects decreased from BL during study treatment. This suggests roxadustat may also treat iron deficiency anemia by increasing iron availability within the subject.

Serum hepcidin, a master regulating hormone of iron metabolism that is generally increased with inflammation and is a major contributor to lack of availability of iron for erythropoiesis, was reversibly suppressed during roxadustat treatment, thus facilitating oral absorption of iron and mobilization of iron for erythropoiesis.

Sixty incident dialysis patients (HD and PD) without ESA treatment have been enrolled in the FGCL-4592-053 study assessing the impact of different iron supplementation regimens on the efficacy of roxadustat. All patients received tiered, weight-based roxadustat doses TIW, for a duration of 12 weeks: 12 each with no-iron, oral iron, and IV iron and 12 in the PD treatment arm, and 12 in a confirmatory arm with no iron supplementation. There was an overall mean maximum Hb increase from baseline of 3.2 g/dL over the 12-week treatment.

After the first 4 weeks of treatment (Weeks 2-5), over 50% of subjects achieved an overall mean Hb change from BL of at least 1 g/dL. This proportion increased to almost 80% after 8 weeks of treatment (Weeks 6-9) and this percentage increased to over 90% by 12 weeks of treatment. Furthermore, it was noted that subjects with lower BL Hb levels were more responsive to roxadustat and able to achieve a higher maximum Hb increase than those with higher BL Hb values. The magnitude of maximum Hb increase is greater when the treatment of roxadustat is accompanied by iron than without iron. However, in contrast to ESA where IV iron is essential and that ferritin ≥ 100 ng/mL (≥ 220 pmol/L) and transferrin saturation (TSAT) ≥20% are required for ESA treatment (Macdougall 1996, EU Summary of Product Characteristics [SmPC] Eprex®), oral iron supplementation is as effective as IV iron supplementation with roxadustat which is effective when ferritin ≥ 50 ng/mL (≥ 110 pmol/L) and TSAT ≥ 10% when correcting anemia in dialysis patients. However, baseline TSAT does not seem to influence the maximal achievable rise in Hb level.

Summary

In summary, roxadustat is an orally active HIF-PH inhibitor with potent erythropoietic effects. Roxadustat administration in anemic CKD patients results in intermittent activation of HIF, a rise in endogenous serum EPO level (although of lower concentrations relative to ESA therapy), and a dose-dependent stimulation of erythropoiesis. Overall, this suggests that roxadustat promotes a coordinated erythropoiesis via mechanisms distinct from ESA therapy. Available clinical data support that roxadustat is generally safe and well tolerated in healthy adult subjects, and in dialysis and nondialysis CKD subjects with anemia.

1.2.3 Clinical Experience with Epoetin alfa

The comparative drug epoetin alfa Eprex® (Janssen-Cilag) is approved since 1995. One of the treatment approved indications is treatment of anemia associated with chronic renal failure in pediatric and adult patients on HD and adult patients on PD.

The pharmacodynamics of erythropoietin is well known and described in the literature.

After IV administration of epoetin, the typical pharmacodynamics profile shows an increase in reticulocytes count within the first 2 weeks followed by an increase in the red blood cell level as manifested by haematocrit or Hb determinations within 2 to 6 weeks. After single subcutaneous (SC) application an increase in reticulocyte count within 3-4 days with a peak around day 8-11 and a return to BL by day 22 has been described [Ramakrishan et al. 2004; Cheung et al 1998]. A linear relationship between reticulocyte area under the plasma concentration curve and epoetin exposure has been described for single doses up to 1800 IU/kg [Cheung et al, 1998]. There is high interindividual variability in the reticulocyte response to epoetin.

Thirteen clinical studies were conducted with epoetin alfa, involving IV administration to a total of 1010 adult anemic patients on dialysis for 986 patient-years. In the 3 largest of these clinical studies, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW. In the U.S. multicenter phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, or less, to maintain

their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 Units/kg, or less, and approximately 10% required a dose of more than 200 Units/kg TIW to maintain their hematocrit at this level. In a 26 week, double-blind, placebo-controlled study, 118 anemic dialysis patients with an average Hb of approximately 7 g/dL were randomized to either PROCRIT® or placebo. By the end of the study, average Hb increased to approximately 11 g/dL in the PROCRIT®-treated patients and remained unchanged in patients receiving placebo. PROCRIT®-treated patients experienced improvements in exercise tolerance and patient-reported physical functioning at month 2 that was maintained throughout the study.

A multicenter unit dose study was also conducted in 119 patients receiving PD who self-administered epoetin alfa subcutaneously for approximately 109 patient-years of experience. Patients responded to epoetin alfa administered SC in a manner similar to patients receiving IV administration [Procrit® Prescribing Information].

1.2.4 Clinical Experience with Darbepoetin alfa

The comparative drug darbepoetin alfa Aranesp® is approved since 2001 in the EU for the treatment of anemia associated with CKD in adults and pediatric patients. It is a commonly used ESA in Europe to treat anemic nondialysis CKD patients and has demonstrated its ability to correct and maintain Hb in several controlled randomized studies.

Two exploratory dose- and schedule-finding studies (NESP-960245 and NESP-960246) investigated the effects of darbepoetin alfa for correction of anemia in HD and PD subjects by IV and SC injection respectively. The results of both studies showed a clear dose-related effect of darbepoetin alfa by IV as well as by SC route independent of the schedule (once or 3 times weekly). At 2 of the selected dose levels, 60% to 70% of subjects produced an optimal rate of rise in Hb, which was the primary endpoint, within the first 4 weeks (1 g/dL). Based on the results of these studies it was concluded that 0.45 to 0.75µg/kg of darbepoetin alfa administered once weekly IV or SC is the most appropriate starting dose for treatment of anemia in CKD [Macdougall et al, 2003].

The PK studies showed that darbepoetin alfa has a slower clearance and a significantly longer terminal half-life in CKD subjects compared to recombinant human EPO (r-HuEPO). There was no evidence of accumulation of darbepoetin alfa over time. There are no special precautions for use based on the PK data, although darbepoetin alfa should be used with caution in patients with acute hepatic failure, as the liver is a likely a route for drug elimination.

The 2 multi-center randomized open-label studies explored the correction of anemia in subjects on dialysis (NESP-980211) or predialysis (NESP-980202). The aim of the studies was to correct anemia and maintain Hb concentration within a predefined target range for up to 20 and 24 weeks, respectively. Subjects were randomized to receive darbepoetin alfa or r-HuEPO. The primary endpoint for both studies was defined as the proportion of subjects that achieved a Hb response (Hb increase of ≥ 1.0 g/dL from BL and a Hb concentration of ≥ 11.0 g/dL during the initial 24 weeks of treatment). The selected starting dose was 0.45µg/kg once weekly for darbepoetin alfa as suggested by the exploratory dose finding

studies. The starting dose for r-HuEPO was approximately equivalent to this dose in study NESP-980202 (50 U/kg twice weekly), and 40% higher than this dose in NESP-980211 (50 U/kg 3 times weekly) [Locatelli et al, 2001; EMEA, Aranesp 2004].

In the first pivotal correction study (NESP-980202) r-HuEPO-naive subjects were not yet on dialysis and study drugs were administered by SC injection. A total of 129 subjects received darbepoetin alfa, 37 received r-HuEPO. A Hb response was achieved in 93% of subjects in the darbepoetin alfa group and 92% in the rHuEPO group. Subjects from this study had the option to extend dosing up to 104 weeks and were as such eligible for long-term efficacy and safety.

In the second pivotal correction of anemia study (NESP-980211, US trial) subjects were on dialysis (mainly HD) and received study drugs by SC or IV injection route. A total of 122 subjects were randomized (darbepoetin alfa: 91; r-HuEPO: 31). A Hb response was achieved in 72% of subjects in the darbepoetin alfa group and 84% in the r-HuEPO group. This reflects the 40% higher starting dose for r-HuEPO in this study.

Two pivotal phase 3 studies (NESP-970200 conducted in Europe and Australia, study duration 52 weeks; and NESP-980117 conducted in US and Canada, study duration 28 weeks) evaluated the ability of darbepoetin alfa to maintain hemoglobin in the predefined target range, when CKD subjects on dialysis and stable on r-HuEPO therapy were converted to darbepoetin alfa therapy. Both studies indicate that darbepoetin alfa was not inferior to r-HuEPO. The lower boundary of the 95% confidence interval (CI) for the difference in mean change in Hb (darbepoetin alfa minus r-HuEPO) was far above the prespecified clinical acceptable difference of –1.0 g/dL for NESP-980117 as well as above the more rigorous criteria of –0.5 g/dL for the NESP-970200. This applied equally to per protocol and intention to treat analysis sets and demonstrates that darbepoetin alfa is not inferior to r-HuEPO for maintaining subjects Hb concentration within the predefined target range.

Data from 1 uncontrolled long-term safety study demonstrated that darbepoetin alfa once weekly/once every 2 weeks by IV or SC route, is safe and effective in maintaining Hb in subjects with CKD undergoing dialysis. Data from a long-term safety study of darbepoetin alfa in subjects who had completed 1 year of treatment on a previous darbepoetin alfa study show that for subjects who have already received 52 weeks of darbepoetin alfa treatment, the Hb concentration can be safely maintained at a stable level without changes in the average weekly darbepoetin alfa dose [EMEA, Aranesp 2004].

Data from Study 20010184 "Trial to Reduce Cardiovascular Events with Aranesp® Therapy" (TREAT) demonstrated that cardiovascular or death events occurred in 632 subjects assigned to darbepoetin alfa and 602 patients assigned to placebo (hazard ratio for darbepoetin alfa vs. placebo, 1.05; 95% CI, 0.94 to 1.17; p = 0.41). Death or ESRD occurred in 652 subjects assigned to darbepoetin alfa and 618 subjects assigned to placebo (hazard ratio, 1.06; 95% CI, 0.95 to 1.19; p = 0.29). Fatal or nonfatal stroke occurred in 101 subjects assigned to darbepoetin alfa and 53 subjects assigned to placebo (hazard ratio, 1.92; 95% CI, 1.38 to 2.68; p<0.001). Red-cell transfusions were administered to 297 patients assigned to darbepoetin alfa and 496 subjects assigned to placebo (p<0.001).

Death or ESRD occurred in 652 subjects in the darbepoetin alfa group (32.4%) and in 618 subjects in the placebo group (30.5%) (hazard ratio for darbepoetin alfa vs. placebo, 1.06; 95% CI, 0.95 to 1.19; P = 0.29). ESRD occurred in 338 subjects in the darbepoetin alfa group (16.8%) and in 330 subjects assigned to placebo (16.3%) (hazard ratio,1.02; 95% CI, 0.87 to 1.18; P = 0.83).

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Roxadustat (Test Drug)

The overall frequency and type of treatment-emergent adverse events (TEAEs) and serious TEAEs observed in the clinical studies thus far generally reflect events that would be expected to occur in the dialysis and nondialysis CKD subject populations, and have not revealed any particular safety concern. The most commonly reported TEAEs (≥4% and ≥1% above placebo rate) in healthy subjects were headache and dizziness. In the pooled data for dialysis and nondialysis CKD, there were no TEAEs reported for 10% or more subjects treated with roxadustat. TEAEs (≥5% and ≥1% above placebo rate) in CKD subjects not on dialysis were diarrhea, nausea, nasopharyngitis, peripheral edema, hyperkalemia, headache and hypertension. TEAEs reported for ≥3%) of CKD subjects on dialysis were diarrhea, nausea, hypertension and upper respiratory tract infection. The only expected nonserious adverse drug reaction is heart rate increase.

Safety analyses did not reveal any association between the rates of occurrence of cardiovascular events with roxadustat, or any effect on adverse event (AE) rates related to either increasing Hb levels or on the rate of change of Hb levels.

AEs commonly reported with ESA use have been reported at lower rates such as hypertension (1% in Study FGCL-SM4592-017, and 6.9% in Study FGCL-4592-041) and thrombosis (overall incidence <1%). No increased cancer risk has been noted with roxadustat treatment. However, the study program was not powered to detect absence of cancer risk.

Liver enzymes were monitored closely throughout the roxadustat clinical development program. Increases in liver enzymes were infrequently seen, and were generally mild and transient in nature. No case of Hy's Law was observed throughout the program. An independent data and safety monitoring committee concluded that there was no concern for hepatotoxicity with roxadustat.

Five pancreatitis events were noted during the roxadustat clinical phase 2 development program, the majority of which have been associated with gallstones or biliary sludge; 1 of which was due to a pancreatic duct stricture and another case had multiple risk factors for pancreatitis. One of the pancreatitis cases was considered as possibly related by the investigator. Amylase levels were routinely measured in the FGCL-4592-040 study and mean levels were not found to be elevated during the course of the study. A higher incidence of pancreatitis in subjects with type 2 diabetes mellitus, and CKD, is well defined in the literature.

For further information please refer to the most recent version of the IB.

1.3.2 Epoetin alfa (Comparative Drug)

In the studies conducted for the U.S. approval of epoetin alfa in adult patients on dialysis (more than 567 patients), the incidence (number of events per patient-year) of the most frequently reported AEs were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year [Procrit Prescribing Information].

Events reported to have occurred within several hours of administration of epoetin alfa were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

AEs observed during post marketing experience included an increased incidence of thrombotic vascular events (TVEs) in patients receiving ESAs including epoetin alfa. These include venous and arterial thrombosis and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis and myocardial infarction. Additionally, cerebrovascular events (including cerebral infarction, cerebral haemorrhage and transient ischaemic attacks) have been reported.

A warning on possible cross reactivity of epoetin antibodies with different epoetins and to a number of adverse drug reactions was added in the SmPC. There are no known clinically significant drug interactions but the effect of epoetin alfa may be potentiated by the simultaneous therapeutic administration of a haematinic agent such as ferrous sulphate when a deficiency state exists. Drugs that decrease erythropoiesis may decrease the response to epoetin alfa. For more details please refer to the Eprex® SmPC.

More recently 2 large prospective randomized controlled studies have raised questions about the appropriate management of anemia with epoetin in CKD and ESRD patients. The Normal Hematocrit Study (NHS), a randomized, open-label study of 1265 patients with CKD on dialysis with documented evidence of congestive heart failure or ischemic heart disease, was designed to test the hypothesis that a higher target hematocrit would result in improved outcomes compared with a lower target hematocrit. In this study, subjects were randomized to epoetin alfa treatment targeted to a maintenance Hb of either 14 ± 1 g/dL or 10 ± 1 g/dL. The study was terminated early with adverse safety findings of higher mortality in the high hematocrit target group. Higher mortality (35% vs. 29%) was observed for the subjects randomized to target Hb of 14 g/dL compared to the subjects randomized to target Hb of 10 g/dL. For all-cause mortality, the HR was 1.27; (95% CI 1.04, 1.54; p = 0.018). The incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target Hb of 14 g/dL.

Similar safety findings were noted in the CHOIR study, a randomized, prospective study conducted in 1432 patients with anemia due to CKD who were not undergoing dialysis and who had not previously received epoetin alfa therapy. Patients randomized to epoetin alfa treatment targeting a maintenance Hb concentration of either 13.5 g/dL or 11.3 g/dL. The study was terminated early with adverse safety findings. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred in 125

of the 715 subjects (18%) in the higher Hb group compared to 97 of the 717 subjects (14%) in the lower Hb group [hazard ratio (HR) 1.34, 95% CI: 1.03, 1.74; p = 0.03].

Finally, the outcome of the CREATE study [Drüeke, 2006] which assessed the efficacy and safety of treatment of anemic nondialysis patients using epoetin beta at two different Hb target ranges led to similar conclusions.

The EMEA's Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party concluded that the benefits of the ESAs including epoetin alfa continue to outweigh their risks in the approved indications. However, the CHMP recommended changes to the product information, and in February 2008 the European Commission made the final decision to amend the SmPCs of all ESAs. The reported risk of TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa, particularly in patients with pre-existing risk factors. In all patients, Hb concentrations should be closely monitored due to a potentially increased risk of thromboembolic events and fatal outcomes when patients are exposed to Hb concentrations above the range for the indication of use (10-12 g/dL in patients with chronic renal failure). For more details please refer to the Eprex® SmPC.

1.3.3 Darbepoetin alfa (Comparative Drug)

The safety profile of darbepoetin alfa was assessed in 1578 CKD subjects treated with darbepoetin alfa and 591 treated with r-HuEPO. Out of the 1578 subjects 847 (54%) received SC darbepoetin alfa. AEs were consistent across all studies and were similar in the 2 treatment groups – darbepoetin alfa and r-HuEPO. The majority of AEs were due to the underlying disease. Only hypertension, vascular access thrombosis and injection-site pain (SC route) were consistently reported as related to study drug. As hypertension is the most common AE with both darbepoetin alfa and r-HuEPO, and as most deaths were due to cardiac events, control of blood pressure is an important consideration in all CKD subjects. There were no overall changes in blood pressure or heart rate in the study although there was considerable variability in individual blood pressure measurements.

The clinical results showed that the safety profile of darbepoetin alfa is similar to that of r-HuEPO when administered by IV or SC. The odds-ratio (95% CI) between darbepoetin alfa and r-HuEPO for the incidence of AEs showed that there is no evidence that AEs occurred more frequently with IV darbepoetin alfa compared to r-HuEPO therapy. When administered by the SC route, the only event that occurred more frequently during darbepoetin alfa treatment was injection site pain.

The AEs observed during post marketing experience with darbepoetin alfa were: aggravated hypertension, cerebrovascular disorders, myocardial infarction, angina pectoris and skin reactions. A warning on possible cross reactivity of epoetin antibodies with different epoetins and to a number of adverse drug reactions was also added in the SmPC. Furthermore a warning was included in section 4.4 of the SmPC to specify that cases of severe hypertension, including hypertensive crisis, hypertensive encephalopathy, and seizures, have been observed in CKD subjects treated with darbepoetin alfa. Further to the request of the CHMP regarding the assessment of outcome of the TREAT study in March 2010,

additional warnings and the results of the TREAT study were included into the current product information for darbepoetin alfa. Also the specific section of the Aranesp Package Leaflet, section 2, "Before you use Aranesp®" was updated to align it with the SmPC, reflecting the concern that elevated Hb concentrations could increase the risk of myocardial infarction, stroke and death [EMEA, Aranesp 2004]. For more details please refer to the Aranesp® SmPC.

1.4 Risk-Benefit Assessment

The primary expected benefit of roxadustat is maintenance of Hb level within the recommended target range in subjects converted from ESA-based anemia treatment. Further, roxadustat may reduce anemia-related symptoms and signs, increase QoL, and reduce the need for IV iron therapy. Additional benefits include absence of a rise in blood pressure that is associated with ESA therapy, and a reduction in serum cholesterol level. Roxadustat is expected to be at least as safe as ESAs, and current data on surrogate outcomes suggest that cardiovascular risk may be lower than with ESAs.

An established dose adjustment algorithm, similar to the 1 used in phase 2 studies, will be applied for optimal roxadustat dose titration strategies. This allows correction and maintenance of Hb levels to the appropriate target range and facilitates close monitoring of Hb fluctuations over time.

Roxadustat doses may be held and the use of therapeutic phlebotomy is allowed in the event of clinical concerns for a subject's high Hb level. Per protocol, rules for the use of supplemental iron (oral or IV) and rescue treatments with epoetin alfa or darbepoetin alfa (roxadustat treated subjects only) and red blood cell transfusions are in place to assure subject safety in case of insufficient response to roxadustat treatment and/or acute need for correction of anemia.

In PK studies with roxadustat there was no evidence of drug accumulation with the proposed clinical regimen of 3 times weekly dosing. The overall frequency and nature of AEs and serious AEs (SAEs) observed in clinical studies generally reflect events what would be expected to occur in the CKD population (dialysis and nondialysis), and did not reveal any particular safety concern.

A drug interaction with statins is a potential risk. To mitigate this risk, recommendations for maximum statin doses are included in the study protocol. Also, the protocol includes a recommendation for the investigator to consider the posology of other concomitantly administered drugs that are substrates of the organic anion transporting polypeptide 1B1 (OATP1B1) and to refer to the SmPCs of these drugs.

Furthermore, there is a drug interaction with phosphate binders: concomitant intake of phosphate binders and roxadustat reduces the absorption of roxadustat.

Subjects should take roxadustat in a consistent manner relative to their phosphate binder intake, and discuss with the investigator before changing their phosphate binder dose or dosing time. As a further risk mitigation this study protocol includes a recommendation that roxadustat be taken separately from phosphate binders.

As it is anticipated that other multivalent cation-containing drugs and mineral supplements (e.g., iron, calcium, magnesium, aluminum), sucralfate or magnesium- or aluminum-containing antacids would produce a similar interaction, the study protocol includes the advice that roxadustat be taken separately from these drugs.

Epoetin alfa and darbepoetin alfa have been chosen as comparators to adequately assess the efficacy, safety and benefit of achieving Hb response and maintenance in anemic subjects treated with roxadustat. These are commonly used ESAs in Europe for the treatment of anemia of ESRD, and have demonstrated their ability to correct and maintain Hb levels in this target population in several randomized controlled studies. The rules for dose adjustment and for events of excessive hematopoiesis in the present study will follow their approved posology. In case of insufficient response to epoetin alfa and/or darbepoetin alfa, rules for RBC transfusions are in place in order to assure safety of the affected study subjects.

The safety of treatment with ESA comparators in this study will be carefully monitored to include AEs, SAEs and laboratory parameters. Emphasis will be placed on cardiovascular and cerebrovascular events, which are not uncommon in the study population; an independent expert panel will assess and adjudicate all significant occurrences of such events. In addition, an independent Data Safety Monitoring Board (DSMB) will perform regular, periodic assessments of blinded and unblinded data to detect any potential safety signals that may arise during the study and advise the sponsor accordingly.

Based on the clinical and nonclinical study results to date, it is anticipated that orally administered roxadustat will be comparable in efficacy to marketed parenteral ESA products in the treatment of anemia of CKD, with an acceptable safety profile. Roxadustat may offer a valuable alternative to the current treatment options in the management of anemia of CKD.

2 STUDY OBJECTIVES, DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in ESRD subjects on stable dialysis.

2.1.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the safety of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in ESRD subjects on stable dialysis.
- Evaluate the effects on health-related quality of life (HRQoL) of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in ESRD subjects on stable dialysis

2.2 Study Design and Dose Rationale

2.2.1 Study Design

2.2.1.1 General

This is a phase 3, multi-center, randomized, open-label, active-controlled study. This study is planned to recruit approximately 750 subjects from approximately 150 study centers, mainly located in Europe.

The study is planned to provide key efficacy and safety data for the approval of roxadustat in the treatment of anemia associated with ESRD on stable dialysis.

2.2.1.2 Study Population

The study population consists of adult subjects with ESRD who are on stable HD or PD and on stable treatment with epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa for anemia. Subjects on polyethylene glycol-epoetin beta (Mircera®) are not to be included. Subjects on hemodiafiltration (HDF) are also allowed to participate in the study and will follow the same study procedures and requirements as HD subjects. Prior to randomization a subject must be on the same mode of dialysis for ≥4 months and on epoetin or darbepoetin alfa treatment for ≥ 8 weeks with stable average weekly doses (defined as ≤30% change) during the last 4 weeks prior to randomization. Anemia is defined as the mean Hb of the 3 most recent screening measurements ≥ 9.5 g/dL and ≤ 12.0 g/dL with an absolute difference ≤ 1.3 g/ dL between the highest and the lowest value. Subjects must be iron replete at baseline; inclusion is permitted if ferritin ≥ 100 ng/mL (≥220 pmol/L) and TSAT ≥ 20%. Anemia of nonrenal origin is to be excluded. Washout periods of at least 4 weeks for any iron-chelating agents, and at least 8 weeks for any RBC transfusion prior to randomization have been mandated in order to exclude a potential impact of these recent anemia treatments on the assessment of efficacy.

2.2.1.3 Description of Study

Subjects assigned to the roxadustat treatment arm will receive roxadustat orally as a combination of tablets of different strengths. Subjects assigned to the ESA treatment arm will be administered epoetin alfa if they were on epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) prior to randomization or darbepoetin alfa in case they were on darbepoetin alfa prior to randomization. Study treatment administration is implemented in an open-label manner. Subjects on polyethylene glycol-epoetin beta (Mircera®) are not to be included.

The study will consist of 3 study periods:

- Screening Period: up to 6 weeks
- Treatment Period: For all subjects in the study the minimum treatment duration will be 52 weeks and the maximum treatment duration will be 104 weeks. The study end date will be declared when the targeted number of MACE* and MACE+** events have been reported across the roxadustat phase 3 development program and consequently the treatment will end for all subjects who have completed 52 weeks at that point. Subjects

who have not completed 52 weeks when the target has been declared will continue until they reach 52 weeks and at that point their treatment will end.

- Follow-up Period: 4 weeks

* MACE: Major cardiovascular adverse events: myocardial infarction, stroke, death from all causes

** MACE+: Myocardial infarction, stroke, death from all causes, chronic heart failure requiring hospitalization, unstable angina requiring hospitalization

During the course of the study, visits and assessments will be performed as defined in the Schedule of Assessments [Table 1].

Screening Period

During the screening period of up to 42 days, eligibility assessments will be performed. Subjects will continue epoetin or darbepoetin alfa treatment per local standard of care.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be randomized at Day 1 (baseline), which marks the end of screening period and start of the treatment period.

Treatment Period

Subjects are randomized to 1 of 2 treatment arms as illustrated in [Table 2].

- Treatment arm 1: subjects will be switched from epoetin or darbepoetin alfa treatment to roxadustat treatment (see Table 3 for doses).
- Treatment arm 2: subjects will continue ESA treatment, i.e. epoetin alfa if pretreated with any epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) and darbepoetin alfa if pretreated with darbepoetin alfa, at approximately the same average weekly dose the subject was on prior to randomization. It is not allowed to switch from epoetin alfa to darbepoetin alfa or vice versa, during the treatment period.

In case of randomization to epoetin alfa, all pretreatment used epoetin derivatives are considered dose equivalent and should be switched in a 1:1 fashion to epoetin alfa.

The randomization will result in an overall 1:1 ratio of subjects receiving roxadustat administered orally, or epoetin alfa or darbepoetin alfa administered by SC or IV injection.

Randomization to treatment arms will occur through an Interactive Response System (IRS).

Table 2 Treatment Arms, Dosing Frequencies and Patient Numbers

Treatment Arms	Study Treatment	Dosing Frequency	N
1	Roxadustat	TIW	375
2	ESA	Dosing per SmPC	375

TIW = 3 times weekly; ESA = epoetin alfa or darbepoetin alfa; SmPC = Summary of Product Characteristics

During the treatment period, subjects will attend weekly study visits from day 1 to week 8, followed by every other week study visits from week 10 to 36. Following week 36, study visits will occur every 4 weeks until the End of Treatment (EOT).

Randomization and administration of the first dose of study treatment (roxadustat or ESA) is to occur on day 1 which should correspond to a day when their next dose of epoetin or darbepoetin alfa would have been administered.

On day 1 all study procedures and assessments will be completed prior to the first study treatment administration.

During the treatment period, the aim is to maintain the Hb levels between 10.0 g/dL and 12.0 g/dL. All subjects receiving roxadustat will initiate and continue roxadustat dosing at a dosing frequency of TIW throughout the entire period and dose adjustment is to follow prespecified dose adjustment rules [Table 4]. Intake should occur at approximately the same time of day and, if possible, dosing days should remain consistent throughout the study. For HD subjects it is recommended that roxadustat is administered any time after completion of dialysis if dosing is scheduled on a dialysis day to avoid potential bias on certain study assessments. Specific rules apply on the dialysis day(s) at which PK sampling is scheduled [Section 5.6].

Epoetin alfa (Eprex®) or darbepoetin alfa (Aranesp®) should be administered IV or SC according to the Package Insert or SmPC (UK SmPC for Eprex® and EU SmPC for Aranesp®). Copies of these SmPCs will be distributed as part of the study materials. During the treatment period, epoetin alfa and darbepoetin alfa will be provided by the sponsor. Dosing, dosing frequencies and dose adjustments should be in accordance with the UK SmPC for Eprex® and EU SmPC for Aranesp®. The protocol-specified frequencies are once weekly, twice weekly or TIW for epoetin alfa; and once weekly or once every other week for darbepoetin alfa. In addition, the protocol allows for administration of epoetin alfa once every other week and darbepoetin alfa once every 4 weeks. These frequencies are only to be used in subjects on low ESA doses that do not fit into the normal frequencies of administration and if deemed clinically appropriate. For PD subjects, darbepoetin dosing every 4 weeks is allowed.

For both treatment arms dose adjustments are to be made based on Hb values using HemoCue®, a point-of-care device.

Subjects will receive study treatment (roxadustat or ESA) for a minimum of 52 weeks and a maximum of 104 weeks.

Follow-up Period

After the end of the treatment period subjects will proceed to the 4-week follow-up period. The choice of anemia treatment during the follow-up period is at the discretion of the investigator and according to local standards.

Post Study Follow-up *(only for subjects prematurely discontinued from treatment)*

Subjects who have prematurely discontinued study treatment will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit. Thereafter, these subjects who have taken at least 1 dose of study treatment, will continue to be followed up at a 6-monthly frequency for vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of the follow-up period (i.e. projected EOS visit) or until consent withdrawn. Data collection during this poststudy follow-up occur through phone calls or information collected from source data of subjects' regular, non-study, visits to the clinic. No additional study visits will be required from these subjects during the poststudy follow-up. The last poststudy follow-up data collection should occur around the projected EOS visit.

2.2.1.4 Randomization and Open-Label

A randomized design has been chosen in order to ensure a balanced allocation of study subjects to the treatment arms and to minimize bias in therapeutic management and assessment of outcomes.

An open-label design was chosen for several reasons. A blinded design warrants a double-blind, double-dummy design to match the active comparator, and this is in principle not feasible given the anticipated need for frequent dose adjustments during the study. In addition ESA study drugs (i.e. epoetin alfa or darbapoetin alfa) are supplied by different manufacturers and differ by SmPC and dosing specifications further hampering the possibility of a blinded design. Another aspect is that a double-blind, double-dummy design may elicit inadvertent unblinding due to differences in the need for iron supplementation between roxadustat and ESA treated subjects. Finally, the primary endpoint of the study is based on Hb level, which is an objective measurement with low risk for introducing bias. Overall an open label study design is therefore considered the most reasonable option.

2.2.1.5 Comparative drug

For subjects randomized to ESA epoetin alfa or darbepoetin alfa, the starting dose, frequency and mode of application (IV or SC) are at the investigator's discretion provided the average weekly dose remains approximately the same as prior to randomization.

2.2.2 Roxadustat Dose Rationale

Initial dose of roxadustat

The initial study drug (roxadustat) dose is based on the dosing scheme shown in [Table 3] and is determined by the subject's average prescribed weekly dose of epoetin or darbepoetin alfa within 4 weeks prior to randomization.

Based on dose data and Hb data from an earlier study in dialysis subjects, a simplified dosing guide for conversion from 3 different dose ranges of epoetin alfa at baseline for Hb maintenance has been developed (see Section 1.2.2.2). Three methods of modeling of dose relationship between roxadustat and baseline stable epoetin dose requirement (change in Hb levels versus Ln dose ratio, doses–Hb change modeling over 19 weeks, dose ratio in the last 4 weeks of treatment), taking into account change in Hb, yield a dose ratio of 17 to 37, epoetin (IU/week) : roxadustat (mg TIW).

Table 3 Initial Dose of Roxadustat

epoetin† (IU/week)	**darbepoetin alfa†** (µg/week)	**roxadustat** (mg/dose) TIW
<8,000	<40	100
8,000 to 16,000	40-80	150‡
>16,000	>80	200§

† Average prescribed weekly dose in the last 4 weeks prior to randomization.
‡ If the initial dose of 150 mg exceeds the maximum dose of 3.0 mg/kg, then 100 mg is to be used as the starting dose.
§ If the initial dose of 200 mg exceeds the maximum dose of 3.0 mg/kg, then 150 mg is to be used as the starting dose.

Dose adjustments for roxadustat

Dose adjustment of roxadustat will be aimed at keeping subjects' Hb levels between 10.0 to 12.0 g/dL and will be based upon current Hb (assessed with the HemoCue® point-of-care device at the investigational site) and change in Hb over the preceding 4 weeks.

More details on dose adjustments are described in Section 5.1.2.1.

Maximum dose for roxadustat

The maximum allowed roxadustat dose in this study is set at 3.0 mg/kg (based on postdialysis weight in HD subjects and weight minus abdominal fluid based on last filling in PD subjects) or 400 mg per administration, whichever is lower. The highest dose tested in healthy subjects is 5 mg/kg single dose and 3.75 mg/kg TIW. The doses were safe and well tolerated with transient dose dependent heart rate increases observed. No maximum tolerated dose was reached in the clinical development of roxadustat based on the observed pharmaco-dynamic response (plasma EPO levels) and the predicted relation between EPO levels and Hb response; therefore exploration of higher doses was not deemed necessary. Plasma EPO levels increased in a supra-linear manner with increasing roxadustat doses. It is expected that the majority of the subjects will show adequate Hb response at substantially lower doses than the maximum allowed dose.

The treatment period of 104 weeks will provide sufficient data on the efficacy and safety of long term treatment of anemia with roxadustat in ESRD subjects on stable dialysis.

2.3 Endpoints

All statistical analyses are performed using the Central Laboratory data.

2.3.1 Primary Endpoint

There are 2 separate regionally based primary efficacy endpoints in this study, depending upon whether the data are being filed to support submission to the US FDA or to Ex-US health authorities, such as the EMA.

- The EU (EMA) primary efficacy endpoint is change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 36), without having received rescue therapy (i.e. RBC transfusion for all subjects or ESA for subjects treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period.
- The US (FDA) primary efficacy endpoint is change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 52), regardless of rescue therapy.

2.3.2 Key Secondary Endpoints

The secondary efficacy endpoints in this study are:

- Hb response, defined as mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

- Change from BL in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol of weeks 12 to 28.
- Mean monthly IV iron use (mg) during day 1 to week 36 (monthly defined as a period of 4 weeks).
- Change from BL in SF-36 Physical Functioning (PF) sub-score to the average PF sub-score of weeks 12 to 28.
- Change from BL in SF-36 Vitality (VT) sub-score to the average VT sub-score of weeks 12 to 28.
- Blood pressure effect
    - Change from BL in mean arterial pressure (MAP) to the average MAP value of weeks 20 to 28.
    - Time to an increase in blood pressure: An increase from BL of ≥ 20 mm Hg systolic blood pressure (SBP) and SBP ≥ 170 mmHg or an increase from baseline of ≥15 mmHg diastolic blood pressure (DBP) and DBP ≥ 100 mmHg during weeks 1 to 36.

2.3.3 Additional Secondary Endpoints

2.3.3.1 Efficacy Endpoints

Hb maintenance:

- Hb response during weeks 28 and 36 regardless of use of rescue therapy. Hb response defined as mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL.
- Hb change from BL to each postdosing time point.
- Hb level averaged over weeks 28 to 36, 44 to 52, and 96 to 104 without use of rescue therapy within 6 weeks prior to and during these 8-week evaluation periods.
- Hb change from BL to the average Hb value of weeks 28 to 36, 44 to 52, and 96 to 104 regardless of the use of rescue therapy.
- Proportion of Hb values within 10.0 to 12.0 g/dL in weeks 28 to 36, 44 to 52, and 96 to 104 without use of rescue therapy within 6 weeks prior to and during these 8-week evaluation periods.

Hospitalizations:

- Occurrence (number) of hospitalizations (HD days are not counted as hospitalizations, even when performed overnight).
- Number of days of hospitalization.

Rescue therapy use:

- Having received rescue therapy [composite of RBC transfusions (all patients) and rescue ESA (roxadustat treated subjects only).
- Having received RBC transfusions.
- Number of RBC packs per subject.
- Volume of RBC transfused per subject.

Iron use:

- Having required IV iron supplementation.
- Mean monthly IV iron (mg) per subject during weeks 37-52 and weeks 53-104 (monthly defined as a period of 4 weeks).
- Having required oral iron supplementation.
- Mean monthly oral iron (mg) use per subject during day 1 to week 36, weeks 37 to 52, and weeks 53-104 (monthly defined as a period of 4 weeks).

Changes in cholesterol levels, apolipoproteins

- Change from BL to each postdosing study visit in
  - Total cholesterol.
  - LDL/High-density Lipoprotein (HDL) ratio.
  - Non-HDL cholesterol.
  - Apolipoproteins A1 and B.
  - ApoB/ApoA1 ratio.
- Occurrence of mean LDL cholesterol <100 mg/dL calculated over weeks 12 to 28.

Blood pressure effect:

- Occurrence of achieved antihypertensive treatment goal in CKD subjects (SBP < 140 mmHg and DBP < 90 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28.

HRQoL and European Quality of Life 5 Domain 5 Level (EQ-5D 5L):

- Change from BL to the average value of weeks 12 to 28 in
  - SF-36 Physical Component Score.
  - Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score.
  - Total FACT-An Score.
  - EQ-5D 5L visual analogue scale (VAS) Score
- Patients' Global Impression of Change (PGIC) (qualitative assessment)

Hepcidin, Iron status, Glycated hemoglobin (HbA1c):

- Changes from BL to each study visit (when measured) in:
  - Serum hepcidin
  - Serum ferritin
  - TSAT
  - Glycated hemoglobin (HbA1c) level

2.3.3.2 Safety endpoints

Safety will be assessed by evaluating the following:

- Occurrence of AEs, SAEs, TEAEs, treatment-emergent serious adverse events (TESAEs) and clinically significant changes in laboratory values from BL.
- Changes from BL in vital signs, electrocardiogram (ECG) findings and clinical laboratory values.

- Occurrence, and time to occurrence, of prespecified adjudicated cardiovascular and cerebrovascular events (will be reported separately). Various region-specific pooled analyses of prespecified adjudicated cardiovascular and cerebrovascular events (such as major cardiovascular adverse events [MACE, MACE+] and other events) will be conducted; these analyses will be detailed in region-specific pooled safety analysis plans.

3 STUDY POPULATION

3.1 Selection of Study Population

The study population consists of adult subjects with ESRD who are on stable dialysis (HD, HDF or PD) and on stable treatment with epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa for anemia. Subjects on polyethylene glycol-epoetin beta (Mircera®) are not to be included.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations has been obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject age is ≥18 years.
3. Subject is on stable HD, HDF or PD treatment with the same mode of dialysis for ≥ 4 months prior to randomization.
4. For subject receiving hemodialysis, the vascular access must be via native arteriovenous (AV) fistula or graft, or permanent, tunneled catheter.
5. Subject is on IV or SC epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or IV or SC darbepoetin alfa treatment for ≥8 weeks prior to randomization with stable weekly doses (≤ 30% change from the maximum prescribed average weekly dose, i.e. ([max-min]/max ≤ 0.3) during 4 weeks prior to randomization. Subjects on polyethylene glycol-epoetin beta (Mircera®) are not to be included.
6. Mean of the subject's 3 most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart, must be ≥ 9.5 g/dL and ≤ 12.0 g/dL with an absolute difference ≤ 1.3 g/dL between the highest and the lowest value. The last Hb value must be within 10 days prior to the randomization visit (day 1).
7. Subject has a ferritin level ≥ 100 ng/mL (≥220 pmol/L) at screening.
8. Subject has a transferrin saturation (TSAT) level ≥ 20% at screening.
9. Subject has a serum folate level ≥ lower limit of normal (LLN) at screening.
10. Subject has a serum vitamin B_{12} level ≥ LLN at screening.

11. Subject's alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are ≤ 3 x upper limit of normal (ULN), and total bilirubin (TBL) is ≤ 1.5 x ULN.
12. Subject's body weight (postdialysis weight) is 45.0 kg to a maximum of 160.0 kg.
13. Female subject is either:
    Of non-childbearing potential:
    - postmenopausal (defined as at least 1 year without any menses) prior to screening,
    - or documented surgically sterile.

    Or if of childbearing potential:
    - agree not to try to become pregnant during the study and for 28 days after the final study drug administration.
    - must have a negative serum pregnancy test at screening and
    - if heterosexually active, agree to consistently use a highly effective form of birth control* starting at screening and throughout the study period, and continue to do so for 28 days after the last study treatment administration. If required by local law, 2 highly effective methods of birth control must be used, 1 of which must be a barrier method.
14. Female subject must agree not to breastfeed starting at screening or during the study period, and continue to do so for 28 days after the final study treatment administration.
15. Female subject must not donate ova starting at screening and throughout the study period and continue to do so for 28 days after final study treatment administration.
16. Male subject and their female spouse/partner(s) who are of childbearing potential must be using a highly effective form of birth control starting at screening and continue to do so throughout the study period, and for 12 weeks after final study treatment administration. If required by local law, 2 highly effective methods of birth control must be used, 1 of which must be a barrier method.
17. Male subject must not donate sperm starting from screening, throughout the study period and up to 12 weeks after final study drug administration.
18. Subject agrees not to participate in another interventional study from the time of signing informed consent until the End of Study visit (EOS).

    * Highly effective forms of birth control include:
    - Consistent and correct usage of established oral contraception.
    - Injected or implanted hormonal methods of contraception.
    - Established intrauterine device (IUD) or intrauterine system (IUS).
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (if allowed by local regulations).
    - Any male partner that has undergone effective surgical sterilization.
    - Any female partner that has undergone effective surgical sterilization, if applicable.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject has received a Red Blood Cell (RBC) transfusion within 8 weeks prior to randomization.
2. Subject has a known history of myelodysplastic syndrome or multiple myeloma.
3. Subject has a known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia, or other known causes for anemia other than CKD.
4. Subject has a known hemosiderosis, hemochromatosis, coagulation disorder, or hyper-coagulable condition.
5. Subject has a known chronic inflammatory disease that could impact erythropoiesis (e.g., systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission.
6. Subject is anticipated to undergo elective surgery that is expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization.
7. Subject has active or chronic gastrointestinal bleeding.
8. Subject has received any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor.
9. Subject has been treated with iron-chelating agents within 4 weeks prior to randomization.
10. Subject has a history of chronic liver disease (e.g. cirrhosis or fibrosis of the liver).
11. Subject has known New York Heart Association Class III or IV congestive heart failure.
12. Subject has had a myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thrombo-embolic event (e.g., deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.
13. Subject has had uncontrolled hypertension, in the opinion of the investigator, within 2 weeks prior to randomization
14. Subject has known hypersensitivity to epoetin alfa (Eprex®), darbepoetin alfa (Aranesp®) or any of their excipients.
15. Subject has a diagnosis or suspicion (e.g., complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma as shown on renal ultrasound, or another appropriate imaging method, within 12 weeks prior to randomization.
16. Subject has a history of malignancy, except for 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.

17. Subject is positive for any of the following:
    - human immunodeficiency virus (HIV)
    - hepatitis B surface antigen (HBsAg), or
    - anti-hepatitis C virus antibody (anti-HCV Ab)
18. Subject has an active clinically significant infection manifested by White Blood Count (WBC) >ULN, and/or fever, in conjunction with clinical signs or symptoms of infection within 1 week prior to randomization.
19. Subject has a known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion.
20. Subject has had any prior organ transplant (that has not been explanted), or subject is scheduled for organ transplantation.
21. Subject has participated in any interventional clinical study or has been treated with any investigational drugs within 30 days or 5 half lives or limit set by national law, whichever is longer, prior to the initiation of screening.
22. Subject has an anticipated use of dapsone in any dose amount or anticipated chronic use of acetaminophen/paracetamol > 2.0 g/day during the treatment or follow-up period of the study.
23. Subject has a history of alcohol or drug abuse within 2 years prior to randomization.
24. Subject has any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENTS

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug

Roxadustat is supplied as red, film-coated, oval tablets for oral administration, in strengths of 20, 50 and 100 mg. All ingredients used for the manufacture of roxadustat tablets comply with US and EU compendial or regulatory standards. Tablet strengths are different in size and debossing reflects the strength (i.e. 20, 50 or 100).

The excipients include lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, and colorant Red Opadry II.

4.1.2 Comparative Drugs

Epoetin alfa (Eprex®) is supplied as a solution for SC or IV injection in a pre-filled syringe. It will be centrally provided by a Contract Research Organization (CRO) in the following strengths: 1000, 2000, 3000, 4000, 6000 and 8000 IU, and needs to be administered according to the UK SmPC of Eprex® (see investigator site file).

Darbepoetin alfa (Aranesp®) is supplied as a solution for SC or IV injection in a pre-filled syringe. It is centrally provided by a CRO in the following strengths: 10, 20, 30, 40, 60 and 100 µg, and needs to be administered according the EU SmPC of Aranesp (see investigator site file).

All administrations will be performed by the investigator or a qualified member of the site staff, by the subject themselves or caregiver, e.g. relative, if well trained and willing to self-administer.

4.2 Packaging and Labeling

All supplied medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at the sponsor Astellas Pharma Europe B.V. (APEB) or sponsor's designee in accordance with APEB or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice guidelines, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

The test drug and comparative drugs will bear a label conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

A Qualified Person of APEB or sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

Roxadustat tablets are presented in white high-density polyethylene bottles with a black lining, for optimal light protection, and closed with a foil induction seal and a white, child resistant cap. Due to the light sensitive nature of roxadustat and to minimize exposure of the active pharmaceutical ingredients to light, tablets should remain in the original packaging until time of administration and be administered as intact tablets only. The tablets are packed in bottles per six tablets. Each bottle will have an unique Kit number.

Epoetin alfa and darbepoetin alfa will be provided as a solution for injection in pre-filled syringes. Each pre-filled syringe will be packaged in a single box. Each box will have a unique kit number.

For storage and administration purposes, please refer to the UK SmPC of Eprex® and EU SmPC of Aranesp® to warrant correct use.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by the investigator/or designee and that:

- such deliveries are recorded,
- study drug is handled and stored according to labeled storage conditions,
- study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- any unused study drug is returned to the sponsor.

Drug inventory and accountability records for the study drugs will be kept by the investigator/or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs at the site's pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense the study drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of the study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the sponsor or designee at the end of the study or upon expiration. Only if agreed by the sponsor, standard procedures for the alternative disposition of the unused study drug can be followed, after drug accountability has been conducted by the sponsor or representative. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request.
- ESA treatment to be given from randomization to EOT will be provided by the sponsor, the ESA medication needed in the screening period or after EOT visit will not be provided by the sponsor.

4.4 Blinding

This section is not applicable as this is an open-label study.

4.5 Assignment and Allocation

Randomization and treatment assignments will occur through an IRS system prepared on behalf of the sponsor (under the responsibility of the Global Data Science Department of APEB). Specific procedures for randomization through the IRS are contained in the study procedures manual.

A total of approximately 750 subjects will be randomized to 1 of the 2 treatment arms in a 1:1 ratio as follows:

- Treatment Arm 1: roxadustat
- Treatment Arm 2: ESA (epoetin alfa or darbepoetin alfa)

See also Table 2 [Section 2.2.1.3] for the treatment arms.

Randomization will be stratified by the following 5 factors:

- Previous ESA treatment (epoetin versus darbepoetin alfa)
- Region (region A versus region B*)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No)
- Average prescribed weekly ESA dose in last 4 weeks prior to randomization (≤200 IU/kg epoetin or ≤ 1 µg/kg darbepoetin alfa versus >200 IU/kg epoetin or > 1 µg/kg darbepoetin alfa)
- Screening Hb value (≤11.0 g/dL versus >11.0 g/dL)

  * Country assignment to region A and B will be determined based on health care system comparability.

5 TREATMENTS AND EVALUATION

Subjects must provide a signed Informed Consent Form (ICF) and be registered in IRS before any screening assessments are performed. Participating study sites are required to document all screened candidates who provided informed consent. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and in the electronic case report form (eCRF).

Registration of subjects into the study, assignment of subject identification numbers, and randomization will take place using a centralized IRS system. Following informed consent and prior to the start of the first screening assessments the investigator will register the subject in IRS, starting the 42-day screening period, and a subject identification number will be assigned. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

If any of the subject's laboratory parameter results does not meet the inclusion criteria or meets an exclusion criteria this laboratory assessment may be repeated once within the 42 day screening period. This includes assessment of an additional (4th) Hb value, bearing in mind that the mean of 3 last Hb values during the 42 day screening period, obtained at least 4 days apart, will be used to calculate the subject's eligibility.

If a subject fails screening, they will be registered in IRS as a screen failure and considered out of the study. However subject may be re-screened once (immediately or later) if deemed appropriate by the investigator. When a subject will be re-screened, the subject must be re-consented and a new 42-day screening period starts and all screening procedures must be repeated. Subject must also be registered in IRS again as re-screened under the same number as first screening.

After all screening assessments have been completed to determine study eligibility, the subject may be randomized. Subjects confirmed not eligible after screening or, if applicable, after re-screening, should be registered in IRS as a screen/re-screen failure.

5.1 Dosing and Administration of Study Drugs and Other Medication

5.1.1 Dose/Dose Regimen and Administration Period

Following the screening period, eligible subjects who are randomized will enter the treatment period (day 1). Treatment will be given in an open label manner.

- Subjects will be randomized via IRS to receive roxadustat or ESA (epoetin alfa or darbepoetin alfa). Randomization and administration of the first dose of study treatment (roxadustat or ESA) are to occur on day 1, which should correspond to a day when the subjects' next dose of epoetin or darbepoetin alfa would have been administered. The first dose of study treatment should be taken after all study assessments have been completed; in HD subjects only, study assessments should also be performed prior to or at initiation of dialysis (except for postdialysis weight and postdialysis vital signs, which should be measured post dialysis).
- All subjects will be treated for a minimum of 52 and a maximum of 104 weeks.

Subjects receiving roxadustat

Roxadustat tablets will be dispensed at each study visit during the treatment period with defined dosing schedule and instructions for self-administration. The tablets are to be swallowed whole with room-temperature drinking water.

The initial roxadustat dose is based on the conversion table shown in Table 3 and is determined by the subject's average weekly dose of epoetin or darbepoetin alfa within 4 weeks prior to randomization.

All HD and PD subjects receiving roxadustat will initiate and continue roxadustat dosing at a dosing frequency of TIW throughout the entire study period. The period between 2 roxadustat administrations should be at least 36 hrs. Dosing days should remain consistent throughout the study. For HD subjects it is recommended that roxadustat is administered any time after completion of dialysis if dosing is scheduled on a dialysis day to avoid potential bias on certain study assessments.

An exception is made for the visit(s) where blood samples are drawn for PK analysis as described in Section 5.6

Dose adjustments of roxadustat are to follow prespecified dose adjustment rules [Table 4] and will be aimed at keeping subject's Hb levels between 10.0 to 12.0 g/dL. Dose adjustments will be based upon current Hb and change in Hb over the preceding 4 weeks as described in Section 5.1.2.1

Subjects receiving ESA

Epoetin alfa (Eprex®) or darbepoetin alfa (Aranesp®) should be administered IV or SC according to the Package Insert or SmPC (UK SmPC for Eprex® and EU SmPC for Aranesp®). The initial dose and frequency of administration are at the investigator's discretion provided that the average weekly dose remains approximately the same as prior to randomization.

During the treatment period, epoetin alfa and darbepoetin alfa will be provided by the sponsor. Dosing, dosing frequencies and dose adjustments should be in accordance with the UK SmPC for Eprex® and EU SmPC for Aranesp®. The protocol-specified frequencies are once weekly, twice weekly or TIW for epoetin alfa; and once weekly or once every other week for darbepoetin alfa irrespective of the frequency of administration prior to randomization. In addition, the protocol allows for administration of epoetin alfa once every other week and darbepoetin alfa once every 4 weeks. These frequencies are only to be used in subjects on low ESA doses that do not fit into the normal frequencies of administration and if deemed clinically appropriate. For PD subjects, darbepoetin dosing every 4 weeks is allowed.

All administrations will be performed by the investigator or a qualified member of the site staff or by the subject themselves or caregiver, e.g. relative, if well trained and willing to self-administer.

For both ESAs the target of treatment is maintaining Hb in the range of 10.0 to 12.0 g/dL.

Investigators and subjects should make every effort to keep dosing days and dosing times consistent throughout the study.

5.1.2 Increase or Reduction in Dose of Study Drug

5.1.2.1 Dose Adjustment Rules

All doses, dose decisions and reasons will be documented in the eCRF for both roxadustat and ESAs.

Subjects receiving roxadustat

Dose adjustments are permitted on a 4-weekly interval from week 4 onwards and will be aimed at keeping subjects' Hb levels between 10.0 to 12.0 g/dL and will be based upon current Hb levels and change in Hb over the preceding 4 weeks as illustrated in [Table 4] (deviation from the 4-week period is allowed anytime during the study in case of excessive hematopoiesis or Hb ≥13.0 g/dL).

Table 4 Dose Adjustment Rules for Roxadustat

Change in Hb Over Past 4 Weeks (g/dL)[a]	Hb (g/dL)		
	<10.5	10.5 to <12.0	12.0 to <13.0
< -1.0	↑	↑	No change
-1.0 to 1.0	↑	No change	↓
> 1.0	No change	↓	↓

Hb: hemoglobin

[a] Subtract first Hb value from last value Hb to calculate the change

- All dose adjustments are made based on Hb values using HemoCue®, a point-of-care device.
- Dose increases by 1 dose step (↑) and reductions by 1 dose step (↓) are pre-set

- If the dose adjustment is 'No change' per the above table, the dose remains unchanged and the next dose adjustment review is 4 weeks after that visit.
- The dose steps for roxadustat are as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.
- The maximum dose is the dose step corresponding to 3.0 mg/kg (based on postdialysis weight in HD subjects and in PD subjects weight minus abdominal fluid based on last filling) per administration or 400 mg, whichever is lower. At study visits where weight is collected the default weight and maximum allowed dose step for a subject will be adjusted if the weight change is ≥ 5% compared to the previous default weight collected in the study. Initial default weight is weight at randomization visit.
- If there is a safety concern, investigators may deviate from the dose adjustment rules for roxadustat. This should be discussed with the medical monitor and documented in the source documentation.
- Contact the medical monitor if dose adjustments would lead to doses outside the limits of the dose step range; i.e. lower than 20 mg or higher than 400 mg.

In the following cases dose adjustment may be made at any time outside the 4-weekly interval:

- Dose reduction in case of excessive hematopoiesis
- Dose increase by 1 step in case subject Hb < 9.0 g/dL (HemoCue®) and no dose adjustment occurred in the preceding 4 weeks.

<u>At any time when Hb ≥13.0 g/dL</u>

- Stop dosing
- Resume dosing when Hb <12.0 g/dL at a dose that is reduced by 2 steps
- Next dose adjustment review is 4 weeks after dose resumption and in 4-weekly intervals thereafter.

<u>Dose Adjustment for Excessive Hematopoiesis</u>

At any time during the Treatment Period:

- If Hb increases by >2.0 g/dL at any time within 4 weeks, the dose should be reduced by 1 dose step

<u>Note: Only 1 dose reduction for excessive hematopoiesis is recommended within a period of 4 weeks. If a blood transfusion has been performed or a course of ESA rescue therapy has been administered within 2 weeks of meeting the criteria for excessive hematopoiesis, it is recommended not to perform a dose reduction for excessive hematopoiesis.</u>

After a dose adjustment due to excessive hematopoiesis, the subject's next dose adjustment review will occur 4 weeks later, and in 4-weekly intervals thereafter.

If the dose adjustment interval falls on a non-visit study week, the dose adjustment review should be performed at the next scheduled study visit.

All dose decisions should be documented in the subject source data.

Subjects receiving ESA (epoetin alfa or darbepoetin alfa)

All dose adjustments are made based on Hb values using HemoCue®, a point-of-care device. Dose adjustments will aim at keeping subjects' Hb level between 10.0 to 12.0 g/dL.

During the treatment period, the active comparator drugs epoetin alfa (Eprex®) and darbepoetin alfa (Aranesp®) will be provided by the sponsor. Dosing, dosing frequencies and dose adjustments should be in accordance with the UK SmPC for Eprex® and EU SmPC for Aranesp®. The protocol-specified frequencies are once weekly, twice weekly or TIW for epoetin alfa; and once weekly or once every other week for darbepoetin alfa. In addition, the protocol allows for administration of epoetin alfa once every other week and darbepoetin alfa once every 4 weeks. These frequencies are only to be used in subjects on low ESA doses that do not fit into the normal frequencies of administration and if deemed clinically appropriate. Contact the medical monitor if dose adjustments would lead to doses lower than 1000 IU epoetin once every other week or 10 µg darbepoetin once every 4 weeks. For PD subjects, darbepoetin dosing every 4 weeks is allowed.

5.1.3 Previous and Concomitant Treatment

5.1.3.1 Previous Medication

Previous medications are any prescription or over-the-counter preparations, including herbal products and "natural remedies", used by a subject prior to screening.

If not specified differently, intake of any medication within 4 months prior to randomization should be documented in the eCRF. The medication name, start and stop date, route, dose and frequency, and indication for each medication will be entered in the eCRF.

The last treatment course of any prior treatment received for anemia (medication or procedures such as ESAs, oral or IV iron, and RBC transfusions) within 12 months prior to randomization will be documented in the eCRF.

Certain prior medications are prohibited for a specified time frame prior and/or during the study treatment period and/or until EOS. These medications and restrictions are described in Section 5.1.3.3.

5.1.3.2 Concomitant Medication

Concomitant medications are any prescription or over-the-counter preparations, including herbal products and "natural remedies", used by a subject from time of informed consent to EOS visit. The medication name, start and stop date, route, dose and frequency and indication for each medication will be entered in the eCRF.

For all concomitant medications, from informed consent to EOS visit, the study site must provide an indication for its use. If the stated indication is a non-specific condition, e.g. "rash", documentation of the condition, as specific as possible, should be recorded in the subject's clinical study records as source documentation.

Supplemental Iron Use

Subjects receiving roxadustat

a. Oral iron

Oral iron treatment is recommended for supplementation to support erythropoiesis and as first-line treatment for iron deficiency, unless the subject is intolerant to this treatment. The recommended daily dose is 200 mg of elemental iron. Subjects should be advised to take roxadustat at least 1 h before or 1 h after oral iron.

b. Intravenous (IV) iron

IV iron supplementation is allowed if all of the following criteria are met:

- The subject's Hb level has not responded adequately to roxadustat following 2 consecutive dose increases or reached the maximum dose limit, **and**
- The subject's ferritin is <100 ng/mL (<220 pmol/L) **or** TSAT < 20%, or the subject is intolerant of oral iron therapy.

Treatment with roxadustat should continue during IV iron administration. Discontinuation of IV iron administration is recommended once ferritin level ≥100 ng/mL (≥220 pmol/L) and TSAT ≥20%. Serum ferritin and TSAT can be measured at any time after IV iron delivery at the discretion of the investigator.

Subjects receiving ESA

For subjects treated with epoetin alfa or darbepoetin alfa, IV iron supplementation will be given according to standard of care.

Statins and Other Substrates for OATP1B1

There is a risk that roxadustat will increase the plasma levels of statins and other drugs that are substrates of OATP1B1, based on results from drug-drug interaction studies. Because statin dose has been known to be associated with the risk for side effects such as myopathy (e.g., myalgia, myositis and rhabdomyolysis), the investigator is advised to consider this potential interaction between roxadustat and statins when deciding on the appropriate dose of statins based on efficacy and safety of statin therapy. Switching to a non-interacting statin (e.g., pravastatin) may be considered. Furthermore, it is recommended not to exceed the proposed maximum daily dose of statins as outlined in Table 5

The investigator is also advised to consider this potential interaction between roxadustat and other drugs that are substrates for OATP1B1 when deciding on the appropriate posology of these drugs. Examples of these drugs are atrasentan, bosentan, ezetimibe, repaglinide, glyburide, SN-38 (active metabolite of irinotecan), rifampin, valsartan and olmesartan. It is recommended to refer to the SmPCs of these drugs for further details and guidance.

Table 5 Proposed Maximum Daily Dose of Statins Not to be Exceeded in Patients on Dialysis

Statin	Proposed maximum dose (mg/day)
Simvastatin	5
Atorvastatin	40
Rosuvastatin	Contraindicated
Fluvastatin	20
Pravastatin	40
Pitavastatin	1

Phosphate Binders and Other Multivalent Cation-containing Drugs and Mineral Supplements

Results from a drug-drug interaction study demonstrated a significant reduction in roxadustat plasma exposure when a single dose of roxadustat was administered simultaneously with the phosphate binders sevelamer carbonate or calcium acetate.

Subjects should take roxadustat in a consistent manner relative to their phosphate binder intake, and discuss with the investigator before changing their phosphate binder dose or dosing time. To reduce the effect of phosphate binders on roxadustat exposure, subjects should take roxadustat at least 1 h before or 1 h after their phosphate binder.

It is anticipated that other multivalent cation-containing drugs and mineral supplements (e.g., iron, calcium, magnesium, aluminum), sucralfate or magnesium- or aluminum-containing antacids would produce a similar interaction; therefore, administration of roxadustat between -1 h and +1 h of intake of these preparations is not recommended.

Anti-hypertensive and lipid-lowering medication

To avoid confounding effects on study endpoints, changes to anti-hypertensive and lipid lowering medications should be minimized as much as possible, and made only if deemed medically necessary by the investigator.

5.1.3.3 Prohibited Medication

The following medications are prohibited during the period identified:

- Any investigational drug: Within 30 days or 5 half lives or limit set by national law (whichever is longer), prior to the initiation of screening until EOS.
- Roxadustat or another hypoxia-inducible factor prolyl hydroxylase inhibitor: at any time prior to randomization. After randomization any hypoxia-inducible factor prolyl hydroxylase inhibitor other than roxadustat, as allocated by randomization, until EOS.
- Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy): from 4 weeks prior to randomization until EOS.
- Androgens: From randomization onwards until EOS.
- Dapsone in any dose amount, or chronic doses of acetaminophen/paracetamol >2.0 g/day, from randomization until EOS.

Use of herbal medicines is discouraged during the course of the study.

5.1.3.4 Procedure and non-drug therapy recording

Any other procedures or non-drug therapies need to be entered in subject's source documentation from informed consent until EOS and will also be recorded in the eCRF.

5.1.4 Treatment Compliance

For subjects randomized to roxadustat, the quantity of study drug dispensed to and returned by the subject will be counted and recorded in the eCRF [Section 5.1.1]. If the subject is non-compliant with study drug intake, the investigator should discuss this with the subject. Deviations should be entered into the eCRF. All roxadustat bottles dispensed to the subject should be returned by the subject to the site (including empty bottles) at each study visit for reconciliation of returned tablet count by the study monitor.

For subjects randomized to ESA, the quantity of study drug dispensed and confirmation of administration will be recorded in the eCRF. All administrations will be performed by the investigator or a qualified member of the site staff or by the subject themselves or caregiver, e.g. relative, if well trained and willing to self-administer.

The quantity and dose of syringes dispensed to the subject and confirmation that all doses have been taken will be recorded in the eCRF. The empty outer packages of ESA with the unique kit number should be returned by the subjects and stored at site for reconciliation by the study monitor. Empty syringes need to be handled and destroyed according to local requirements.

5.1.5 Rescue Therapy Guidelines

Rescue therapy guidelines are provided to optimize standardization of the use of rescue therapy by investigators and to ensure safety of the individual study subjects. Details of the rescue therapy will be recorded in the eCRF.

1. ***RBC Transfusion*** (for all subjects)

RBC transfusion is allowed if rapid correction of anemia is required to stabilize the patient's condition or the investigator is of the opinion that the RBC transfusion is a medical necessity. Study treatment may continue during or after transfusion administration. Hb needs to be measured pre- and posttransfusion (HemoCue®).

2. ***ESA*** (only for subjects treated with roxadustat)

One course of rescue ESA is allowed. If the investigator considers administration of ESA as a medical necessity, 1 course of rescue ESA may be initiated if the following criteria are met:

- the Hb level has not responded adequately despite 2 or more roxadustat dose increases in the previous 8 weeks, or the roxadustat dose has reached the maximum dose limit, and
- the subject's Hb level is < 9.0 g/dL (HemoCue®) as confirmed at 2 consecutive study visits, and
- reducing the risk of alloimmunization in transplant eligible subjects and/or reduction of other RBC transfusion-related risks is a goal.

Prior to the initiation of rescue ESA (epoetin alfa for subjects treated with any epoetin prior to randomization; and darbepoetin alfa for subjects treated with darbepoetin alfa prior to randomization), the subject's Hb response, as well as factors influencing the Hb response, such as iron status, inflammatory status, hemolysis, blood loss or other potential reasons for Hb decrease should be considered and, where applicable, addressed by the investigator. Prior to initiating ESA rescue therapy, iron deficiency should be corrected (i.e. 100 ng/mL [220 pmol/L] ferritin and 20% TSAT).

The subject may continue on study, however, the subject is not allowed to be administered both rescue ESA and roxadustat during the same time period. The course of rescue ESA (i.e. the amount that may be administered) will be limited by duration of therapy and effect on Hb, including that 1 course of treatment with rescue ESA will not exceed 4 weeks in duration, and that ESA rescue will be stopped as soon as Hb ≥9.0 g/dL as measured by HemoCue. Treatment with roxadustat may be resumed as soon as possible after the following intervals:

- At least 2 days after stop of epoetin alfa
- At least 1 week after stop of darbepoetin alfa

If a subject requires a second course of rescue with ESA, the subject must be discontinued from study treatment. The subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit, and will continue to be followed up at a 6-monthly frequency for vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion or until consent withdrawn.

Doses: The doses of rescue therapies are at investigator's discretion.

Emergency procedure

Therapeutic Phlebotomy

If there are clinical concerns for a subject's high Hb levels, the investigator may decide to perform a therapeutic phlebotomy instead of, or in addition to, a study treatment dose hold. This should be documented in the eCRF and source documentation, and discussed with the study medical monitor.

5.1.6 Restrictions During the Study

- Subjects are not permitted to consume more than 3 alcohol-containing drinks per day during the treatment or follow-up periods.
- If heterosexually active, female subjects of childbearing potential will be required to use a highly effective form of birth control. If required by local law, 2 highly effective methods of birth control must be used, 1 of which must be a barrier method.
- Heterosexually active male subjects with female partners of childbearing potential should also use a highly effective form of birth control. If required by local law, 2 highly effective methods of birth control must be used, 1 of which must be a barrier method.

- Contraception must be practiced from start of screening until 28 days (female subjects), and until 12 weeks (male subjects with female partners of childbearing potential) after the last dose of study treatment. If a subject discontinues prematurely, contraception must be practiced for 12 weeks (male subjects) and 28 days (female subjects) following final administration of study treatment.
- Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported (see Section 5.5.8).

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic data recorded during screening, including date of birth (depending on local regulations, if full date of birth cannot be recorded only year of birth will be recorded), sex and race will be recorded in the eCRF.

5.2.2 Medical History

A detailed medical history, including detailed cardiovascular history and family cardio-vascular history, will be obtained at screening. All relevant past and present conditions as well as previous and current tobacco use will be recorded in the subject's eCRF. Relevant conditions include conditions that have been treated with medication within 4 months prior to randomization. Additionally, family history of cardiovascular diseases in first degree relatives (occurring before the age of 60) will be obtained.

5.2.3 Renal Ultrasound

A renal ultrasound examination can be performed at any time during the screening period. This can be replaced by a pre-existing examination (or other renal imaging modality such as CT or MRI scan if it was conducted within 12 weeks prior to randomization and it conclusively excludes the presence of renal cell carcinoma). Examination results must be available prior to randomization (see exclusion criterion 15). The date and assessment for the absence, presence or suspicion of renal cell carcinoma will be collected in the eCRF.

5.2.4 Diagnosis of the Target Disease, Severity, and Duration of Disease

A detailed anemia and CKD history for each subject will be obtained at screening and recorded in the eCRF. This includes date of diagnosis and symptoms of anemia, the date of diagnosis of CKD, etiology, vascular access history, date of initiation of current and first dialysis and mode of current and first dialysis. Also the nondrug therapy history and medication history for anemia (last 12 months) and the nondrug therapy history for CKD (last 4 months) prior to randomization will be obtained.

Anemia will be measured by repeated Hb measurements (central laboratory assessment) during screening; the mean of the 3 most recent Hb values during the screening period, obtained at least 4 days apart, must be $\geq$ 9.5 g/dL and $\leq$ 12.0 g/dL, with an absolute difference of $\leq$ 1.3 g/dL between the highest and the lowest values. The last Hb value must be within 10 days prior to randomization.

Exclusion of other causes of anemia should be based on an integrated assessment of clinical and laboratory signs and symptoms as well as medical history.

5.2.5 Further Laboratory Testing Prior to Randomization

Other laboratory tests mandatory prior to randomization of a subject, for eligibility or baseline purposes, include enzyme-linked immunosorbent assay for human immunodeficiency virus, Hepatitis B surface antigen and anti-hepatitis C antibody and serum pregnancy test for women of childbearing potential only, serum chemistry and serum lipid panel.

For more details on the laboratory tests please refer to Section 5.4.3.

5.3 Efficacy Assessment

5.3.1 Primary Efficacy Assessment

The assessment of the efficacy of the study treatments will be based primarily upon Hb as assessed by central laboratory from IV blood sampling.

For the exact timing of Hb assessments refer to the Schedule of Assessments [Table 1].

The use of concomitant medication (as recorded in the eCRF) will be taken into account for the evaluation of the primary efficacy assessment.

5.3.2 Secondary Efficacy Assessments

5.3.2.1 Blood Pressure

Blood pressure will be assessed as per schedule of assessment, SBP and DBP will be measured and MAP will be calculated. Blood pressure will be measured before and after dialysis in HD patients. In PD patients, blood pressure will only be measured at 1 time point on the examination day, irrespective of current dialysis cycle. For details on the measurement of blood pressure refer to Section 5.4.1.1

5.3.2.2 Serum Lipid Panel

Blood sampling for serum lipids should be done in a fasting condition, wherever possible. The following parameters will be assessed: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apolipoproteins A1 and B.

5.3.3 Additional Assessments

5.3.3.1 Health Related Quality of Life Questionnaires

All study subjects will be required to complete the following 4 QoL questionnaires: SF-36, FACT-An, EQ-5D 5L and PGIC (see Appendices). The timing of the questionnaires is indicated in the Schedule of Assessments [Table 1].

In HD subjects the QoL questionnaires are to be completed by the subject prior to or at the latest at the start of the dialysis session. It is important that the investigator does not discuss the status of the subject prior to completion of the questionnaires.

In PD subjects, the QoL questionnaires are to be completed prior to any other study assessment.

5.3.3.1.1 Short Form-36 Health Survey (SF-36)

The SF-36 is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. It is aimed at both adults and adolescents aged 18 years and older. The SF-36 consists of 8 domains of health status: Physical functioning (10 items), Role-physical (4 items), Bodily pain (2 items), General health (5 items), Vitality (4 items), Social functioning (2 items), Role emotional (3 items) and Mental health (5 items). Two component scores, the Physical Component Summary and the Mental Component Summary can also be calculated. For both the SF-36 domain scores and summary scores, higher scores indicate better health status. The SF-36 has a recall period of the 'past 4 weeks'.

5.3.3.1.2 Functional Assessment of Cancer Therapy –Anemia (FACT-An)

The Functional Assessment of Cancer Therapy- General (FACT-G) Version 4 contains 27 items that cover 4 dimensions of physical well-being (PWB)—7 items, functional (FWB)—7 items, social/family (SWB)—7 items each, and emotional (EWB)—6 items. A subscale of 13 fatigue specific items (the Fatigue Subscale) plus seven additional items related to anemia were developed for use in conjunction with the FACT-G [Cella , 1997]. The 13 fatigue items plus the 7 additional items related to anemia comprise the Anemia Subscale (AnS). Administration of the FACT-G plus the AnS is referred to as the FACT-An (Appendix 12.5). The FACT-An has a recall period of the 'past seven days'. Respondents are asked to provide responses, (i.e. 'Not at all', 'A little bit', 'Somewhat', 'Quite a bit' and 'Very much'), to a list of statements which are either positively or negatively phrased. For all FACT-An scales, a higher score indicates better QoL.

5.3.3.1.3 EuroQol Questionnaire – 5 Dimensions 5 Levels (EQ-5D-5L)

The EuroQol Questionnaire -5 Dimensions -5 Levels (EQ-5D-5L) is a self-reported questionnaire. The EQ-5D is being used as a measure of respondents' Health Related Quality of Life (HRQoL) and utility values. The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems. The VAS records the respondent's self-rated health status on a graduated (0–100) scale, where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state' with higher scores for higher HRQoL. EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index. The EQ-5D-5L is shown in Appendix 12.6

5.3.3.1.4 Patient Global Impression of Change Scale (PGIC)

The PGIC (Appendix 12.7) is a subject-rated instrument that measures change in subjects' overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse), when compared to the start of the study treatment.

5.3.3.2 Hospitalizations

Details on hospitalizations will be collected at each study visit as indicated in the Schedule of Assessments. Reason, admission and discharge dates and type and reason for hospitalization

will be recorded in the eCRF. Details of hospitalizations will also be collected at poststudy follow-up visits in subjects who prematurely discontinued treatment (only if they have taken at least 1 dose of study drug), until the projected date of the EOS visit.

HD within the hospital is not considered to be a hospitalization, even when occurring overnight.

5.3.3.3 Iron Status, HbA1c and glucose

Serum iron, TSAT, ferritin, HbA1c and fasting blood glucose will be assessed (central laboratory) according to the Schedule of Assessments.

5.3.3.4 Additional Assessments

Exploratory assessments in this study include the following parameters:

- High Sensitivity C-reactive protein (hs-CRP)

Relevant selected biomarkers for the further characterization of the mode of action or adverse effects of roxadustat or for determination of their prognostic value in dialysis patients, may be assessed from archived serum/plasma samples.

5.4 Safety Assessment

5.4.1 Vital Signs

The vital signs blood pressure, heart rate, and respiratory rate will be assessed at the visits as described in the Schedule of Assessments.

5.4.1.1 Blood Pressure

Blood pressure measurement is recommended to be done with the subject comfortably seated in the dialysis bed or a chair, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum). The subject will be instructed to relax as much as possible and to not talk during the measurement procedure; ideally, 5 minutes should elapse before the first reading is taken. Preferably measurement will be done with an electronic automated oscillometric device. The same device should preferably be used for the subject during the course of the study, timing as indicated in the Schedule of Assessments. Also the same arm should be used consistently for readings throughout the study.

Blood pressure is recommended to be measured singly on each of the 3 visits during the screening period, and in triplicate with at least 2 minute intervals for all other study visits. All values will be reported in the eCRF.

In HD subjects both pre- and postdialysis measurements will be collected.

5.4.1.2 Heart Rate

Measurement of heart rate is recommended to be done at rest in a sitting position wherever possible. It can be performed with an oscillometric device as used for blood pressure measurement [Section 5.4.1.1], by using any other suitable device or manually (wrist heart rate within 1 minute). The same methodology and device should preferably be used for the

subject throughout the study, timing as indicated in the Schedule of Assessments. Heart rate will be measured singly on each of the 3 visits during the screening period and in triplicate with at least 2 minute intervals at day 1 and on all other visits. All values will be reported in the eCRF.

In HD subjects heart rate will be measured pre- and postdialysis.

5.4.1.3 Respiratory Rate

Measurement of respiratory rate will be done at rest in a sitting position wherever possible. It can be performed with any suitable device or manually (number of breathing cycles within 1 minute). The same methodology and device should preferably be used for the subject throughout the study, timing as indicated in the Schedule of Assessments. Respiratory rate will be measured singly during all visits.

In HD subjects a pre- and postdialysis respiratory measurement should be performed.

5.4.2 Adverse Events

AEs will be collected at all study visits. AE collection starts after obtaining signed informed consent and continues until the EOS visit. For subjects who continue in the post study follow-up period, SAEs and cardiovascular and thromboembolic AEs will be collected. AEs will not be collected during the period between first screen where subject has failed screening and first rescreening visit. See Section 5.5 for detailed information regarding AE collection and data handling. The collection and adjudication of prespecified cardiovascular and cerebrovascular events will be detailed in a separate adjudication charter.

5.4.2.1 Adverse Events of Possible Hepatic Origin

Subjects with AEs of hepatic origin accompanied by liver function test (LFT) abnormalities should be carefully monitored.

See Appendix 12.2 for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in the study and receiving study drug is accompanied by increases in LFTs (e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

In the event of a confirmed, severe hepatic abnormality as defined in Appendix 12.2 it is the investigator's responsibility to ensure contact with the medical monitor of the sponsor/delegated CRO by telephone or fax immediately (i.e. within 24 hours of awareness) for further follow-up.

5.4.3 Laboratory Assessments

In Table 6, the laboratory tests that will be performed during the conduct of the study are listed. The study visit collection time points are also described in the Schedule of Assessments (Table 1). In HD subjects, laboratory assessments should be performed prior to or at the initiation of dialysis. All details on the processing of the samples, storage and shipment conditions will be provided in a separate laboratory manual.

Table 6 Laboratory Tests

Lab Assessment Type	Parameters to be Analyzed
Hematology	**Complete Blood Count (CBC) with Red Cell indices and WBC differential** Hemoglobin (Hb) Hematocrit (Hct) Erythrocytes (RBC) Mean corpuscular volume (MCV) Mean corpuscular Hb (MCH) Mean corpuscular Hb concentration (MCHC) Leukocytes (WBC) Differential WBC • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils Platelet count
	Reticulocyte count and Hb in reticulocytes (CHr)
Serum Chemistry	Sodium Potassium Calcium Chloride Glucose Creatinine Magnesium Bicarbonate Phosphorus Uric Acid Albumin Total protein Lactate dehydrogenase Blood urea nitrogen Lipase
	Liver Function Tests: • AST • ALT • Bilirubin (Total and direct) • Gamma glutamyl transferase (GGT) Alkaline phosphatase (ALP)
	Lipid Panel (in **fasting** condition wherever possible): • Total Cholesterol • LDL • HDL • Triglycerides • Apolipoproteins A1, B
	Iron Ferritin TSAT TIBC
	Pregnancy test (female subjects of child-bearing potential only)
	HbA1c
	Vitamin B_{12} Folate

Table continued on next page

Lab Assessment Type	Parameters to be Analyzed
Serology (Immunology):	• HIV Ab • HBsAg • Anti-hepatitis C virus (HVC) Antibody Tests
Special Laboratory Analytes	High sensitivity C-reactive protein (hs-CRP)
	Serum Hepcidin
Serum Biomarkers	Archival of serum samples for biomarkers
PK analysis	Plasma – Level of roxadustat Covariates for PK • Albumin • α1-AGP
Dialysate (CAPD subjects)	Level of roxadustat
Genotyping (optional)	DNA isolation

The clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

5.4.4 Physical Examination

A **comprehensive** physical examination will be conducted during the screening visit, day 1 and at the EOT visit and recorded in the source documents. This examination (in HD subjects prior to dialysis) will include general appearance and the following body regions and systems: head, eyes, ears, neck and throat, lungs, heart, chest and back, abdomen, genitourinary, extremities, skin, and any other, if deemed necessary.

Height is measured only at screening. Weight is measured according to the Schedule of Assessments. For HD subjects weight is measured after completion of dialysis (postdialysis weight). For logistical reasons the weight to be recorded in the IRS for HD subjects is the postdialysis weight from last dialysis session before the scheduled study visit. For day 1 visit the postdialysis weight on the third screening visit is to be recorded in the IRS for HD subjects. For PD subjects weight is measured at the same time physical examination is done. For PD subjects weight is defined as weight minus weight of abdominal fluid based on last filling. One liter PD fluid is to be considered as 1 kg of weight. In case a subject's abdominal cavity is empty of fluid, the measured weight should be recorded as the true weight. Height and body weight will be recorded in the eCRF.

A **targeted** physical examination (e.g., respiratory and cardiovascular) will be conducted throughout the study as described in Schedule of Assessments [Table 1], and recorded in the source documents.

Only the date of the physical examination will be recorded in the eCRF. Any clinically relevant adverse change will be recorded as an AE in the eCRF (see Section 5.5.1).

5.4.5 ECG

12-lead ECGs will be performed at specific time points as described in the Schedule of Assessments as to local routines. A single ECG will be taken after the subject has been lying quietly in the supine position for 5 minutes. Any abnormalities must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the investigator

should determine if it is clinically significant. Clinically significant abnormalities should be reported as an AE.

Only the ECG date, Heart Rate, PR interval, QRS Interval, QT Interval, clinical significant and relevant comments will be recorded in the eCRF. The RR interval will be calculated in the eCRF using the Heart Rate. ECG recordings will be kept as source documents.

5.5 Adverse Events and Other Safety Aspects

Safety will be assessed throughout the study. A complete baseline profile of each subject will be established through medical history, clinical laboratory values, vital signs, physical assessments, and ECGs. During the course of the study, vital signs, comprehensive and targeted physical examinations, laboratory tests, and ECGs will be performed as described in the schedule of assessments. Any medically significant changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Clinical laboratory tests, vital signs or physical examinations etc. may be assessed at additional times on unscheduled visits for safety reasons.

AEs, SAEs, and concomitant medication usage will be monitored and recorded throughout the study.

5.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the (e)CRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

AEs present **prior** to starting study treatment at day 1 will be considered as 'non-treatment emergent'. Baseline conditions that worsen during the study will be recorded as AEs. AEs with a start date after subjects have completed EOS procedures will not be captured.

For AEs that resolve during the subject's participation in the study, a resolution date will be documented in the eCRF. AEs will be followed until resolved, stable, or until the subject's

last study visit or lost to follow up. AEs ongoing at the EOS visit will be followed up for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes and documented in source documents only.

Data to be recorded in the eCRF include a description of the event, date of onset, onset status (onset before/after first dose of study medication), end date of the event, severity, meeting seriousness criteria, action with respect to study medication, treatment required, relationship to study treatment and outcome of the event.

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 28 days after the last dose of study treatment or through to EOS, except for pregnancy reporting [Section 5.5.8]. For subjects that continue into the post study follow-up period, SAEs, cardiovascular and thromboembolic AEs will be captured until their projected date of completion of the follow-up period (i.e. projected EOS visit).

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from baseline or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever possible diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff. New indications for medications started after informed consent until 28 days after the last dose of study treatment or through to EOS visit, will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Abnormal, clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the investigator to meet criteria of an AE.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest ("Special Situations") on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

All of the events of interest noted above should be recorded on the SAE and/or Special Situation worksheet and within the timelines of reporting SAEs, thus within 24 h of becoming aware of this event, regardless whether or not a (S)AE occurred. The above special situations will not be captured on the AE form in the eCRF, instead they will be captured in the dosing and accountability forms within the eCRF.

Lack of efficacy (Hb decrease, worsening anemia without significant clinical symptoms) is not to be recorded or reported as an AE in this study, as the study end point monitors the effect of the study drug.

Due to the method of oral administration of roxadustat, the risk of transmission of infectious agents is limited for which reason these events do not need to be reported.

Off-label use of roxadustat can be excluded for reporting as the product is under development.

If a special situation also induces an AE, this AE should be recorded on the AE page of the eCRF. Note, the seriousness criteria described in this section do not apply for the above special situations themselves but only for their potentially induced AEs. This means that on the SAE worksheet the seriousness criteria for a special situation only should be left blank.

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested as well as expedited reporting within the timelines as demanded for SAEs.

If a subject becomes pregnant during treatment, this should be reported as if it were an SAE. Refer to Section 5.5.7

5.5.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.5.5 Reporting of Serious Adverse Events

In the case of an SAE, the investigator must contact the delegated CRO (INC Research) by telephone, e-mail or fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the delegated CRO by fax immediately (within 24 h of awareness). Toll free fax number for each country are provided on the fax coversheet of the SAE worksheet. In case of fax failure the SAE Worksheet should be emailed to the delegated CRO.

If the faxing of an SAE Worksheet is not possible or is not possible within 24 h, the local drug safety contact should be informed by phone.

The contact details of the delegated CRO are:

E-mail: INCDrugSafety@INCResearch.com
Fax (general): +49 89 99 39 13 422
Tel: +49 89 99 39 13 198

After checking for completeness and accuracy, the delegated CRO will send the SAE Worksheet and (when present) source documents (within 24 hours of receipt) to the sponsor.

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor or his/her designee or the delegated CRO (for contact details, see Section II of the protocol and as specified on the contact list in the investigator site file).

Follow-up information for the event should be sent promptly (within 7 days after awareness).

Full details of the SAE should be recorded on the medical records and on the eCRF. The investigator must ensure that information on the SAE Worksheet is reconciled with the information on the AE pages within the eCRF.

The following minimum information is required to be completed on the SAE Worksheet:

- The International Study Number (ISN)/Study number 1517-CL-0613,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

All SAEs, including death, should be reported, when occurring up to EOS visit or up to 28 days after the last intake of study medication, whichever is last. In addition, any event leading to hospitalization and/or death during the poststudy follow-up period should also be reported as an SAE.

The sponsor or sponsor's designee will submit expedited safety reports to the regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB)/ IEC within timelines set by regional regulations (i.e. EU). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The delegated CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs, which require submission per local requirements IRB/IEC/head of the study site.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

Please contact the sponsor's medical monitor for any other problem related to the safety, welfare, or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the AE progresses to an ″SAE″, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to Appendix 12.2 for detailed instructions on Drug Induced Liver Injury.

5.5.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are progression to ESRD. This does NOT change the investigator’s reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common serious adverse events”. The sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.5.5

5.5.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 12 weeks from the discontinuation of dosing, the investigator should report the information in specific forms to the delegated CRO, with timelines as if it is an SAE. Besides completion of the SAE Worksheet, a separate Pregnancy Form should be completed: part A at time of pregnancy reporting and part B when outcome of pregnancy is known. Additional details should be provided in part C during the pregnancy and/or after the delivery.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus and will report the outcome to the sponsor as if the pregnancy is an SAE.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below:

- “Spontaneous abortion” includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug

- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator
- In the case of a delivery of a living newborn, the “normality” of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

If during the conduct of this study and up to 12 weeks after the EOT visit, the partner of a male subject becomes pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the delegated CRO as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected roxadustat overdose, the subject should receive supportive care and monitoring. If clinically indicated, phlebotomy may be performed [Section 5.1.5]. The sponsor’s medical monitor should be contacted as applicable.

In the event of suspected epoetin alfa or darbepoetin alfa overdose, refer to the SmPCs.

The therapeutic margin of darbepoetin alfa is very wide. Even at very high serum levels, no symptoms of overdose have been observed. In the event of polycythemia, darbepoetin alfa should be temporarily withheld. If clinically indicated, phlebotomy may be performed (see Section 5.1.5).

The therapeutic margin for epoetin alfa is also wide and it has approximately a 3-fold shorter half-life than darbepoetin alfa. Similar to darbepoetin alfa, no specific symptoms of overdose have been observed. In case of polycythemia, same interventions as for darbepoetin alfa should be applied, e.g. temporarily withheld dosing and, if clinically indicated, phlebotomy.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed and will inform the subjects. Obtaining renewed signature on an adapted ICF may be required.

5.6 Test Drug Concentration

For evaluation of PK in subjects on HD/HDF and PD (continuous ambulatory peritoneal dialysis [CAPD] and automated peritoneal dialysis [APD]), blood samples will be obtained from roxadustat treated subjects only. The intention is to collect 6 blood samples per roxadustat treated subject at the following time points:

A. 2 to 0 hours prior to dosing
B. 1 to 2 hours after dosing
C. 2 to 3 hours after dosing, at least 60 minutes after sample B
D. 3 to 5 hours after dosing, at least 60 minutes after sample C
E. 4 to 6 hours after dosing, at least 60 minutes after sample D
F. 6 to 10 hours after dosing, at least 2 hours after sample E.

The blood samples can be collected at 1 visit, or over 2 to 3 visits for HD/HDF (as illustrated in [Table 7]). The preferred schedule and order of PK visits is a joint decision by the investigator and study subject. For APD subjects, it is recommended to collect all 6 samples in a single visit (as illustrated in [Table 8]). For CAPD subjects, all 6 samples must be collected in a single visit (as illustrated in [Table 9]). The PK visits should take place between weeks 2 and 8 of the treatment period.

- Samples A, B and C should be collected during the same visit.
- Samples D and E should be collected on the same visit
- Sample F can be collected during the same visit as samples D and E, or during a separate visit. Sample F should be collected as late as possible during the PK visit (last assessment of the visit).

During weeks 1 to 8 subjects treated with roxadustat will be instructed to record the date and time of roxadustat intake in the Study Medication Diary. The information will be used to record the date and time of the roxadustat intake on the occasion prior to PK sampling and the day of PK sampling in the eCRF. The date and time of each PK sample and the actual study drug dose taken on the day of sampling will be recorded in the eCRF.

Sample A should be scheduled on a day when previous study drug intake was less than 3 days prior to the current visit to ensure quantifiable predose samples.

During each PK visit 1 additional sample will be collected for determination of alpha 1-Acid Glycoprotein (α1-AGP) and albumin concentration.

Subjects on HD/HDF*:*

According to Section [5.1] of the protocol, for HD subjects it is recommended that roxadustat is administered any time after completion of dialysis if dosing is scheduled on a dialysis day to avoid potential bias on certain study assessments.

However, at all days when PK sampling is scheduled roxadustat must be taken prior to dialysis start. Roxadustat must be taken at the site for PK visit 1 [Table 7].

In addition, at the PK visits, the start and end time of the dialysis should also be recorded in the eCRF.

Table 7 Examples of Sampling Schedules for Population PK for Subjects on Hemodialysis/Hemodiafiltration

Schedule †	PK Visit 1	PK Visit 2	PK Visit 3
1	Collect predose sample A. Take roxadustat at site. Start hemodialysis. Collect samples B to E. [Stop hemodialysis.]‡ Collect sample F.	None	None
2	Collect predose sample A. Take roxadustat at site. Start hemodialysis Collect samples B and C. [Stop hemodialysis.]‡	Take roxadustat. Start hemodialysis. Collect samples D to E. [Stop hemodialysis.]‡ Collect sample F.	None
3	Collect predose sample A. Take roxadustat at site. Start hemodialysis Collect samples B and C. [Stop hemodialysis.]‡	Take roxadustat. Start hemodialysis. Collect sample D and E. [Stop hemodialysis.]‡	Take roxadustat. Start hemodialysis. [Stop hemodialysis.]‡ Collect sample F.

† The order of the PK visits for schedule 2 and 3 is a joint decision by the investigator and study subject.

‡ The stop of hemodialysis is independent of blood sample collection. Hemodialysis must not start before roxadustat is taken on PK days.

Subjects on APD:

For APD subjects, it is recommended to collect all 6 samples in a single visit. At PK visit 1, roxadustat must be taken at the site. Day-time (manual) PD fluid changes for APD patients are not allowed on the day of PK sampling. In case of subsequent PK visits, roxadustat must be taken after draining the last night-time PD fluid prior to the site visit.

Table 8 Example of Preferred Sampling Schedule for Population PK for Subjects on APD

Schedule	PK Visit 1	PK Visit 2	PK Visit 3
1	Collect predose sample A. Take roxadustat at site. Collect samples B to F.	None	None

Subjects on CAPD:

PK sampling

Subjects on CAPD must complete all PK sampling on a single visit (PK visit 1). Roxadustat must be taken at the site prior to initiation of the first dialysis cycle at the site.

Dialysate

Collection of dialysate is to be performed on the same day as PK sampling (roxadustat treated subjects only). For the evaluation of the roxadustat concentration in dialysate, a dialysate sample of 20 mL is collected at the end of the first dialysis cycle at the site. The sample should be withdrawn from the drainage bag after draining the complete volume. The total infused

volume and drained volume of the first dialysis, the start and end time and date of the first dialysis cycle at site and the start time of the second dialysis cycle at site must be recorded in the eCRF. The start time of the dialysis cycle is defined as the start of the infusion of a solution bag into the abdominal cavity and end time is defined as the time when draining of the volume into the drainage bag is completed. All details on the processing of the sample, storage and shipment conditions will be provided in the laboratory manual.

Table 9 Example of Sampling Schedule for Population PK for Subjects on CAPD

Schedule	PK Visit 1	PK Visit 2	PK Visit 3
1	Collect predose sample A. Take roxadustat at site. Start first dialysis cycle. Collect samples B to D. Collect dialysate. Start second dialysis cycle at site. Collect samples E to F.	None	None

5.6.1 Blood Samples for roxadustat PK Analysis

Samples of venous blood for bioanalysis of roxadustat and related metabolites of roxadustat will be collected into appropriately labeled tubes containing sodium-heparin as anticoagulant.

All further details on the processing of the samples, storage and shipment conditions will be provided in the laboratory manual.

5.7 Other Measurements, Assessments or Methods

5.7.1 α1-AGP and Albumin in Serum

Serum levels of albumin and α1-AGP will be evaluated as covariates in the PK analysis, since both albumin and α1-AGP are involved in plasma protein binding of roxadustat. Serum albumin and α1-AGP will be analyzed by the central laboratory using a standardized assay. All details on the processing of the samples, storage and shipment conditions will be provided in the laboratory manual.

5.7.2 Hepcidin in Serum

For the determination of hepcidin, serum samples will be drawn at the visits as indicated in Schedule of Assessment. All details on the processing of the samples, storage and shipment conditions will be provided in the laboratory manual.

5.7.3 Archival of Serum Samples for Biomarker Analysis

Serum samples will be drawn at the visits as indicated in the Schedule of Assessments. The processed samples will be stored and archived for potential future analysis of relevant biomarkers, linked with the efficacy or safety of the study drugs, prognosis and outcomes. These archival samples will be destructed (if not used in total), maximally 5 years after the last subject completed the study. All details on the processing of the samples, storage and shipment conditions will be provided in the laboratory manual.

5.7.4 Optional Genotyping Sample

It is now known that roxadustat is a substrate of various transporters as well as metabolizing enzymes. Some of these proteins are polymorphic resulting in different phenotypes in the standard human population. In order to clarify and explain the possible differences observed in the study subjects, exploratory (and optional) genotyping sampling will be included in this study for subjects randomized to the roxadustat arm.

If a separate (optional) informed consent is signed by the subject, a 5 mL whole blood sample for genotyping can be done after randomization, preferably on day 1. The sample will be collected into prelabeled polypropylene collection tubes containing EDTA as anticoagulant. The sample will be taken via venipuncture or cannulation of a forearm vein. The genotyping tube will not require any further processing. Genotyping samples will be stored at -20°C or lower until they are shipped to the delegated CRO and analyzed under the responsibility of Bioanalysis-Europe of Astellas Pharma Europe B.V. All details on the processing of the samples, storage and shipment conditions will be provided in the laboratory manual. The genotyping samples (whole blood and isolated deoxyribonucleic acid) will be managed in strictly secured condition and they will be destroyed maximally 5 years after the last subject completed the study according to relevant guidances and procedures.

5.8 Total Amount of Blood

The total amount of blood to be collected per subject during the study (screening period, treatment period and the follow-up period) is estimated to be approximately 475 mL.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who was enrolled into the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to discontinue from study treatment or withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Discontinued subjects will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit procedures. The appropriate documentation must be entered on the eCRF.

Premature Treatment Discontinuation

Subjects should be prematurely discontinued from study treatment for any of the following reasons:

- Physician decision that it is in the best interest of the subject to be discontinued from study treatment.
- Significant noncompliance with study procedures, as determined by principal investigator and/or sponsor.
- Pregnancy in a study subject.
- Subject no longer consents to participate in treatment phase of the study.
- Subject receives an organ transplant
- Subject randomized to roxadustat who requires a second course of ESA rescue therapy

If subjects have prematurely discontinued study treatment and have taken at least 1 dose of study drug), they will continue to be followed up at a 6-monthly frequency for the subject's vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of follow-up period (i.e. projected EOS visit) or until consent withdrawn.

Study Withdrawal

Subjects should be withdrawn from the study for any of the following reasons:

- Subject no longer consents to participate in the study.
- Subject is lost to follow-up despite reasonable efforts by the investigator to contact the subject.

The sponsor may decide to prematurely stop the entire study, e.g. for safety considerations.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor. The sponsor may terminate the study at a study site in exceptional circumstances, such as a prolonged period without any enrolments at the site or significant non-adherence to the protocol or GCP requirements.

6.3 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APEB. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. As this is an open-label study, the SAP will be finalized prior to accumulation of a substantial amount of data to ensure lack of bias. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to database lock, a final review meeting of data and Tables/Listings/Figures will be held. Additionally, a meeting to determine analysis set classifications will also take place

prior to database lock. If required, consequences on the statistical analysis will be discussed and documented.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

The study is sufficiently powered for both regionally-based primary efficacy endpoints. Approximately 750 subjects will be randomized to receive roxadustat or ESA in an open-label fashion in a 1:1 ratio. Randomization will be stratified by the following 5 factors:

- Region (region A versus region B*)
- Previous ESA treatment (epoetin versus darbepoetin alfa)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No)
- Average prescribed weekly ESA dose in last 4 weeks prior to randomization (≤ 200 IU/kg epoetin or ≤ 1 μg/kg darbepoetin alfa versus >200 IU/kg epoetin or > 1 μg/kg darbepoetin alfa)
- Screening Hb value (≤11.0 g/dL versus >11.0 g/dL)

* Country assignment to region A and B will be determined based on health care system comparability.

EU (EMA)

Results from simulations of the EU primary efficacy endpoint in stable dialysis subjects suggest that dosing levels of ESA prior to randomization may play a role in Hb response. Therefore, the EU primary analysis of this study will be tested both in the overall population and in the subgroup of patients defined as subjects with an average prescribed weekly epoetin or darbepoetin dose within the last 4 weeks prior to randomization ≤ 200 IU/kg or ≤ 1 μg/kg respectively, following a parametric chain procedure [Millen et al, 2011; Spiessens et al, 2010]. The information fraction will be calculated at the time of database hard lock; it is defined as the number of subjects in the subgroup with respect to the number of subjects in the total study population.

Assuming that the Per Protocol Set (PPS) analysis will consist of 80% of the randomized subjects, 750 randomized subjects will lead to approximately 600 subjects in the PPS. The overall 1-sided significance level (alpha) is fixed at 0.025 and the non-inferiority margin for the EU primary endpoint has been fixed to 0.75 g/dL. The overall alpha will be equally allocated to each of the 2 test populations. If we assume an information fraction of 0.80, this rule will lead to a significance level of 0.0174.

In this setting, 300 subjects for the roxadustat treatment group and 300 subjects for the ESA treatment group will provide 97% power to statistically demonstrate noninferiority of roxadustat versus ESA in the EU primary endpoint in both the total study population and the planned subgroup analysis assuming a difference (roxadustat minus ESA) of -0.25 g/dL in the Hb change from baseline and an SD of 1.5 g/dL. In the case that these assumptions do not hold across the overall population, the planned procedure can still allow for a successful conclusion for the subgroup.

US (FDA)

With 750 randomized subjects (Intention To Treat Set [ITT]), the study will provide at least 99% power to demonstrate statistical non-inferiority of roxadustat versus ESA in the primary endpoint for US submission.

7.2 Analysis Set

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

The following analysis sets are defined and will be used for the statistical analysis:

- Intention To Treat Set (ITT)
- Full Analysis Set (FAS)
- PPS
- Safety Analysis Set (SAF)
- Pharmacokinetic Analysis Set (PKAS)

7.2.1 ITT

All randomized subjects will be included in the ITT.

The primary US endpoint will be analyzed using the ITT. The primary EU endpoint and selected secondary efficacy endpoints will be analyzed using the ITT in secondary analyses.

7.2.2 FAS

All randomized subjects who received at least 1 dose of study drug and have at least 1 postdose Hb assessment will be included in the FAS.

The primary US and EU endpoints will be analyzed using the FAS in secondary analyses. Selected secondary efficacy endpoints will be analyzed using the FAS.

7.2.3 PPS

All FAS subjects who received at least 12 weeks of study treatment with at least 1 postdose Hb assessment and without any criteria for PPS exclusion will be included in the PPS.

Criteria for PPS exclusion will be defined in the SAP. The primary EU endpoint will be analyzed using the PPS. Selected secondary efficacy endpoints will be analyzed using the PPS.

Additional PPS sub-populations (e.g. PPS-36) will be described in the SAP.

7.2.4 SAF

All subjects that received at least 1 dose of study drug will be included in the SAF. All safety data will be analyzed using the SAF.

7.2.5 PKAS

The PKAS consists of all randomized subjects who meet the following criteria:

- Received at least 1 dose of study drug, and

- At least 1 quantifiable plasma concentration of roxadustat was obtained and dosing and sampling history has been recorded.

The PKAS will be used for all tables and graphical summaries of the population PK analysis.

7.3 Demographics and Other Baseline Characteristics

Demographic (age, race, sex) and other baseline characteristics, including stratification factors, and subject disease characteristics will be summarized for the SAF, FAS, ITT and PPS populations.

Descriptive statistics will be calculated for continuous variables (e.g., age, weight, baseline Hb, body mass index, and average weekly ESA [epoetin and darbepoetin alfa] dose in last 4 weeks prior to randomization) by treatment arm. Frequency counts and percentages will be tabulated for categorical variables (e.g., sex, race, previous ESA treatment, average prescribed weekly ESA [epoetin and darbepoetin alfa] dose in last 4 weeks prior to randomization [categorical], baseline Hb [categorical], region, mode of dialysis, and history of cardiovascular, cerebrovascular or thromboembolic disease) by treatment arm.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

There are 2 separate regionally based primary efficacy endpoints in this study, depending upon whether the data are being filed to support submission to the US FDA or to Ex-US health authorities, such as the EMA.

- The EU (EMA) primary efficacy endpoint is change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 36), without having received rescue therapy (i.e. RBC transfusion for all subjects or ESA for subjects treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period.
- The US (FDA) primary efficacy endpoint is change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 52), regardless of rescue therapy.

The central laboratory reported Hb values will be used for this analysis.

7.4.1.1 Primary Analysis

EU (EMA)

The EU primary efficacy endpoint will be analyzed using a Mixed Model Of Repeated Measures (MMRM) method with an unstructured covariance matrix. The model will contain terms for treatment arm, baseline Hb measurement, visit, visit x treatment arm and other stratification factors.

For subjects who require rescue therapy, the reported values after the initiation of rescue therapy will be set to missing for 6 weeks; the MMRM model will implicitly impute missing data via the within-patient correlation structure.

Difference of least square means (roxadustat minus ESA) and its 100x(1-α*2)% CI will be estimated for the average of weeks 28 to 36. The significance level α is fixed by the parametric chain procedure explained below.

The primary analysis of the EU primary efficacy endpoint will be tested both in the overall population and in the subgroup of patients defined as subjects with an average prescribed weekly epoetin or darbepoetin dose within the last 4 weeks prior to randomization ≤ 200 IU/kg or ≤ 1 μg/kg, respectively, following a parametric chain procedure [Millen et al., 2011; Spiessens et al, 2010].

The 2 null hypotheses to be tested are:

- H_{A0}: Hb change from baseline in the roxadustat arm ≤ Hb change from baseline in the ESA arm minus 0.75 g/dL in the total study population
- H_{B0}: Hb change from baseline in the roxadustat arm ≤ Hb change from baseline in the ESA arm minus 0.75 g/dL in the subgroup population

The alternative hypotheses H_{A1} and H_{B1} are defined as the negation of the null hypotheses H_{A0} and H_{B0} respectively. The information fraction will be calculated at the time of database hardlock as the number of subjects in the subgroup with respect to the number of subjects in the total study population.

The overall 1-sided significance level (alpha) is fixed at 0.025. The overall alpha will be equally allocated to each of the 2 null hypotheses defined above. In case of an information fraction of 0.80, this rule will lead to significance level of 0.0174. Following the parametric chain procedure, if at least 1 of both hypotheses is rejected at the significance level of 0.0174, the other 1 can be tested at a significance level of 0.025 while still strongly controlling the overall type I error. The study will be successful for the EU primary efficacy endpoint if either of the null hypotheses is rejected, i.e. if the lower limit of the 2-sided 100x(1-α*2)% CI for the difference in least square means from the MMRM model is greater than -0.75g/dL.

The EU primary analysis will be tested on the PPS.

The analysis will be repeated on the FAS and ITT as secondary analyses. In addition, an Analysis of Covariance (ANCOVA) model with Last Observation Carried Forward (LOCF) will be used for imputation of missing values (see Section 7.4.1.2 for secondary analyses).

US (FDA)

The US primary efficacy endpoint will be analyzed using an MMRM method with an unstructured covariance matrix. The model will contain terms for treatment arm, baseline Hb measurement, visit, visit x treatment arm and other stratification factors.

The null hypothesis to be tested for the US primary efficacy analysis is:

- H_0: Hb change from baseline in the roxadustat arm ≤ Hb change from baseline in the ESA arm minus 0.75 g/dL

The alternative hypothesis H_1 is defined as the negation of the null hypothesis H_0. The overall 1-sided significance level (alpha) is fixed as 0.025. The study will be successful for the US primary endpoint if the null hypothesis is rejected.

The US primary analysis will be tested on the ITT.

The analysis will be repeated on the FAS and PPS as secondary analyses. In addition, an ANCOVA model with LOCF will be used for imputation of missing values (see Section 7.4.1.2 for secondary analyses).

Justification of the non-inferiority margin

The clinical importance of a -0.75 g/dL change in Hb has been selected whilst taking into consideration the biological variability in Hb, the effect on Hb from transfusing a single unit of packed RBCs, and clinical factors that affect Hb measurements.

7.4.1.2 Secondary Analyses

Interpretation of results will be based on the primary analysis sets (PPS for EU primary efficacy endpoint and ITT for US primary efficacy endpoint). Sensitivity (secondary) analyses with other analysis sets will be conducted to assess the robustness of the results from the statistical tests.

The same analysis of the primary endpoint as described in Section 7.4.1.1 will be repeated using the following analysis sets:

- For the EU primary efficacy endpoint, the FAS and the ITT,
- For the US primary efficacy endpoint, the PPS and the FAS.

Another sensitivity analysis for the EU and US primary efficacy endpoints will be performed to handle missing data using an ANCOVA model including baseline Hb and other stratification factors as covariates. Missing data will be imputed using the LOCF method.

In addition, a sensitivity analysis on the 2 primary efficacy endpoints (EU and US) will be performed on the subgroup of patients being randomized after the implementation of protocol v2.0, using the PPS (EU primary efficacy endpoint) and the ITT (US primary efficacy endpoint).

Additional sensitivity analyses will be described in the SAP.

7.4.1.3 Subgroup Analysis

The analyses will be repeated separately for the following subgroups:

- Subjects pretreated with epoetin versus subjects pretreated with darbepoetin alfa.
- HD (including hemodiafiltration) versus PD.
- Subjects with an average prescribed weekly epoetin or darbepoetin dose within the last 4 weeks prior to randomization ≤ 200 IU/kg or ≤ 1 µg/kg versus subjects with an average > 200 IU/kg or > 1 µg/kg respectively.

Other subgroup analyses will be described in the SAP.

7.4.2 Analysis of Key Secondary Endpoints

Once a primary hypothesis has been rejected for the EU primary efficacy endpoint, the secondary endpoints will be tested as described below using a fixed sequence testing procedure.

These tests will be performed only for the overall population in the case that the primary hypothesis was rejected for the overall study population. If the EU primary analysis was not successful for the overall population, but only for the subgroup, then the tests will be performed only for the subgroup. The subgroup population is defined as subjects with an average prescribed weekly epoetin or darbepoetin dose within the last 4 weeks prior to randomization ≤ 200 IU/kg or ≤ 1 μg/kg.

The central laboratory reported Hb values will be used for this analysis.

7.4.2.1 Primary Analysis

The EU primary analysis set will be tested on the PPS for the non-inferiority tests and the FAS for the superiority tests.

The secondary endpoints will be tested using a fixed sequence testing procedure, as depicted below in Table 10 in order to maintain the overall 1-sided type I error rate for the set of secondary endpoints at 0.025. If the null hypothesis is rejected, the claim of superiority (or non-inferiority) will be considered successful and the test will progress to the next comparison in sequence as follows:

Table 10 Key Secondary Endpoints Fixed Sequence Testing Procedure

Test	Variable	Comparison
1	Proportion of Hb responders in the average of weeks 28 to 36 without having received rescue therapy. The non-inferiority margin for the difference between groups is 0.15.	Non-inferiority of roxadustat versus ESA
2	LDL cholesterol change from BL to the average of weeks 12 to 28.	Superiority of roxadustat versus ESA
3	Monthly IV iron (mg) use per subject during weeks 1 to 36.	Superiority of roxadustat versus ESA
4	SF-36 PF sub-score change from BL to the average of weeks 12 to 28. The non-inferiority margin is fixed as a difference of 3 points.	Non-inferiority of roxadustat versus ESA
5	SF-36 VT sub-score change from BL to the average of weeks 12 to 28. The non-inferiority margin is fixed as a difference of 3 points.	Non-inferiority of roxadustat versus ESA
6	MAP change from BL to the average MAP of weeks 20 to 28. The non-inferiority margin for the difference between groups is 1 mmHg.	Non-inferiority of roxadustat versus ESA
7	Time to an increase in blood pressure during weeks 1 to 36. The non-inferiority margin is fixed as a hazard ratio of 1.3.	Non-inferiority of roxadustat versus ESA

Table continued on next page

Test	Variable	Comparison
8	MAP change from BL to the average MAP of weeks 20 to 28.	Superiority of roxadustat versus ESA
9	Time to an increase in blood pressure during weeks 1 to 36.	Superiority of roxadustat versus ESA

1. The difference in the proportion of Hb responders in the average of weeks 28 to 36 between roxadustat and ESA will be calculated using the Miettinen & Nurminen [Miettinen et al, 1985] approach adjusting for the stratification factors. The null hypothesis will be rejected if the lower bound of the 2-sided 100x(1-α*2)% CI for the difference of proportions (roxadustat minus ESA) is greater than -0.15.
2. Change from BL in LDL cholesterol to the average value of LDL cholesterol of weeks 12-28 will be compared (roxadustat versus ESA) using an MMRM method including BL Hb value and other stratification factors as covariates. Superiority will be declared if the upper bound of the 2-sided 100x(1-α*2)% CI of the difference (roxadustat minus ESA) is lower than 0 mg/dL.
3. Monthly IV iron use (mg) during weeks 1 to 36 will be compared (roxadustat versus ESA) using an MMRM method including BL Hb and other stratification factors as covariates. Superiority will be declared if the upper bound of the 2-sided 100x(1-α*2)% CI of the difference (roxadustat minus ESA) is lower than 0 mg.
4. Change from BL in PF subscore of SF-36 to the average of weeks 12–28 will be compared (roxadustat versus ESA) using an MMRM method including BL Hb value and other stratification factors as covariates. Non-inferiority can be concluded if the lower bound of the 2-sided 100x(1-α*2)% CI of the difference (roxadustat minus ESA) is greater than -3 points.
5. Change from BL in VT subscore of SF-36 to the average of weeks 12–28 will be compared (roxadustat versus ESA) using an MMRM method including BL Hb value and other stratification factors as covariates. Noninferiority can be concluded if the lower bound of the 2-sided 100x(1-α*2)% CI of the difference (roxadustat minus ESA) is greater than -3 points.
6. Change from BL in MAP to the average of weeks 20–28 will be compared (roxadustat versus ESA) using an MMRM including BL Hb value and other stratification factors as covariates. Noninferiority can be concluded if the upper bound of the 2-sided 100x(1-α*2)% CI of the difference (roxadustat minus ESA) is lower than 1 mmHg.
7. Time to an increase in blood pressure during weeks 1 to 36 will be compared (roxadustat relative to ESA) using a Cox Proportional Hazards regression analysis including BL Hb value and other stratification factors as covariates. Noninferiority will be declared if the upper bound of the 2-sided 100x(1-α*2)% CI of the hazard ratio (roxadustat relative to ESA) is lower than 1.3.
8. Change from BL in MAP to the average of weeks 20–28 will be compared (roxadustat versus ESA) using an MMRM method including BL Hb value and other stratification

factors as covariates. Superiority will be declared if the upper bound of the 2-sided 100x(1-α*2)% CI of the difference (roxadustat minus ESA) is lower than 0 mmHg.

9. Time to an increase in blood pressure during weeks 1 to 36 will be compared (roxadustat relative to ESA) using a Cox Proportional Hazards analysis including BL Hb value and other stratification factors. Superiority will be declared if the upper bound of the 2-sided 100x(1-α*2)% CI of the hazard ratio (roxadustat relative to ESA) is lower than 1.

7.4.2.2 Secondary Analyses

The analysis of the secondary endpoints as described in Section 7.4.2.1 will be repeated using the following analysis sets:

- For non-inferiority tests, the FAS and the ITT
- For superiority tests, the PPS and the ITT.

For all secondary endpoints analyzed using an MMRM method, an additional sensitivity analysis will be performed to handle missing data using an ANCOVA model with the LOCF method.

Additional sensitivity analyses will be defined in the SAP.

7.4.2.3 Subgroup Analysis

All secondary endpoints of this study will be analyzed separately using the same subgroups as for the primary endpoint (see Section 7.4.1.3).

7.4.3 Analyses of Additional Secondary Endpoints

The statistical analyses of the additional secondary endpoints will be detailed in the SAP.

7.5 Analysis of Safety

Safety analyses will be performed using the SAF. Safety parameters include AEs, SAEs laboratory parameters (with special emphasis on excessive Hb response and LFTs), vital signs and ECG parameters.

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

All safety analyses will be presented both by treatment group and by visit (if relevant).

The number and percentage of subjects reporting TEAEs and TESAEs in each treatment group will be tabulated. Descriptive statistics will be presented for laboratory, vital signs values and ECG parameters by visit and for the changes from BL to each visit. Further details will be described in the SAP.

Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be conducted by an independent DSMB. The statistical method for analysis of adjudicated safety data will be detailed in a separate SAP. Adjudicated safety data will be reported in a separate report.

7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

An AE (classified by preferred term) occurring during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or if it was present prior to the first dose of study drug but increased in severity during the treatment period. An AE that occurs more than 28 days after the last dose of study medication will not be counted as a TEAE.

The number and percentage of subjects reporting TEAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study medication. If more than 1 event occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study medication.

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

The proportion of subjects with TEAEs, fatal SAEs (i.e. events that caused death), and AEs leading to discontinuation of study drug will be summarized by SOC, preferred term and treatment group.

TEAEs will also be reported in terms of cumulative incidence versus time and as an incidence rate per subject-exposure-year.

For the purpose of EU regulatory filing and other submissions: Adjudicated MACE+ events (i.e., myocardial infarction, stroke, death from all causes, hospitalization for chronic heart failure, hospitalization for unstable angina) and other pre specified events will be pooled and analyzed across multiple studies in the global phase 3 program. This analysis will be described in a separate pooled safety statistical analysis plan. For the purpose of US FDA regulatory filing: Adjudicated major cardiovascular adverse events (MACE; i.e., myocardial infarction, stroke, death from all causes) will be pooled across multiple studies in the global phase 3 program to serve as primary safety endpoint. The adjudicated MACE events in this study will be part of this pooled analysis, but will not be a self-contained endpoint within this individual study.

Adjudicated safety data will be reported in a separate report.

Listings will be presented of subjects with SAEs, subjects with AEs leading to discontinuation and subjects who died.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements, descriptive statistics will be used to summarize results (in International System of Units [SI]) and change from baseline by treatment group and time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, respiratory rate and heart rate) and their changes from BL at each visit and the end of study and for the maximum and minimum value on treatment will be presented by treatment group.

7.5.4 ECGs

Descriptive statistics for ECG parameters (see Section 5.4.5) at BL, and changes from BL, at each assessment time point and for the maximum and minimum value on treatment will be presented by treatment group. The QT interval corrected for heart rate (QTc) will be calculated using both Bazett [$QTcB = QT/(RR^{1/2})$] and Fridericia [$QTcF = QT/(RR^{1/3})$] corrections. Presence of Potentially Clinically Significant ECG values will be reported using similar statistics as mentioned for TEAEs.

7.6 Analysis of Pharmacokinetics

Plasma concentration data of roxadustat will be subjected to population PK analysis. The aim of this analysis is to describe the PK behavior of roxadustat in the target population and to evaluate the effects of selected covariates on the PK of roxadustat. The results of the population PK analysis will not be reported in the CSR but in a separate population PK report. Plasma concentration listings will be presented only in the CSR.

7.7 Analysis of Pharmacodynamics

Pharmacodynamic data may be submitted to population pharmacodynamic or population pharmacokinetic/pharmacodynamic modeling. When deemed necessary, data from this study may be combined with data from other studies. Results will be reported in a separate population pharmacokinetic/pharmacodynamic modeling report.

7.8 Protocol Deviations and Other Analyses

Protocol deviations as defined in Section 8.1.6 will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received prohibited concomitant treatment.

7.9 Interim Analysis

There will be no interim analysis of the 52 week data.

Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be completed by an independent DSMB [Section 10.1].

7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

The primary analysis method to handle missing data of the efficacy primary and secondary endpoints with repeated measures over time will be the MMRM. In addition, as a sensitivity analysis to handle missing data, an LOCF method will be performed for these endpoints.

Visit time windows and additional sensitivity analyses will be detailed in the SAP.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data into an eCRF using an Electronic Data Capture system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF as soon as possible after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site. Subject diaries and questionnaires will be completed by the subject on paper. The investigator or site designee should review the diaries and questionnaire data while the subject is at the site. The investigator or site designee will enter the relevant information from the subject diary (i.e. study medication intake data related to PK sampling) and all questionnaire data directly into the Electronic Data Capture system. eCRFs, diaries and questionnaires and any supporting documents should be available for review or retrieval at any given time.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at a central laboratory. Laboratory results will be provided to the site via a site portal. More details are described in a separate laboratory manual. Laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The laboratory will provide the sponsor or designee with a complete and clean copy of the data.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Subject identification number
- Demographic data (date of birth, sex, race, height and body weight)

- Inclusion and exclusion criteria details
- The identification of the participation in study and the study number 1517-CL-0613
- Original signed and dated ICFs
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data
- AEs and concomitant medication
- Results of HemoCue® device Hb assessments on all visits
- Decision on study drug dosage on all visits
- Results of relevant examinations such as ECG charts, renal ultrasound outcome.
- Laboratory printouts (such as Central Laboratory assessments, including certification by the investigator of abnormal laboratory data being clinically relevant or not)
- Dispensing and return of study drug details, including study medication Kit numbers and tablets returned
- Reason for premature treatment discontinuation or study withdrawal (if applicable)
- Method of contraception for subjects or subject's partner of childbearing potential.

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2) when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science department of the sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF Completion Guidelines. Coding of medical terms and medications will be performed using the MedDRA and WHO Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria (PD1).
- Developed withdrawal criteria during the study and not withdrawn (PD2).
- Received wrong treatment or incorrect dose (PD3).
- Received prohibited concomitant treatment (PD4).

When a deviation from the protocol is identified for an individual subject, the local monitor, investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Study in All Participating Countries

The end of study is defined as the Last Subject's Last Visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 IRB / IEC / Competent Authorities

GCP requires that the clinical protocol, any protocol amendments, the IB, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information

and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious AEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The sponsor shall submit a summary of the final clinical study report to the IRB/IEC and the Regulatory Agency within 1 year after last subject out or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. The sponsor will develop an ICF containing all relevant information on the study and the investigational products. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

The investigator or his/her representative will immediately inform the subject verbally whenever new information becomes available that may be relevant to the subject's consent or

may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reactions). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.

The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor will ensure that the use and disclosure of protected health information obtained during a research study complies with the regional legislation related to the privacy and protection of personal information.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is described in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, as applicable)
- IB (and amendments, as applicable)
- Investigational Medicinal Product Dossier (IMPD)
- Questionnaires and SAE Report Worksheets
- Investigator's File
- Study drugs with all necessary documentation
- Clinical Trial Agreement
- Approval of regulatory authority and all documents related to submission.

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54
- Signed and dated FDA form 1572
- If the investigator submits to the IRB/IEC: Submission letter to the IRB/IEC
- Signed confidentiality agreement
- Signed Investigator's Statement in this protocol
- Executed Study Contract
- IRB/IEC approval of the protocol, protocol amendments (if applicable) and ICF (and separate authorization form, if appropriate), stating clearly the sponsor's name, study number and study drug, including a membership list with names and qualifications
- Current Curricula Vitae of all investigators (signed and dated, brief and in English.)
- Medical/Laboratory/Technical procedures/tests certifications or accreditations or established quality control or other validation, where required.

At the end of the study, the sponsor is responsible for the collection of:

- Study documentation,
- Unused study drug and study drug containers of used study drugs

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, Questionnaires and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation: until at least 15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 15 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The sponsor will notify the site/investigator if the MAA is granted or if the IMPD is discontinued.

The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the CRFs supplied for each subject.

The documents of the Efficacy and Safety Evaluation Committee (minutes and standard operating procedures and others) and the judgment committee outside the study sites (minutes and standard operating procedures and others) shall be retained by the Sponsor.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable). Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the informed consent, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new informed consent must also be forwarded to the sponsor.

8.3.4 Insurance of Subjects and Others

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 DSMB and Other Evaluation Committee(s)

A DSMB will review prespecified safety data of the current study and of other studies conducted by the sponsor with roxadustat periodically in collaboration with the Sponsor to ensure subject safety.

A DSMB charter will establish the process, meeting frequency and scope of responsibilities.

An Independent Event Review Committee will adjudicate all relevant cardiovascular and cerebrovascular events in a blinded manner to ensure consistent safety assessment. Details of event identification and process of adjudication will be described in an Independent Event Review Committee charter.

10.2 Other Study Organization

This section is not applicable in the study.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

Excluded concomitant medications are mentioned in Section 5.1.3.3

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN, or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. Alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3× ULN	or	> 2× ULN
Severe*)	> 3× ULN	and	> 2× ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8× ULN
- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST > 3× ULN and International Normalized Ratio (INR) > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that can be activated in the eCRF for any study or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a Serious AE (SAE). The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'AEs' on the AE page of the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis is seen in obese hyperlipoproteinemic, and/or diabetic subjects and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
- acute viral hepatitis (A,B, C, D, E or other infectious agents)
- ultrasound or other imaging to assess biliary tract disease
- other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5) (If INR testing is applicable/evaluated)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*) Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant). The two "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and

untreated subjects to be discriminating"). 2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006 Apr;15(4):241-3.]

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.3 Instructions for Roxadustat-treated Subjects Moving from Protocol v1.0 to Protocol v2.0

Subjects that have entered the study under protocol version 1.0 will, at the next scheduled visit, receive a dose adjustment as needed according to the conversion table below.

Current TIW dose (mg)	**120**	**350**
If no dose titration needed	100	300
If up titration needed*	150	400
If down titration needed*	100	300

* Up or down titrations are only applicable when the criteria for dose adjustment have been met.

12.4 Short Form-36 Health Survey (SF-36 v2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3 The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

12.5 Functional Assessment of Cancer Therapy- Anemia (FACT-AN)

FACT-An (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English (Universal)

16 November 2007
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FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

12.6 EuroQol Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

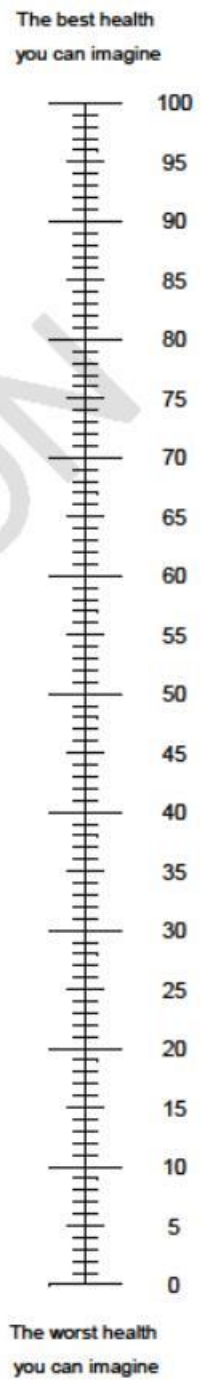
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



12.7 Subject's Global Impression of Change (PGIC) Scale

PATIENT OVERALL IMPRESSION OF CHANGE
(UK English version of **PGIC**)

Since the start of the study, my general state of health is:

tick (✓) one box only:

[1] ☐ Very Much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No Change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very Much Worse

(UK/English)

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 2

I. The purpose of this amendment is:

Substantial Changes
1. Change in Treatment Period
DESCRIPTION OF CHANGE:
The treatment period was 104 weeks and is being changed to a variable treatment period with a minimum of 52 weeks and a maximum of 104 weeks.
RATIONALE:
This study is part of a global clinical development program involving several protocols in dialysis patients; the other studies are event-driven and the program will be stopped once sufficient clinical safety data has been collected in the overall program. The planned change will reduce the treatment exposure of study subjects.
2. Deletion of Interim Analysis
DESCRIPTION OF CHANGE:
An interim analysis was to be performed when all subjects had completed 52 weeks of treatment; this interim analysis is removed.
RATIONALE:
There are two separate regionally based primary efficacy endpoints in this study. All data for these primary efficacy endpoints are collected in 52 weeks of treatment. The interim analysis was scheduled to ensure timely reporting of the primary efficacy endpoints for submission of the dossier. The treatment period is being changed to a variable duration. This is aligned with the other clinical studies in the program for which the safety data will be pooled for analysis across all studies in the dialysis population. Therefore, the interim analysis is not necessary to ensure timely reporting and is being removed.

Nonsubstantial Changes
1. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
The medical monitor contact details are updated.
RATIONALE:
There has been a change in medical monitor and therefore the contact details in the protocol are updated.
2. Change in Completion of Follow-up Period

DESCRIPTION OF CHANGE:
The completion of the poststudy follow-up period was previously designated as the projected week 108 visit. This is changed to the projected end of study (EOS) visit.
RATIONALE:
This minor change is being made to accommodate the variable treatment period of 52 weeks to 104 weeks in this study.

II. Amendment Summary of Changes:

A. Substantial Changes:

IV Synopsis and 2 Study Objectives, Design and Endpoints *2.2.1.3 Description of Study*
WAS:
The study will consist of three study periods: ● Screening Period: up to 6 weeks ● Treatment Period: 104 weeks ● Follow-up Period: 4 weeks AND Subjects will receive study treatment (roxadustat or ESA) for 104 weeks.
IS AMENDED TO:
The study will consist of three study periods: ● Screening Period: up to 6 weeks ● Treatment Period: ~~104 weeks~~ **For all subjects in the study the minimum treatment duration will be 52 weeks and the maximum treatment duration will be 104 weeks. The study end date will be declared when the targeted number of MACE* and MACE+** events have been reported across the roxadustat phase 3 development program and consequently the treatment will end for all subjects who have completed 52 weeks at that point. Subjects who have not completed 52 weeks when the target has been declared will continue until they reach 52 weeks and at that point their treatment will end.** ● Follow-up Period: 4 weeks *** MACE: Major cardiovascular adverse events: myocardial infarction, stroke, death from all causes** **** MACE+: Myocardial infarction, stroke, death from all causes, chronic heart failure requiring hospitalization, unstable angina requiring hospitalization** AND Subjects will receive study treatment (roxadustat or ESA) for **a minimum of 52 weeks and a maximum of** 104 weeks.

5 Treatment and Evaluation *5.1.1 Dose/Dose Regimen and Administration Period*
WAS:
• All subjects will be treated for 104 weeks.
IS AMENDED TO:
• All subjects will be treated for **a minimum of 52 and a maximum of** 104 weeks.

IV Synopsis and 7 Statistical Methodology *7.9 Interim Analysis*
WAS:
An interim analysis will be performed when all subjects have completed 52 weeks of treatment. Since all primary (for US and EU submissions) and secondary analyses have been defined over this period of time, no multiplicity adjustment is required. Once the study is completed, efficacy and safety will be analyzed again and reported including the complete study treatment of 104 weeks.
IS AMENDED TO:
~~An interim analysis will be performed when all subjects have completed 52 weeks of treatment. Since all primary (for US and EU submissions) and secondary analyses have been defined over this period of time, no multiplicity adjustment is required. Once the study is completed, efficacy and safety will be analyzed again and reported including the complete study treatment of 104 weeks.~~ **There will be no interim analysis of the 52 week data.**

B. Nonsubstantial Changes:

II Contact Details of Key Sponsor's Personnel	
WAS:	
Medical Monitor:	[redacted]
IS AMENDED TO:	
Medical Monitor:	[redacted]

IV Synopsis, 2 Study Objectives, Design and Endpoints and 6 Discontinuation *2.2.1.3 Description of Study and 6.1 Discontinuation of Individual Subject(s)*
WAS:
Subjects that have prematurely discontinued study treatment will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and End of Study (EOS) visit. Thereafter, these subjects (only if they have taken at least 1 dose of study drug) will continue to be followed up at a 6-monthly frequency for vital status, serious adverse events (SAEs) and cardiovascular and thromboembolic adverse events (AEs) until their projected date of completion of the follow-up period (i.e. projected week 108) or until consent withdrawn. AND If subjects have prematurely discontinued study treatment (and have taken at least 1 dose of study drug), they will continue to be followed up at a 6-monthly frequency for the subject's vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of follow-up period (i.e. projected week 108) or until consent withdrawn. AND The last poststudy follow-up data collection should occur around the projected week 108.
IS AMENDED TO:
Subjects that have prematurely discontinued study treatment will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and End of Study (EOS) visit. Thereafter, these subjects (only if they have taken at least 1 dose of study drug) will continue to be followed up at a 6-monthly frequency for vital status, serious adverse events (SAEs) and cardiovascular and thromboembolic adverse events (AEs) until their projected date of completion of the follow-up period (i.e. projected **EOS visit** ~~week 108~~) or until consent withdrawn. AND If subjects have prematurely discontinued study treatment (and have taken at least 1 dose of study drug), they will continue to be followed up at a 6-monthly frequency for the subject's vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of follow-up period (i.e. projected **EOS visit** ~~week 108~~) or until consent withdrawn. AND The last poststudy follow-up data collection should occur around the projected **EOS visit** ~~week 108~~.

V Flow Chart and Schedule of Assessments

Table 1 Schedule of Assessments

WAS:

Study Period:	**Screening Period**			**Treatment Period**					**Follow-up Period**		**Unscheduled Visits**	Poststudy Follow-up[c]
Visit/Week:	**2-6 Weeks[a]**			**Day 1[b]**	Weekly (Wks 1 to 8) ± 2 days	Every 2 Weeks (Wks 10 to 36) ± 2 days	Every 4 Weeks (Wks 40 to 100) ± 3 days	EOT[c] (Week 104) ± 3 days	EOT + 2 wks ± 3 days	EOS[c] (EOT + 4 wks) ± 3 days		Every 6 months until projected Wk 108
	S1	**S2**	**S3**									
Dialysis procedure	◄	―	―	―	―	―	―	―	―	―	―	
ESA pre-treatment	◄	―	┤									
Written informed consent	X											
Randomization				X								
Eligibility Criteria	X			X								
Demographics	X											
Height, weight [d]	X	X	X	X		Wks 12, 24, 36	Wks 52, 76	X		X	O	
Medical History	X											
Physical Examination	X			X		Wks 12[e], 24[e], 36[e]	Wks, 52[e], 76[e]	X		X[e]	O	
Blood pressure[f], heart rate[f], respiratory rate[g]	X	X	X	X	X	X	X	X		X	O	
CBC with WBC diff, red cell indices and platelets	X			X	Wks 1, 2, 3, 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
Hemoglobin[h,i]		X	X		X	X	X		X		O	
HemoCue Assessment[i]				X	X	X	X				O	
Reticulocyte count and Hb in reticulocytes (CHr)	X			X	Wks 1, 2, 4, 6, 8	Wks 12, 16, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
12-lead ECG	X			X		Wks 12, 24, 36	52, 76	X			O	
Serum Chemistry[j]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X	X	X	O	
Renal Ultrasound [k]		X									O	
Liver Function Tests (LFTs) [l]					Wks 2, 6	Wk 16					O	
Table continued on next page												
Serum Lipid Panel[m]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wks 44, 52, 68, 84	X		X	O	
Serum iron, ferritin, TIBC, TSAT[n]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other	X		X	O	

							8 wks					
HbA1c	X			X		Wk 12, 28, 36	Wks 44, 52, 60, 84	X		X	O	
Vitamin B_{12}, folate	X										O	
HIV, HBsAg, anti-HCV Antibody	X										O	
Serum Pregnancy Test (HCG)[o]	X					Wks 12, 24, 36	Wks 48, 60, 72, 84, 96	X			O	
high sensitivity C-reactive protein (hs-CRP), hepcidin				X	Wk 4	Wks 12, 20, 36	Wk 52	X		X		
Archival Serum Samples for Biomarkers				X	Wk 4	Wks 12, 20	Wks 52, 76	X		X		
Blood Sample for PK[p]					Wks 2 to 8							
QoL Questionnaires[q]				X	Wk 8	Wks 12, 28, 36	Wks 52, 76	X				
Dialysate[r]					Wks 2 to 8							
Optional genotyping[s]				O								
Study Treatment: roxadustat dispensing OR ESA administration[t]				├	———	———	———				O	
Dose Adjustment Review[u]					X	X	X				O	
AE and Concomitant Medication Recording	◄	———	———	———	———	———	———	———	———	———	►	
Procedure and non-drug Therapy Recording	◄	———	———	———	———	———	———	———	———	———	►	
Vital status, SAEs, cardiovascular and thromboembolic AEs												X

[c] In case of premature treatment discontinuation, the subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit. Thereafter subjects who have taken at least 1 dose of study drug will continue to be followed up at a 6-monthly frequency for vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of the follow-up period (i.e. projected week 108 date) or until consent withdrawn. No additional study visits will be required during the poststudy follow-up.

IS AMENDED TO:

Study Period:	**Screening Period**			**Treatment Period**					**Follow-up Period**		**Unscheduled Visits**	Poststudy Follow-up[c]
Visit/Week:	**2-6 Weeks[a]**			**Day 1[b]**	Weekly (Wks 1 to 8) ± 2 days	Every 2 Weeks (Wks 10 to 36) ± 2 days	Every 4 Weeks (Wks 40 to 100) ± 3 days	EOT[c] (Week 104) ± 3 days	EOT + 2 wks ± 3 days	EOS[c] (EOT + 4 wks) ± 3 days		Every 6 months until projected **EOS** ~~Wk 108~~
	S1	**S2**	**S3**									
Dialysis procedure	◄										►	
ESA pre-treatment	◄											
Written informed consent	X											
Randomization				X								
Eligibility Criteria	X			X								
Demographics	X											
Height, weight [d]	X	X	X	X		Wks 12, 24, 36	Wks 52, 76	X		X	O	
Medical History	X											
Physical Examination	X			X		Wks 12[e], 24[e], 36[e]	Wks, 52[e], 76[e]	X		X[e]	O	
Blood pressure[f], heart rate[f], respiratory rate[g]	X	X	X	X	X	X	X	X		X	O	
CBC with WBC diff, red cell indices and platelets	X			X	Wks 1, 2, 3, 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
Hemoglobin[h,i]		X	X		X	X	X		X		O	
HemoCue Assessment[i]				X	X	X	X				O	
Reticulocyte count and Hb in reticulocytes (CHr)	X			X	Wks 1, 2, 4, 6, 8	Wks 12, 16, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
12-lead ECG	X			X		Wks 12, 24, 36	52, 76	X			O	
Serum Chemistry[j]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X	X	X	O	
Renal Ultrasound [k]		X									O	
Liver Function Tests (LFTs) [l]					Wks 2, 6	Wk 16					O	
Table continued on next page												
Serum Lipid Panel[m]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wks 44, 52, 68, 84	X		X	O	
Serum iron, ferritin, TIBC, TSAT[n]	X			X	Wks 4, 8	Wks 12, 20, 28, 36	Wk 44 + every other 8 wks	X		X	O	
HbA1c	X			X		Wk 12, 28, 36	Wks 44, 52, 60,	X		X	O	

							84					
Vitamin B_{12}, folate	X										O	
HIV, HBsAg, anti-HCV Antibody	X										O	
Serum Pregnancy Test (HCG)[o]	X					Wks 12, 24, 36	Wks 48, 60, 72, 84, 96	X			O	
high sensitivity C-reactive protein (hs-CRP), hepcidin				X	Wk 4	Wks 12, 20, 36	Wk 52	X		X		
Archival Serum Samples for Biomarkers				X	Wk 4	Wks 12, 20	Wks 52, 76	X		X		
Blood Sample for PK[p]					Wks 2 to 8							
QoL Questionnaires[q]				X	Wk 8	Wks 12, 28, 36	Wks 52, 76	X				
Dialysate[r]					Wks 2 to 8							
Optional genotyping[s]				O								
Study Treatment: roxadustat dispensing OR ESA administration[t]				←			→				O	
Dose Adjustment Review[u]					X	X	X				O	
AE and Concomitant Medication Recording	←										→	
Procedure and non-drug Therapy Recording	←										→	
Vital status, SAEs, cardiovascular and thromboembolic AEs												X

[c] In case of premature treatment discontinuation, the subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit. Thereafter subjects who have taken at least 1 dose of study drug will continue to be followed up at a 6-monthly frequency for vital status, SAEs and cardiovascular and thromboembolic AEs until their projected date of completion of the follow-up period (i.e. projected **EOS** ~~week 108~~ date) or until consent withdrawn. No additional study visits will be required during the poststudy follow-up.

5 Treatment and Evaluation *5.3.3.2 Hospitalizations and 5.5.1 Definition of Adverse Events*
WAS:
5.3.3.2 Hospitalizations: Details of hospitalizations will also be collected at poststudy follow-up visits in subjects who prematurely discontinued treatment (only if they have taken at least one dose of study drug), until the projected date of the EOS visit (week 108). AND 5.5.1 Definition of Adverse Events: For subjects that continue into the poststudy follow-up period, SAEs, cardiovascular and thromboembolic AEs will be captured until their projected date of completion of the follow-up period (i.e. projected week 108).
IS AMENDED TO:
5.3.3.2 Hospitalizations: Details of hospitalizations will also be collected at poststudy follow-up visits in subjects who prematurely discontinued treatment (only if they have taken at least one dose of study drug), until the projected date of the EOS visit ~~(week 108)~~. AND 5.5.1 Definition of Adverse Events: For subjects that continue into the poststudy follow-up period, SAEs, cardiovascular and thromboembolic AEs will be captured until their projected date of completion of the follow-up period (i.e. projected **EOS visit** ~~week 108~~).

14 SPONSOR'S SIGNATURES

ELECTRONIC SIGNATURE PAGE

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*UTC: Coordinated Universal Time