A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis

ISN/Protocol 1517-CL-0610

ClinicalTrials.gov Identifier: NCT02021318

Date of Protocol Version 3.0: 31 Mar 2016

Sponsor: Astellas Pharma Europe B.V.

Sylviusweg 62

2333 BE Leiden

The Netherlands

A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis

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

ISN/Protocol 1517-CL-0610

Version 3.0

Incorporating Substantial Amendment 2 [See Attachment 1]

31 March 2016

EudraCT number 2013-000951-42

Sponsor:

Astellas Pharma Europe B.V.

Sylviusweg 62, 2333 BE Leiden

The Netherlands

Protocol History:
Version 1.0 [14 Aug 2013]
Version 2.0 [18 May 2015]

[a] The originator of the compound under study is FibroGen Inc and the code name used by FibroGen Inc is FG-4592. Astellas is the development partner and uses the code name ASP1517. The sponsor of this study is Astellas. The compound has received the International Nonproprietary Name (INN) roxadustat.

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors) 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 Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis

ISN/Protocol 1517-CL-0610

Version 3.0 / Incorporating Substantial Amendment 2

31 March 2016

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: ....

<Insert name, department/affiliation, name of institution> 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 Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis

ISN/Protocol 1517-CL-0610

Version 3.0 / Incorporating Substantial Amendment 2

31 March 2016

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: .....

<Insert name and qualifications of the Investigator> 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:	PPD Global Medical Science Astellas Pharma Europe B.V. PPD
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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
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AnS	Anemia Subscale
anti-HCV Ab	Anti-hepatitis C Virus
APEB	Astellas Pharma Europe BV
ASP1517	= FG-4592 (codename of investigational product) or roxadustat (international nonproprietary name)
AST	Aspartate Aminotransferase
AT	Aminotransferases
AUC	Area under the plasma concentration – time curve
BIW	twice weekly
BL	Baseline
BL Hb	Baseline Hemoglobin (please refer to key definitions for information)
BP	Blood Pressure
CA	Competent Authority
CBC	Complete Blood Count
CHMP	Committee for Medicinal Products for Human Use
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CHr	Hemoglobin content of reticulocytes
CKD	Chronic Kidney Disease
CL/F	Apparent total body clearance
C_{max}	Maximum concentration
CRO	Contract Research Organization
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DD-CKD	Dialysis-dependent chronic kidney disease
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic CRF
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked ImmunoSorbent Assay
EOS	End of Study
EOT	End of Treatment
EPAR	European Public Assessment Report
EPO	Erythropoietin
EQ-5D 5L	Health Related Quality of Life Questionnaire Consisting of Five Levels
ESA	Erythropoiesis Stimulating Agent
ESRD	End Stage Renal Disease
EU	European Union
EWB	Emotional Well being

Abbreviations	Description of abbreviations
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) or roxadustat (international nonproprietary name)
FWB	Functional Well-being
GCP	Good Clinical Practice
GDS	Global Data Science
GGT	Gamma Glutamyl Transferase
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HbA1c	Hemoglobin A1c; Glycated hemoglobin
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HD	Hemodialysis
HDF	Hemodiafiltration
HDL	High-density Lipoprotein
HEENT	Head, Eyes, Ears, Neck and Throat
HIF	Hypoxia-inducible factor
HIF-PH	Hypoxia-inducible factor prolyl hydroxylase
HIF-PHI	Hypoxia-inducible factor prolyl hydroxylase inhibitor
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRQoL	Health-Related Quality of Life
hs-CRP	High Sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IERC	Independent Event Review Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug (Application)
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra Uterine Device
IUS	Intra Uterine System
ISN	International Study Number
IV	Intravenous(ly)
k_a	First order absorption rate constant
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	Kilogram
LDL	Low-density Lipoprotein
LA-CRF	Liver Abnormality Case Report Form
LFT	Liver Function Tests

Abbreviations	Description of abbreviations
LOCF	Last Observation Carried Forward
LLN	Lower Limit of Normal
LSO	Last Subject Out
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial Infarction
mL	Milliliters
MMRM	Mixed Model of Repeated Measures
MTD	Maximum Tolerated Dose
NASH	Non-alcoholic steatohepatitis
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NDD-CKD	Nondialysis-dependent chronic kidney disease
NONMEM	Non-linear Mixed Effects Modeling
OATP1B1	Organic anion transporting polypeptide 1B1
PCS	Physical Component Scores
PD	Pharmacodynamic
PF	Physical Functioning
PGIC	Patients' Global Impression of Change
PHI	Protected Health Information
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PL	Package Leaflet
PPK	Population Pharmacokinetics
PPKPD	Population Pharmacokinetic/Pharmacodynamic
PPS	Per Protocol Set
PR	Partial Response
PWB	Physical Well-being
QoL	Quality of Life
QRS	QRS interval
QTc	QT Interval corrected for heart rate
QW	Once weekly
RBC	Red Blood Cell
r-HuEPO	Recombinant Human Erythropoietin
RRT	Renal Replacement Therapy
SAE	Serious AE
SAF	Safety Analysis Set
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWB	Social Well-being
$t_{½}$	Apparent Terminal Elimination Half-life

Abbreviations	Description of abbreviations
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TIBC	Total Iron-Binding Capacity
TIW	Three times weekly
t_{max}	Time to Attain C_{max}
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	Transferrin Saturation (also known as FeSAT, iron saturation)
UACR	Urine albumin/creatinine ratio
ULN	Upper Limit of Normal
USRDS	United States Renal Data System
VAS	Visual Analogue Scale
V/F	Apparent volume of distribution
VT	Vitality
WBC	White Blood Cell
Wk(s)	Week(s)
WPAI:ANS	Work Productivity and Activity Impairment questionnaire: Anemic Symptoms

List of Key Study Terms

Terms	Definition of terms
Adverse Event	An adverse event (AE) is as any untoward medical occurrence in a subject administered roxadustat or darbepoetin alfa, 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 visit. AEs will not be collected during the period where a 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 three Hb values: the last two Hb values during screening and the Hb value at the day of randomization (day 1), all assessed by the central laboratory.
Discontinuation	A discontinuation is a subject who enrolled into the study and for whom study treatment is permanently discontinued prematurely for any reason. 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 trial; transitive and intransitive. Informed consent precedes enrollment, which precedes randomization.
Hb Correction	Hemoglobin level ≥ 11.0 g/dL and a Hb increase from baseline BL Hb ≥ 1.0 g/dL as assessed by the central laboratory at two consecutive study visits separated by at least 5 days in the correction period.
Hb Response	Hemoglobin level ≥ 11.0 g/dL and a Hb increase from baseline BL Hb ≥ 1.0 g/dL in case BL Hb was > 8.0 g/dL, or an increase in Hb from BL Hb by ≥ 2.0 g/dL in case BL Hb was ≤ 8.0 g/dL, as assessed by the central laboratory at two consecutive study visits separated by at least 5 days.
Post study follow-up	Period of time from EOS visit to projected week 108 or until consent withdrawn. This period is only applicable to subjects who prematurely discontinued treatment. These subjects will be followed up every 6 months for vital status, serious adverse events (SAEs), cardiovascular and thromboembolic adverse events (AEs).
Randomization	The process of assigning trial 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 darbepoetin alfa from day 1 until End Of Treatment [EOT].)
Rescreening	Process of repeating screening. If subject fails screening they may be re-screened once if deemed appropriate; all screening procedures will be repeated.
Rescreening failure	Subject who is rescreened, but did not fulfill protocol inclusion and/or exclusion criteria for a second time and failed to receive randomized treatment,

Terms	Definition of terms
	or decided not to participate anymore (withdrew consent) prior to the treatment period.
Screening	1) Process for retrieving candidates for the study. 2) Process for checking the eligibility of subjects usually done during the "pre-investigational period."
Screen failure	Potential subject who did not meet one or more inclusion and/or exclusion criteria required for participation in a trial. *See also screening of subjects*.
Serious Adverse Event	An adverse event 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 trial
TEAE	A treatment-emergent adverse event (TEAE) is an AE that started during the treatment period and was not present prior to the first dose of study drug, or the AE 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.
Treatment period	It is the period of time - between first dose of the test drug and EOT visit - where major interests of protocol objectives are observed, and where roxadustat (study drug) or darbepoetin alfa (comparative drug) is given to a subject. The treatment period consists of the correction and maintenance periods.
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:	31 March 2016 / Version 3.0
Sponsor: Astellas Pharma Europe B.V. (APEB)	**Protocol Number:** 1517-CL-0610
Name of Study Drug: Roxadustat (ASP1517/FG-4592)	**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 Treatment of Anemia in Chronic Kidney Disease Patients Not on Dialysis	
Planned Study Period: From 1Q2014 to 2Q2021	
Study Objectives: The primary objective of this study is to evaluate the efficacy of roxadustat compared to darbepoetin alfa in the treatment of anemia in nondialysis-dependent Chronic Kidney Disease (NDD-CKD) subjects. The secondary objectives of this study are to: • Evaluate the safety of roxadustat compared to darbepoetin alfa in the treatment of anemia in NDD-CKD subjects. • Evaluate the health-related quality of life (HRQoL) benefit of roxadustat compared to darbepoetin alfa in the treatment of anemia in NDD-CKD subjects.	
Planned Total Number of Study Centers and Locations: Approximately 200 study centers globally.	
Study Population: The study population consists of subjects with CKD stages 3, 4, and 5 (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) who are anemic and not on dialysis.	
Number of Subjects to be Randomized: Approximately 570 subjects will be randomized; this will lead to approximately 450 subjects in the Per Protocol Analysis Set (PPS).	
Study Design Overview: This is a multicenter, randomized, open-label, active-controlled study. The study will consist of three study periods: • Screening period: up to 6 weeks • Treatment period: 104 weeks • Follow-up period: 4 weeks Subjects that have discontinued treatment prior to their projected week 104 will continue to be followed for vital status, serious adverse events (SAEs), cardiovascular and thromboembolic adverse events (AEs) in a post study follow-up period. During the course of the study, visits and assessments will be performed as defined in the Schedule of Assessments. During the treatment period, subjects will attend weekly study visits from day 1 to week 2, followed by every other week study visits from weeks 4 to 24 and thereafter every four weeks until the end of treatment (EOT). Subjects will receive study treatment - roxadustat or darbepoetin alfa - for 104 weeks.	

Screening Period

During the screening period (up to 42 days duration), hemoglobin (Hb) levels will be assessed in a central laboratory for matching the inclusion criterion (mean of two Hb values must be ≤ 10.5 g/dL, see inclusion criterion 4 below). Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be randomized at day 1, which marks the end of screening period and start of the treatment period. If a subject fails screening, the subject may be rescreened once (immediately or later) if deemed appropriate by the investigator. The subject must be re-consented. A new rescreening period will start and all screening procedures must be repeated.

Treatment Period (Correction Period and Maintenance Period)

The treatment period consists of a correction period and a maintenance period. Subjects are randomized to 1 of 2 treatment arms in a 1:1 ratio: one treatment arm will receive roxadustat administered orally and one treatment arm will receive darbepoetin alfa administered subcutaneously (SC) or intravenously (IV). Study treatment administration is implemented in an open-label manner.

Table 1: Treatment Arms and Dosing Frequency

Treatment Arm	Study Treatment	Dosing Frequency in Treatment Period	
		Correction Period	Maintenance Period
1	Roxadustat	TIW	TIW
2	Darbepoetin alfa	Dosing per European (EU) SmPC	

SmPC = Summary of Product Characteristics; TIW = three times weekly

Correction Period

The aim of the correction period is to correct Hb levels to ≥ 11.0 g/dL **and** a Hb increase from BL Hb ≥ 1.0 g/dL as measured at two consecutive study visits separated by at least 5 days (as assessed by central laboratory).
Dosing and dose adjustments of roxadustat will follow prespecified dose adjustment rules. Dosing and dose adjustments of darbepoetin alfa will be per EU approved Summary of Product Characteristics (SmPC).
Once Hb is corrected (Hb ≥ 11.0 g/dL or higher, **and** a Hb increase from BL Hb ≥ 1.0 g/dL) the subjects will enter into the maintenance period.

Maintenance Period

The aim of the maintenance period is to treat to a Hb target level of 11.0 g/dL by maintaining the Hb level between 10.0 g/dL and 12.0 g/dL.
Dose adjustments of roxadustat will follow prespecified dose adjustment rules.
Dose adjustments of darbepoetin alfa will be per EU approved Summary of Product Characteristics (SmPC).

Follow-up Period

After the treatment period, subjects proceed to the 4-week follow-up period.

Post Study 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 one dose of study drug) will continue to be followed up every 6 months for vital status, SAEs, 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.

Data Safety Monitoring Board

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.

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

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 has a diagnosis of CKD, with Kidney Disease Outcomes Quality Initiative (KDOQI) Stage 3, 4 or 5, not on dialysis; with an eGFR < 60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation.
4. The mean of the subject's two most recent (prior to randomization) Hb values during the screening period, obtained at least 4 days apart, must be ≤ 10.5 g/dL, with a difference of ≤ 1.0 g/dL. The last Hb value must be within 10 days prior to randomization.
5. Subject is deemed suitable by the investigator for treatment with erythropoiesis stimulating agents (ESA) using the criteria specified in the Kidney Disease Improving Global Outcomes (KDIGO) 2012 recommendation considering the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia.
6. This criterion has been removed.
7. This criterion has been removed.
8. Subject has a serum folate level ≥ lower limit of normal (LLN) at screening.
9. Subject has a serum vitamin B_{12} level ≥ LLN at screening.
10. 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.
11. Subject's body weight is 45.0 kg to a maximum of 160.0 kg.
12. Female subject is either:

    Of non-childbearing potential:
    - post-menopausal (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 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.
13. Female subject must not be breastfeeding at screening or throughout the study period, and for 28 days after the final study treatment administration.

14. Female subject must not donate ova starting at screening and throughout the study period and for 28 days after final study drug administration.
15. 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.
16. Male subject must not donate sperm starting from screening, throughout the study period and up to 12 weeks after final study drug administration.
17. 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.

Exclusion Criteria:

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

1. Subject has received any ESA treatment within 12 weeks prior to randomization.
2. Subject has received any dose of IV iron within 6 weeks prior to randomization.
3. Subject has received a Red Blood Cell (RBC) transfusion within 8 weeks prior to randomization.
4. Subject has a known history of myelodysplastic syndrome or multiple myeloma.
5. 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.
6. Subject has a known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition.
7. 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.
8. 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.
9. Subject has active or chronic gastrointestinal bleeding.
10. Subject has received any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI).
11. Subject has been treated with iron-chelating agents within 4 weeks prior to randomization.
12. Subject has a history of chronic liver disease (e.g., cirrhosis or fibrosis of the liver).
13. Subject has known New York Heart Association Class III or IV congestive heart failure.
14. Subject has had a myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (e.g., deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.

15. Subject has one or more contraindications for treatment with darbepoetin alfa:
    - Uncontrolled hypertension in the opinion of the investigator, or two or more blood pressure values of systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 95 mmHg (within 2 weeks prior to randomization).
    - Known hypersensitivity to darbepoetin alfa, recombinant human erythropoietin, or any of the excipients.
16. 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 within 12 weeks prior to randomization.
17. 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.
18. 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).
19. Subject has an active clinically significant infection that is manifested by White Blood Count (WBC) > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection within one week prior to randomization.
20. Subject has a known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion.
21. Subject has had any prior organ transplant (that has not been explanted), subject is scheduled for organ transplantation, or subject is likely to initiate renal replacement therapy including dialysis within the first year of the study in the opinion of the investigator.
22. Subject will be excluded from participation if any of the following apply:
    a. subject has received investigational therapy within 30 days or 5 half lives or limit set by national law, whichever is longer, prior to initiation of screening, or
    b. any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
23. Subject has an anticipated use of dapsone in any dose amount or chronic use of acetaminophen/paracetamol > 2.0 g/day during the treatment or follow-up period of the study.
24. Subject has a history of alcohol or drug abuse within 2 years prior to randomization.
25. 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 Product:
Roxadustat (ASP1517/FG-4592)

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

Mode of Administration:

- Oral

Doses:

The initial study drug (roxadustat) dose (per dose amount) is based on the tiered, weight-based dosing scheme shown in the table below:

Table 2: Initial Dosing of Roxadustat

Study Drug (Dose Frequency)	**Weight** (≥ 45.0 to ≤ 70.0 kg)	**Weight** (> 70.0 to ≤ 160.0 kg)
Roxadustat (TIW)	70 mg	100 mg

After randomization, the subject will enter the correction period. Roxadustat will be dosed TIW for Hb correction. The initial dose can be adapted if Hb increase is insufficient (see dose adjustment rules below). After reaching Hb correction, the subject will enter the maintenance period and will continue to be dosed TIW.

Dose adjustment of roxadustat can be done from week 4 onward when the subject has been on stable roxadustat treatment for 4 weeks, and every 4 weeks thereafter until week 104 according to Hb levels and change in Hb over the preceding 4 weeks as illustrated in the table below.

Table 3: Dose Adjustment Rules

	Correction Period	**Maintenance Period**		
Change in Hb over past 4 weeks (g/dL)[a]	**(When Hb correction has not been reached)**	**Hb <10.5 g/dL**	**Hb 10.5 to <12.0 g/dL**	**Hb 12.0 to <13.0 g/dL**
< -1.0	↑	↑	↑	No change
-1.0 to 1.0	↑	↑	No change	↓
> 1.0	No change	No change	↓	↓

[a] Subtract 4 weeks' previous Hb value from the present Hb value to calculate the change

- All dose adjustments are made based on Hb values using HemoCue®, a point-of-care device.
- If the dose adjustment is 'No change' per Table 3, the next dose adjustment review is 4 weeks after that visit.
- Dose increases by one dose step (↑) and reductions by one dose step (↓) are pre-set per the dose steps.
- The dose steps for roxadustat are as follows: 20, 40, 50, 70, 100, 150, 200, 250 and 300 mg.
- The maximum dose is the dose step corresponding to 3.0 mg/kg per administration or 300 mg, whichever is lower. The default weight is initially set as weight measured at day 1. At study visits where weight is collected, the maximum allowed dose step and the default weight for a subject will be adjusted if the weight change is ≥ 5% compared to the previous default weight collected in the study. For randomized subjects who require chronic dialysis during the treatment period, the maximum dose step is the dose step corresponding to 3.0 mg/kg per administration or 400 mg, whichever is lower.
- At week 4 only, in a subject whose baseline Hb level was < 8.0 g/dL, if the dose adjustment is to increase, then dose increase could be made with either a 1 or 2 step increase per investigator's discretion to minimize the probability of requiring rescue therapy treatment.
- 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 300 mg.
- 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.

<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 two steps

- Next dose adjustment review is 4 weeks after dose resumption and in 4-weekly intervals thereafter.

Dose Adjustment for Excessive Hematopoiesis

If at any time during the treatment period Hb increases by > 2.0 g/dL within 4 weeks:

- The dose should be reduced by one dose step
- Only one dose reduction for excessive hematopoiesis is recommended within a period of 4 weeks. If a blood transfusion or ESA treatment has been performed within 2 weeks of meeting the criteria for excessive hematopoiesis, it is recommended not to perform a dose reduction for excessive hematopoiesis.
- 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.

Comparative Drug:

- Darbepoetin alfa (Aranesp®) solution for injection in a pre-filled syringe.
- Range of strengths: 20, 30, 40, 60 and 100 µg.

Mode of Administration:

- Subcutaneous (SC) or intravenous (IV) as judged appropriate by the investigator.

Dose:

Darbepoetin alfa dosing is to follow the EU SmPC. All administrations will be performed by the investigator or a qualified member of the site staff or, after 36 weeks of treatment, by the subject themselves or caregiver, e.g., relative, if well trained and willing to self-administer.

- Initial dose:

  0.45 µg/kg body weight as a single SC or IV injection once weekly; alternatively 0.75 µg/kg body weight SC once every two weeks.

- Dose adjustment:

  If the increase in Hb is inadequate (less than 1.0 g/dL within 4 weeks) increase the dose by approximately 25%. During the correction period, dose increases must not be made more frequently than once every four weeks; during the maintenance period, dose changes should not be made more frequently than every two weeks.

  If the rise in Hb is greater than 2.0 g/dL in 4 weeks, reduce the dose by approximately 25%. Once the target Hb level has been achieved with once every 2-week dosing, darbepoetin alfa may be administered SC once monthly using an initial dose equal to twice the previous once every 2-week dose.

  All dose adjustments are made based on Hb values assessed using the HemoCue® device.

Target of treatment is achieving Hb response (defined as Hb values of ≥ 11.0 g/dL and Hb increase from BL Hb ≥ 1.0 g/dL at 2 consecutive study visits separated by at least 5 days [as assessed by the central laboratory]) and thereafter maintaining Hb in the target range of 10.0 to 12.0 g/dL.

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.

1. RBC Transfusion (for all subjects)

In the event of acute or severe blood loss, RBC transfusion is allowed if clinically indicated. In a situation where there is no obvious blood loss, RBC transfusion will be permitted if the subject has moderate to severe symptom(s) from his/her anemia, e.g., dyspnea at rest or on mild exertion, and the

investigator is of the opinion that the blood transfusion is a medical necessity. Study treatment may be continued even if a blood transfusion has been administered.

2. ESA (only for subjects treated with roxadustat)

If the investigator considers administration of ESA as a medical necessity, darbepoetin alfa may be initiated if the following criteria are met:

- the subject's Hb level is < 9.0 g/dL (HemoCue) as confirmed at two consecutive visits,

and

- the subject's Hb level has not responded adequately despite 2 or more roxadustat dose increases in the previous 8 weeks, or the roxadustat dose reached the maximum dose limit,

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 darbepoetin alfa, 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.

The subject may continue in the study while on rescue treatment with darbepoetin alfa, however, it is not allowed to administer roxadustat during the same time period.

The course of darbepoetin alfa (i.e., the amount that may be administered) will be limited by duration of therapy and effect on Hb. The course of darbepoetin alfa rescue treatment will not exceed 4 weeks in duration, and darbepoetin alfa rescue will be stopped as soon as Hb ≥ 9.0 g/dL. To continue study participation, treatment with roxadustat study drug should be resumed within one week after the last administration of darbepoetin alfa at the dose level the subject was on prior to initiating darbepoetin alfa rescue therapy.

If a subject requires a second course of rescue darbepoetin alfa, the subject must be discontinued from treatment.

Doses:
The doses of rescue therapies are per 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 (stop dosing). The therapeutic phlebotomy should be documented in the eCRF and source documentation, and discussed with the Medical Monitor.

Concomitant Medication Restrictions and/or Requirements:

Supplemental Iron Use

For subjects receiving roxadustat

i. Oral iron

For subjects receiving roxadustat, oral iron is recommended for supplementation to support erythropoiesis and as the first-line treatment for iron deficiency, unless the subject is intolerant to this treatment. The recommended daily dose is 200 mg of elemental iron. Administration of roxadustat between -1 hour and +1 hour of intake of oral iron is not recommended.

ii. Intravenous iron

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

- The subject has not responded adequately to 2 or more dose increases of roxadustat or has reached the maximum dose limit, and
- The subject has iron deficiency (either ferritin < 100 ng/mL [< 220 pmol/L] or TSAT < 20%) or the subject does not tolerate oral iron therapy.

Treatment with roxadustat may 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%.

For subjects receiving darbepoetin alfa

For subjects treated with darbepoetin alfa, oral or IV iron supplementation is required to maintain iron repletion. IV iron should only be administered if ferritin is < 100 ng/mL (< 220 pmol/L) or TSAT is < 20%. IV iron may be administered per local practice. Discontinuation of IV iron therapy is recommended once ferritin levels are ≥ 100 ng/mL (≥ 220 pmol/L) and TSAT ≥ 20%.

Anti-hypertensive Medication

To avoid confounding effects on study endpoints, changes to anti-hypertensive medications should be minimized, and made only if deemed medically necessary by the investigator or if pre-specified changes in blood pressure are met.

Prohibited Medication

The following medications are prohibited during the period identified:

- Any ESA: within 12 weeks prior to randomization until EOT.
- IV iron: within 6 weeks prior to randomization.
- RBC transfusion: within 8 weeks prior to randomization.
- Any investigational drug: within 30 days or 5 half lives or limit set by national law (whichever is longer), prior to screening until EOS.
- Roxadustat or another HIF-PHI: at any time prior to randomization. After randomization any HIF-PHI 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 day of randomization until EOS.
- Dapsone in any dose amount or chronic use of acetaminophen/paracetamol >2.0 g/day from the day of randomization until EOS.

Duration of Treatment:

104 weeks

Formal Stopping Rules:

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

- Subject no longer consents to participate in the treatment phase of the study.
- 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.
- Subjects randomized to roxadustat: requirement of a second course of rescue therapy with darbepoetin alfa deemed necessary by the investigator based upon the criteria for use of rescue treatment.

- Subject receives an organ transplant.

Subjects that 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 one dose of study drug will continue to be followed up every 6 months for vital status, SAEs, cardiovascular and thromboembolic AEs until their projected date of completion of follow-up period (i.e., projected week 108 date) or until consent is 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.
- Death of a study subject.
- The Sponsor may decide to prematurely stop the study, e.g., for safety considerations.

Endpoints for Evaluation

Primary:

The primary efficacy variable is:

- Hb response defined as: Hb ≥ 11.0 g/dL and a Hb increase from BL Hb by ≥ 1.0 g/dL in any subject with BL Hb > 8.0 g/dL, OR an increase from BL Hb by ≥ 2.0 g/dL in any subject with BL Hb ≤ 8.0 g/dL as measured at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response.

Key Secondary:

- 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.
- 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) per subject during weeks 1 to 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.
    - Occurrence and time to occurrence of hypertension (defined as either systolic blood pressure [SBP] > 170 mmHg AND an increase from BL of ≥ 20 mmHg SBP or diastolic blood pressure [DBP] >110 mmHg AND an increase from BL of ≥ 15 mmHg DBP on 2 consecutive visits) during weeks 1 to 36.

Additional Secondary:

Hb correction and maintenance:

- Hb change from BL to the average Hb value of weeks 28 to 52 regardless of the use of rescue therapy.
- Time (weeks) to achieve the first Hb response as defined by primary endpoint.
- Hb response defined as: Hb ≥ 11.0 g/dL and a Hb increase from BL Hb by ≥ 1.0 g/dL in any subject with BL Hb > 8.0 g/dL, OR an increase from BL Hb by ≥ 2.0 g/dL in any subject with BL Hb ≤ 8.0 g/dL as measured at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment regardless of administration of rescue therapy prior to Hb response.

- Hb averaged over weeks 28 to 36, 44 to 52, 72 to 80, 96 to 104, without use of rescue therapy within 6 weeks prior to and during this evaluation period.
- Hb value and Hb change from BL at each post-dosing time point.
- Hb change from BL to the average Hb value of weeks 28 to 36, 44 to 52, 72 to 80, 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, 72 to 80, 96 to 104, without use of rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

Hospitalizations

- Occurrence (number) of hospitalization(s).
- Number of days of hospitalization.

Rescue therapy use

- Having received rescue therapy (either RBC transfusions [for all subjects] or darbepoetin alfa use [for roxadustat treated subjects only])
- Having received RBC transfusions.
- Number of RBC packs per subject.
- Volume of RBC transfused per subject.

Changes in cholesterol levels

- Change from BL to each post-dosing scheduled measurement in:
  - Total cholesterol
  - LDL/High-density Lipoprotein (HDL) ratio
  - Non-HDL cholesterol
  - Apolipoproteins A1 and B, and ApoB/ApoA1 ratio
- Occurrence of mean LDL cholesterol < 100 mg/dL (mean LDL calculated over weeks 12 to 28, and weeks 36 to 52 of treatment).

Blood pressure effect

- Occurrence of achieved antihypertensive treatment goal (SBP < 130 mmHg systolic and DBP < 80 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28 and 36 to 52 of treatment with study drug.

HRQoL and EQ5D 5L benefits

- Change from BL to the average value of weeks 12 to 28 and 36 to 52 in:
  - Physical Component Score (PCS) of SF-36
  - Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score
  - Total FACT-An Score
  - EQ-5D 5L VAS Score
  - WPAI:ANS Score
- PGIC (qualitatively by assessment)

Iron, HbA1c, and CKD progression

- Changes from BL to each scheduled measurement in:
  - Serum ferritin
  - TSAT
  - HbA1c level
  - Fasting blood glucose
  - eGFR (including eGFR slope over time)
  - Urine albumin/creatinine ratio
- Serum creatinine having doubled during the study in comparison with baseline

- Occurrence of End Stage Renal Disease (ESRD)

Safety:

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 of prespecified adjudicated cardiovascular and cerebrovascular events.

Statistical Methods

Sample Size Justification:

Approximately 570 subjects will be randomized to receive roxadustat or darbepoetin alfa as follows:

Table 4: Sample Size Calculations per Treatment Arm

Treatment Group	Protocol version 1.0		Protocol versions 2 and 3		Total	
	Randomized	PPS	Randomized†	PPS	Randomized	PPS
Roxadustat	100	80	210	168	310	248
Darbepoetin alfa	50	40	210	168	260	208
Total	150	120	420	336	570	456

† The number of subjects under protocol v2 and v3 will depend on the number of subjects randomized under protocol v1.

Randomization will be stratified by the following four factors:

- Region: region A versus region B*

  * *Assignment to region will be determined based on health care comparability.*
- Screening Hb values (≤ 8.0 g/dL versus > 8.0 g/dL)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No)
- eGFR (< 30 mL/min/1.73 m^2 versus ≥ 30 mL/min/1.73 m^2).

Assuming that the PPS analysis will consist of 80% of subjects in the Full Analysis Set (FAS), 570 randomized subjects in the FAS will lead to 456 subjects in the PPS. Two hundred and forty eight (248) subjects for the roxadustat treatment group and 208 subjects for the darbepoetin alfa treatment group will provide at least 98% test power to demonstrate statistically non-inferiority of roxadustat versus darbepoetin alfa in the primary endpoint assuming that the proportion of subjects with response in both groups is the same and at least 80% and a non-inferiority margin for the difference of proportions of 15%. The power for the sensitivity analysis of post-amendment data (336 subjects) will be at least 93%.

Analysis Sets

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

- Intent-to-Treat (ITT)
- Full Analysis Set (FAS)
- Per-Protocol Set (PPS)
- Safety Analysis Set (SAF)
- Pharmacokinetic Analysis Set (PKAS)

Efficacy:

Analysis of Primary Endpoint

The difference in the proportion of responders in the primary efficacy endpoint between pooled roxadustat and darbepoetin alfa will be calculated using Mattinen & Nurminen approach adjusting for

the stratification factors. The primary hypothesis to be tested for the primary efficacy analysis is:

H_0: Hb responder rate in the pooled roxadustat group < Hb responder rate in the darbepoetin alfa group minus 15%

versus

H_1: Hb responder rate in the pooled roxadustat group ≥ Hb responder rate in the darbepoetin alfa group minus 15%

This null hypothesis will be rejected if the two-sided 95% confidence interval for the difference of proportions lies entirely above -15%.

In addition, a 95% CI will be calculated for the proportion of responders on roxadustat and darbepoetin alfa based on the exact method of Clopper-Pearson. Sensitivity analyses will be conducted to assess the consistency of the results before and after protocol amendments 1 and 2.

Efficacy:

Analysis of Key Secondary Endpoints

Once the primary hypothesis has been rejected for the primary endpoint, the key secondary variables will be tested using a fixed sequence testing procedure as follows:

1. Hb change from BL to the average Hb of weeks 28 to 36 (non-inferiority of pooled roxadustat versus darbepoetin alfa) without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period. The non-inferiority margin for the difference between groups is 0.75 g/dL.
2. LDL cholesterol change from BL to the average of weeks 12 to 28 (superiority of pooled roxadustat versus darbepoetin alfa).
3. Mean monthly IV iron (mg) use per subject during weeks 1 to 36 (superiority of pooled roxadustat versus darbepoetin alfa).
4. SF-36 PF sub-score change from BL to the average of weeks 12 to 28 (non-inferiority of pooled roxadustat versus darbepoetin alfa). The non-inferiority 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 (non-inferiority of pooled roxadustat versus darbepoetin alfa). The non-inferiority 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 pooled roxadustat versus darbepoetin alfa). The non-inferiority margin for the difference between groups is 1 mmHg.
7. Incidence of hypertension (non-inferiority of pooled roxadustat versus darbepoetin alfa). The non-inferiority 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 pooled roxadustat versus darbepoetin alfa).
9. Incidence of hypertension (superiority of pooled roxadustat versus darbepoetin alfa).

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

Pharmacokinetics:

Population PK data will be generated for roxadustat from a timed blood sampling scheme. 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 (PPKPD) modeling. When deemed necessary, data from this study may be combined with data from other studies. Results will be reported in a separate PPKPD modeling report.

Safety:

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

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

The statistical method for analysis of adjudicated safety data will be detailed in a pooled cardiovascular safety Statistical Analysis Plan (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.

Interim Analyses:

An interim analysis will be performed when all subjects have completed 36 weeks of treatment; efficacy and safety data will be analyzed and reported, excluding the endpoints measured after 36 weeks. Since all primary and secondary analyses have been defined over this period of time, no multiplicity adjustment is required as the information fraction at the interim analysis is 100%.

In addition, a descriptive analysis on both safety and efficacy will be performed to provide information from this study for regulatory filings of roxadustat in case the planned interim analysis has not been reached. This will include only descriptive statistics by arm (i.e., without formal hypothesis testing).

Once the study is completed, efficacy and safety will be analyzed again and reported including the complete study treatment of 104 weeks.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

STUDY DESIGN 3.0

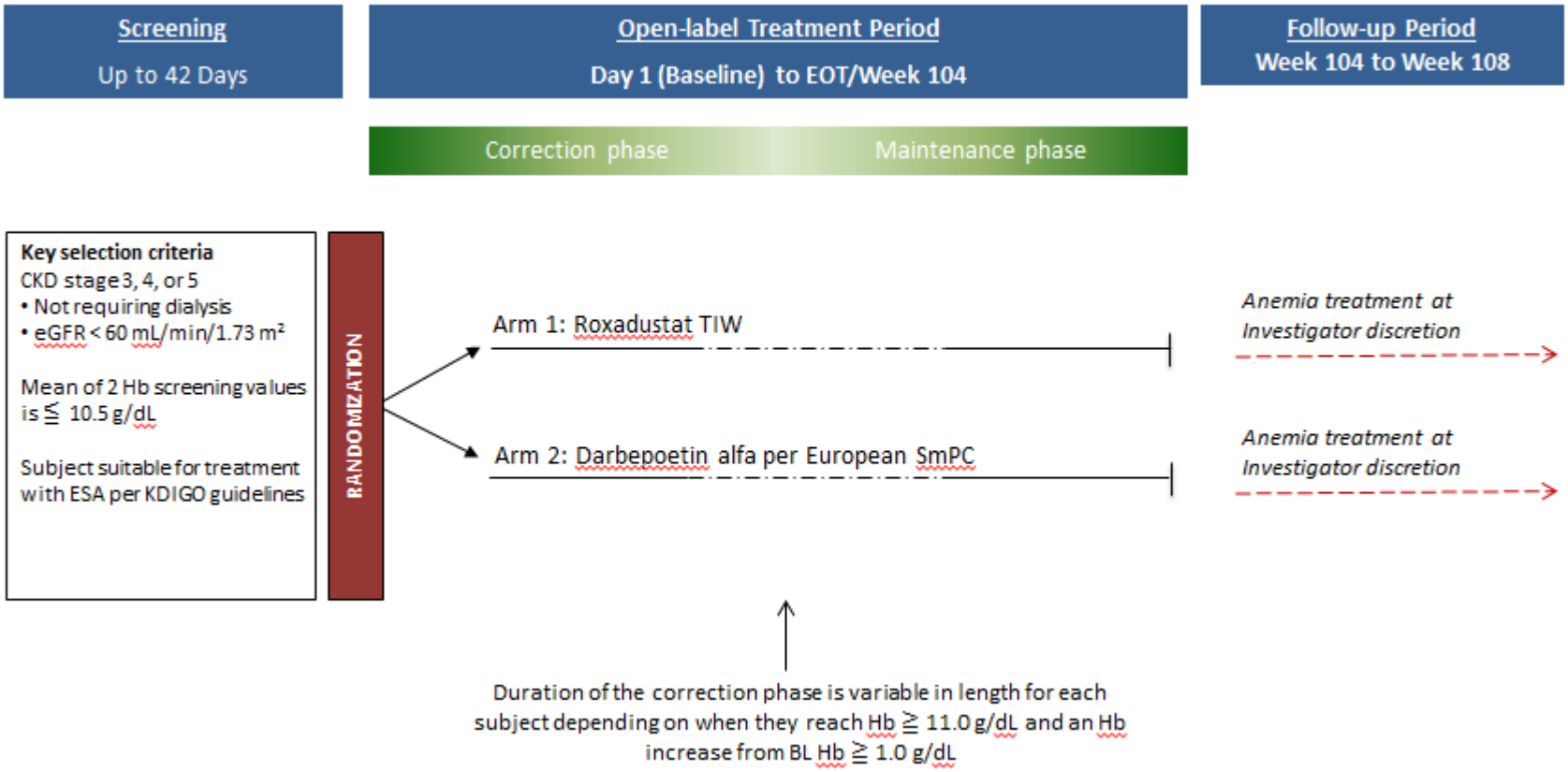


Table 1 Schedule of Assessments

Assessments	Screening Period		Treatment Period (Correction Period and Maintenance Period)					Follow-up Period		Unscheduled Visits	Post study Follow-up [c]
Visit / Week	Up to6 weeks [a]		Day 1[b]	Weekly (wks 1 - 2) ± 2 days	Every 2 Weeks (wks 4 - 24) ± 2 days	Every 4 Weeks (wks 28 - 100) ± 3 days	EOT [c] (wk 104) ± 3 days	EOT[c] + 2 wks ± 3 days	EOS [c] (EOT + 4 wks) ± 3 days		Every 6 months until projected wk 108
	S1	S2									
Written informed consent	X										
Randomization			X								
Eligibility criteria	X		X								
Demographics	X										
Medical history	X										
Physical examination	X		X		wks 12[d], 24[d]	wks 36[d], 52[d], 76[d]	X		X[d]	O[d]	
Height[e], weight	X		X		wks 12, 24	wks 36, 52, 76	X		X	O	
Blood pressure[f], heart rate[f], respiratory rate[g]	X	X	X	X	X	X	X		X	O	
CBC with WBC diff, red cell indices and platelets	X		X	X	wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
Hemoglobin[h]		X[i]			X	X		X		O[il]	
HemoCue assessment[j]			X	X	X	X				O	
Reticulocyte count and Hb in reticulocytes (CHr)	X		X	X	wks 4, 6, 8, 12, 16, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
12-lead ECG	X		X		wks 12, 24	wks 36, 52, 76	X			O	
Serum chemistry	X		X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X	X	X	O	
LFTs[k]				wk 2	wks 6, 16					O	
Renal ultrasound[l]	X									O	
Serum lipid panel[m]	X		X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O	
Serum iron, ferritin, TIBC, TSAT	X		X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
HbA1c	X		X		wk 12	wks 28, 36, 44, 60, 84	X		X	O	
Vitamin B_{12}, folate	X										
HIV immunoassay, HBsAg, anti-HCV antibody	X										
Serum pregnancy test[n]	X				wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O	

Table continued on next page

Assessments	**Screening Period**		**Treatment Period** (Correction Period and Maintenance Period)					**Follow-up Period**		**Unscheduled Visits**	**Post study Follow-up [c]**
Visit / Week	**Up to6 weeks [a]**		**Day 1[b]**	**Weekly (wks 1 - 2) ± 2 days**	**Every 2 Weeks (wks 4 - 24) ± 2 days**	**Every 4 Weeks (wks 28 - 100) ± 3 days**	**EOT [c] (wk 104) ± 3 days**	**EOT[c] + 2 wks ± 3 days**	**EOS [c] (EOT + 4 wks) ± 3 days**		**Every 6 months until projected wk 108**
	S1	**S2**									
eGFR[o]	X		X		wk 20	wks 36, 52, 68, 84	X		X	O	
hs-CRP			X		wks 4, 12, 20	wks 36, 52	X		X		
Archival serum samples for biomarkers[p]			X		wks 4, 12, 20	wks 52, 76					
Blood sample for PK[q]				wks 2 to 8							
Genotyping[r]				O							
QoL questionnaires[s]			X		wks 8, 12	wks 28, 36, 52, 76	X			O	
Urinary testing[t]			X		wks 12, 24	wks 36, 52, 64, 76, 88	X			O	
Archival urine samples for biomarkers			X		wk 24	wks 52, 76					
Study drug dispensing[u]			├	─	─	─ ┤				O	
Dose adjustment review[v]				X	X	X				O	
Hospitalization recording[w]	X	X	◄	─	─	─	─	─	─ ►		X
AE recording	X	X	◄	─	─	─	─	─	─ ►		
Concomitant medication, procedure and non-drug therapy recording	X	X	◄	─	─	─	─	─	─ ►		
Vital status, SAEs, cardiovascular and thromboembolic AEs[w]											X

S1/S2 = Screening visit 1and 2; EOT = End of Treatment; EOS = End of Study; Wk(s) = Week(s); X = mandatory test/assessment; O = optional test/assessment.

Note: see Appendix 12.4 Instructions for Subjects Requiring Dialysis.

a The requirement of a 4-day separation between the screening Hb values defines the minimum duration of the screening period. The maximum duration of the screening period is 6 weeks. Sites are recommended to schedule the two screening visits in the shortest time span possible.

b All study assessments are to be performed prior to first study drug administration.

c In case of premature treatment discontinuation or withdrawal during the treatment period, subjects will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and EOS visit. Thereafter, subjects who have taken at least one dose of study drug will continue to be followed up at a 6-monthly frequency for vital status, SAEs, 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.

d Targeted physical examination only (e.g., respiratory and cardiovascular).

e Height measurement only required at first screening visit.

Footnotes continued on next page

f Blood pressure and heart rate measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period that measurements should occur prior to study drug administration if study medication is taken on same day of visit; except for visits where subjects are instructed to take study medication at home for PK sampling purpose. For subjects requiring dialysis, BP and heart rate will be recorded prior to and after dialysis (hemodialysis [HD]/hemodiafiltration [HDF] subjects only).

g Respiratory rate measured singly during screening period and all other visits. It is recommended during the treatment period that measurement should occur prior to study drug administration except for visits where subjects are instructed to take study medication at home for PK sampling purposes. For subjects requiring dialysis, respiratory rate will be recorded prior to dialysis (HD/HDF subjects only).

h Separate Hb should be collected at all the visits where Complete Blood Count (CBC) is not collected (i.e., Hb at weeks 6, 10 until the end of the study).

i An additional (third) Hb value may be collected if necessary. Only for subjects who are switched from protocol version 2.0 to 3.0 during (re) screening can a fourth Hb value be collected, as was applicable under protocol version 2.0.

i1 If during an unscheduled visit, Hb needs to be assessed, this should always be done with the HemoCue AND a central laboratory Hb assessment.

j If during an unscheduled visit Hb needs to be assessed, this should always be done with the HemoCue AND a central laboratory Hb assessment. This HemoCue assessment should be done on the blood sample that is collected for Hb analysis for the central laboratory.

k In addition to LFTs collected as part of Serum Chemistry, LFTs will separately be collected at the indicated weeks.

l Renal ultrasound examination within 12 weeks prior to randomization. Not required if results of a previous renal ultrasound (or other renal imaging modality such as CT scan or MRI) within 12 weeks prior to randomization is available and ruling out renal cell carcinoma. If other imaging modality, a conclusive report on the kidney should be available.

m Fasting whenever possible.

n Collect from female subjects of childbearing potential only.

o Using Modification of Diet in Renal Disease (MDRD) formula; calculated by the central laboratory.

p At day 1, week 20, 52, and 76, two equal volume samples should be collected.

q Sampling roxadustat will be done at 6 time points over 1 to 3 visits between weeks 2 and 8. See Section 5.6. At each pharmacokinetic visit, one additional sample will be collected for determination of Alpha 1-Acid Glycoprotein (α1-AGP) and albumin concentration.

r Optional assessment for subjects treated with roxadustat. A separate informed consent form must be signed before genotyping sample is collected. Sample collection can be done at any timepoint throughout the treatment period of the study.

s Including SF-36, FACT-An, EQ-5D 5L, PGIC and WPAI:ANS. PGIC will not be performed on day 1. Questionnaires to be completed by the subject preferably prior to any study assessments. When subjects need dialysis therapy, Quality of Life (QoL) questionnaires will be completed on the day of first dialysis (preferably before the dialysis is started), 4 weeks later and 12 weeks later.

t Ideally, the sample should be from the first morning void. Urinary testing includes qualitative testing with dipstick testing (for protein, pH, glucose) and quantitative assessment of albumin and creatinine for calculation of albumin/creatinine ratio.

u Dosing of darbepoetin alfa per EU SmPC.

v Subjects randomized to roxadustat: dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (wks 4, 8, 12 etc), except in the event 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 visit.

w Telephone or in-person follow-up call with subject.

1 INTRODUCTION

1.1 Background

1.1.1 Epidemiology of Chronic Kidney Disease and End Stage Renal Disease

Chronic Kidney Disease (CKD) is a growing worldwide public health challenge associated with significant morbidity and mortality, yet it is under-diagnosed and under-treated. It is characterized by progressive loss of kidney function, ultimately resulting in premature death or renal replacement therapy (kidney transplant or dialysis). In 2007, CKD affected 13% of the US adult population (approximately 29 million US adults) and its prevalence is growing rapidly [Coresh et al, 2007]. In Europe, the average prevalence of CKD regardless of age lies between 5 and 11% [Zoccali et al, 2010]. All-cause mortality risk increases exponentially as CKD stages advance [Tonelli et al, 2006].

The number of CKD patients suffering from End Stage Renal Disease (ESRD) also continues to increase worldwide. The US has one of the highest prevalence rates of ESRD in the world: in 2010, the US had over 1700 ESRD patients per million population, a 23% increase compared to 10 years prior (United States Renal Data System [USRDS, 2011]. In 2009, there were approximately 570,000 ESRD patients in the US, of whom 370,000 were receiving hemodialysis, 27,000 were receiving peritoneal dialysis, and 173,000 had a functioning kidney transplant [USRDS, 2011]. In Europe, over the period 1992–2005, the overall crude prevalence of renal replacement therapy (RRT) for ESRD increased from 480 to 807 patients per million population [Zoccali et al, 2010].

The average expected remaining lifetime of a dialysis patient in the US is 5.9 years, compared to 16.4 years for a transplant patient, and 25.2 years for someone of comparable age in the general population [USRDS, 2009]. The prevalence of ESRD is projected to grow to 774,000 by the year 2020 [USRDS, 2009]. Data from selected countries in Europe indicate that the five-year mortality rates in incident RRT patients are 52% in all patients, and 21%, 32% and 73% for patients 0 to 14, 15 to 64 and over 65 years of age, respectively [Zoccali et al, 2010].

1.1.2 Anemia Associated with CKD

Anemia is a common complication in patients with CKD, and although its pathogenesis is multi-factorial, the decreased production of erythropoietin (EPO), a hormone produced primarily in the kidneys, is considered an important etiologic factor. The impaired ability of the body to absorb and utilize iron is likely another etiologic factor.

Anemia may first present in early stages 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 requiring dialysis [Coresh et al, 2007; Go et al, 2004]. Over 90% of patients undergoing dialysis are anemic: 50.1% of the dialysis patients had hemoglobin (Hb) levels below 10 g/dL and approximately 28% had Hb below 9 g/dL [USRDS, 2003]. Some studies from Europe provide data on anemia rates in patients who have been under care of nephrologists. In 1999 Jungers prospectively studied 403 consecutive ambulatory pre-dialysis

patients and found 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]. Between 2003 and 2005 Thilly studied pre-dialysis anemia care in 6271 incident dialysis patients. The average level of pre-dialysis Hb was 10.3 g/dL and 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 impact of anemia on organ function is reduced oxygen delivery to tissues, it affects almost every organ system.

Anemia contributes to the excess morbidity and mortality in CKD and ESRD. In patients with CKD, the severity of anemia correlates directly with the risk of hospitalization, cardiovascular disease, and death [Collins et al, 1998]. Patients with the lowest Hb have worse outcomes, as was discussed in the post hoc analysis of mortality by Hb quintiles for the Normal Hematocrit and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) studies in the Food and Drug Administration (FDA) briefing document for the October 2007 Cardiovascular and Renal Drugs Advisory Committee [Unger, 2007]. Similar data are found in the USRDS mortality data stratified by Hb. All-cause mortality stratified by Hb (1993–1996) showed significantly higher first-year death rates in patients with Hb levels < 9 and 9 to < 10 g/dL, compared to 11 to <12 g/dL. This trend continued to worsen, as reflected in 1998–1999 data, where the death rate rose by approximately 75% compared to the 1993-1996 period [USRDS, 2000; USRDS, 2002]. This increase coincides with the introduction of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in 1997. The relative risk of all-cause mortality for patients with Hb <9 g/dL is twice that of patients with Hb > 12 g/dL [USRDS, 2002]. The relative risk of cardiovascular hospitalization increased significantly to 1.26 in patients with Hb levels < 9 g/dL compared to those with Hb at 11 to 12 g/dL [USRDS, 2001].

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

1.1.3 Treatment of Anemia

In less severe anemia first-line therapy consists of iron monotherapy (oral or intravenously). However, therapy with erythropoiesis-stimulating agents (ESAs) in combination with iron supplementation is a major alternative to transfusion in managing more severe anemia associated with CKD. Anemic patients with CKD or ESRD will require life-long treatment. For those patients not resistant to ESAs, parenteral administration of exogenous recombinant human erythropoietin (epoetin alfa or beta) or pegylated analogues has been a widely accepted approach for treatment of anemia in patients with CKD [Eschbach et al, 1987; Eschbach & Adamson, 1989; Winearls et al, 1986; US Recombinant Human Erythropoietin Predialysis Study Group, 1991], despite the documented safety risks such as hypertension and thrombosis.

Although the treatment of anemia in CKD and ESRD is thought to contribute positively to a patient's quality of life (QoL), functional well-being and physical performance, several

studies in ESRD and nondialysis-dependent chronic kidney disease (NDD-CKD) patients 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, 2004] of ESRD patients who received higher ESA doses. A treatment option that avoids supraphysiologic levels of circulating plasma EPO levels may be a safer alternative. Additionally, ESA therapy for anemia in ESRD patients on hemodialysis usually requires concomitant intravenous (IV) iron supplementation.

There is currently an unmet medical need for an oral treatment that will correct anemia in NDD-CKD and dialysis-dependent chronic kidney disease (DD-CKD) patients to a target Hb level that is safe and well tolerated.

Roxadustat[b] is an oral medication that could potentially deliver effective treatment for CKD-related anemia with less need for iron supplementation and without producing supraphysiologic levels of circulating EPO.

1.2 Non-clinical and Clinical Data

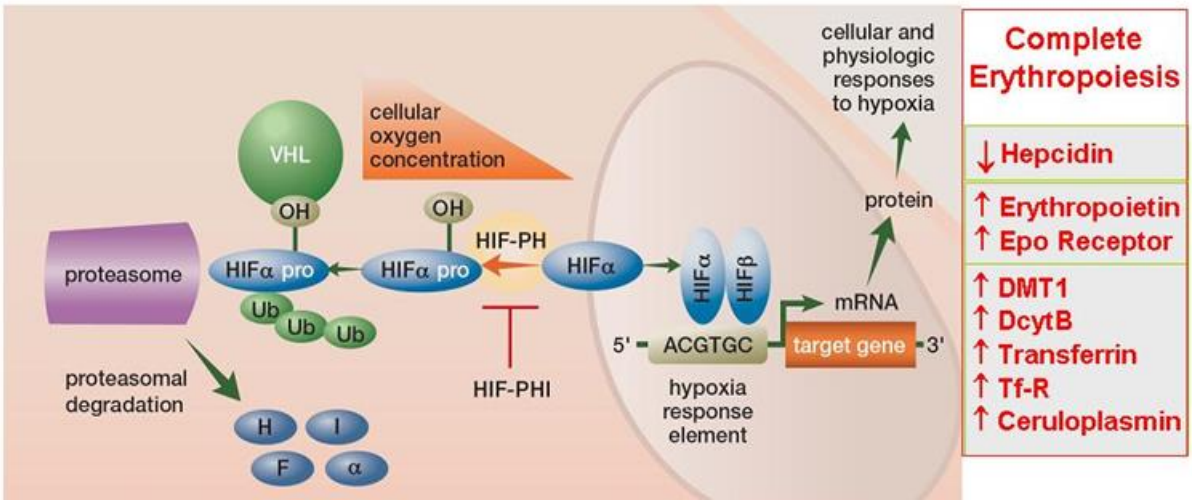
1.2.1 Mechanism of Action of Roxadustat

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 three 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].

[b] The originator of the compound under study is FibroGen Inc and the code name used by FibroGen Inc is FG-4592. Astellas is the development partner and uses the code name ASP1517. The sponsor of this study is Astellas. The compound has received the INN roxadustat.

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 (DNA) 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 hypoxia-inducible factor 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 is a potent and reversible hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that transiently induces HIF stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure of humans to intermittent hypoxia. HIF induces expression of not only EPO, but also 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-PHIs 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 non-clinical 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.

1.2.2 Clinical Experience with Roxadustat

Roxadustat is currently being studied in DD-CKD and NDD-CKD subjects with anemia. Numerous Phase 1 and 2 clinical studies have been completed in the United States, Europe and Asia. Information from these studies is provided in the Investigator's Brochure. As of 07 September 2014, an estimated total of 1,485 subjects have been exposed to roxadustat in the clinical development program, comprising 571 healthy subjects and an estimated 483 subjects with NDD-CKD and 431 subjects with DD-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 three 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 DD-CKD and NDD-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 (PD) of roxadustat were characterized in studies in healthy subjects and in DD-CKD and NDD-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 hours in healthy subjects, and 15 to 19 hours in dialysis subjects (after single doses of 1 and 2 mg/kg). The exposure was higher in dialysis subjects compared to healthy subjects.

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 two formulations.

With an intermittent dose regimen of once weekly (QW), twice weekly (BIW) or three times weekly (TIW), no or limited accumulation in mean area under the plasma concentration (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 (Ki) 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.

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 hour before or 1 hour after the phosphate binder minimized the interactions.

In healthy adult male volunteers (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 (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 PD studies conducted with roxadustat in CKD subjects not on dialysis (Study FGCL-4592-017), the mean maximum EPO increase from BL ranged from 82-443 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 pre-dialysis and post-dialysis. These increases in endogenous EPO were transient and the effect disappeared within approximately 48 hours.

In contrast, EPO levels associated with therapeutic ESA dosing range from 1,500 to over 10,000 mIU/mL [Besarab et al, 2009]. In a clinical study with dialysis subjects, the reported mean administered individual ESA dose was 8,000 IU, which would correspond to plasma EPO C_{max} levels exceeding 3,000 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 volunteers. 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, 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 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 NDD-CKD subjects. Dosing frequency reduction, once Hb correction is achieved, appears to be feasible to maintain Hb in the target range.

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). In 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 had 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 to be durable in roxadustat treatment arms (combined) over a 19-week period.

For further information, refer to the most recent version of the Investigator Brochure.

1.2.2.3 Summary

In summary, roxadustat is an orally active HIF-PH inhibitor with potent erythropoietic effects. Repeated intermittent dosing of roxadustat results in intermittent activation of HIF, intermittent induction of endogenous EPO, and a dose-dependent erythropoiesis. The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in healthy adult subjects, and in DD-CKD and NDD-CKD subjects with anemia who have been enrolled and treated in completed and ongoing clinical studies. Roxadustat leads to a robust dose-related erythropoietic response in subjects with CKD-associated anemia. Roxadustat dosing induces a transient elevation in endogenous EPO level that is close to the physiologic range, but much lower than the plasma EPO level associated with IV ESA dosing, suggesting a coordinated erythropoiesis mechanism that is different from that of ESA therapy.

1.2.3 Clinical Experience with Darbepoetin alfa

The comparative drug darbepoetin alfa (Aranesp®) is approved since 2001 in the European Union (EU) for the treatment of anemia associated with chronic renal failure in adults and pediatric subjects. It is a commonly used ESA in Europe for the treatment of anemic NDD-CKD subjects and has demonstrated its ability to correct and maintain Hb in subjects in several controlled randomized trials.

Two exploratory dose- and schedule-finding studies (NESP-960245 and NESP-960246) investigated the effects of darbepoetin alfa for correction of anemia in hemodialysis (HD) and peritoneal dialysis subjects by IV and subcutaneous (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 and independent of the schedule (once or three times weekly). At two 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 (1g/dL). Based on the results of these studies it was concluded that 0.45 to 0.75 μg/kg of darbepoetin alfa administered once weekly IV or SC is the most appropriate starting dose for treatment of anemia in CKD subjects [Macdougall et al, 2003].

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

The two multi-center randomized open-label trials explored the correction of anemia in subjects on dialysis (NESP-980211) or pre-dialysis (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 baseline and a Hb concentration of ≥ 11.0 g/dL during the initial 24 weeks of treatment). The selected starting dose was

0.45 µg/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 three times weekly) [Locatelli et al, 2001; EMEA, EPAR 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 so eligible for long-term efficacy and safety.

In the second pivotal correction of anemia study (NESP-980211, US trial) subjects were on dialysis (mainly hemodialysis) 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 trial.

Two pivotal phase 3 studies (NESP-970200 conducted in Europe and Australia with a study duration of 52 weeks, and NESP-980117 conducted in United states and Canada with a study duration of 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% CI for the difference in mean change in hemoglobin (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 one uncontrolled long-term safety study demonstrated that darbepoetin alfa once weekly/once every two weeks by the IV or SC route is safe and effective in maintaining Hb in subjects with CKD undergoing dialysis. Data from a long-term safety of darbepoetin alfa in subjects who had completed one year of treatment on a previous darbepoetin alfa clinical trial 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, 2004; EMEA, 2003].

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Roxadustat

The overall frequency and type of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) observed in the clinical studies conducted with roxadustat reflect events that would be expected to occur in CKD subjects. The most commonly reported AEs in healthy subjects were headache, pharyngolaryngeal pain, and nasal congestion. The most commonly reported AEs (> 5%) in CKD subjects not on dialysis were diarrhea, nausea, urinary tract infection, nasopharyngitis, peripheral edema, hyperkalemia, headache and

hypertension. The most commonly reported adverse events (AEs) (> 3%) in CKD subjects on dialysis were diarrhea, nausea, hypertension and upper respiratory tract infection. The only expected non-serious adverse drug reaction was heart rate (HR) increase.

Safety analyses did not reveal any association between the rates of occurrence of cardiovascular events with roxadustat, or any effect on 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, though it should be noted that 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 phase 2 clinical development program, the majority of which have been associated with gallstones or biliary sludge; one of which was due to a pancreatic duct stricture, and another case had multiple risk factors for pancreatitis. Only 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, has been well defined in the literature.

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

1.3.2 Darbepoetin alfa

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 two treatment groups – darbepoetin alfa and r-HuEPO. The majority of AE were due to 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 HR 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 the IV or SC route. 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 Summary of Product Characteristics (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 Committee for Medicinal Products for Human Use (CHMP) regarding the assessment of outcome of Study 20010184 "Trial to Reduce Cardiovascular Events with Aranesp® Therapy" (TREAT) 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 (PL), section 2 "Before you use Aranesp®" was updated to align it with the SmPC, reflecting the concern that elevated hemoglobin concentrations could increase the risk of myocardial infarction, stroke and death [EMEA, 2004].

1.4 Risk-Benefit Assessment

Based upon the results of the studies described above, the expected benefit of roxadustat is the correction of anemia and relief of signs and symptoms of anemia resulting in an increased quality of life, improved physical functioning and performance. Treatment with roxadustat triggers a pharmacodynamic response which translates into correction of anemic Hb levels and maintenance of these corrected Hb levels.

An established dose adjustment algorithm, similar to the one used in phase 2 studies with roxadustat, will be used during the current study to titrate roxadustat doses to enable subjects to achieve and maintain Hb levels within target range, while allowing investigators to closely monitor the rate of rise of Hb levels. Roxadustat doses may be held and/or the use of therapeutic phlebotomy is allowed in the event of excessive hematopoiesis. In case of insufficient response to study drug roxadustat rules for the use of supplemental IV iron and rescue treatments such as darbepoetin alfa (for roxadustat treated subjects) or RBC transfusion are in place in order to assure safety of the affected study subjects.

In PK studies with roxadustat there was no evidence of drug accumulation with the proposed clinical regimen of up to three times weekly dosing. The overall frequency and nature of AEs and SAEs observed in clinical studies thus far generally reflect events what would be expected to occur in the DD-CKD and NDD-CKD patient populations, 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, aluminium), sucralfate or magnesium- or aluminium-containing antacids would produce a similar interaction, the study protocol includes the advice that roxadustat be taken separately from these drugs.

Darbepoetin alfa has been chosen as comparator to adequately assess the efficacy, safety and benefit of achieving Hb correction and maintenance in anemic subjects treated with roxadustat. It is a commonly used ESA in Europe for the treatment of anemic NDD-CKD subjects and has demonstrated its ability to correct and maintain Hb in subjects in several controlled randomized trials.

The rules for dose adjustment and for events of excessive hematopoiesis in the present study will follow the approved posology of darbepoetin alfa. In case of insufficient response to darbepoetin alfa, rules for RBC transfusions are in place in order to assure safety of the affected study subjects.

The safety of treatment with roxadustat and darbepoetin alfa in this study will be carefully monitored to include AEs and SAEs, laboratory parameters such as electrolytes, liver enzymes, serum lipase and iron indices. Emphasis will be placed on cardiovascular, cerebrovascular, and thrombo-embolic events, which are not uncommon in the study population; an independent event review committee (IERC) will assess and adjudicate all significant occurrences of such events. In addition, an independent Data and 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 non-clinical experimental results of the orally administered roxadustat to date, it is anticipated that roxadustat will be comparable in safety and efficacy to the marketed, parenterally administered darbepoetin alfa in the treatment of anemia of CKD. The risk mitigation measures applied in this protocol are deemed to sufficiently assure that major risks for the subject can be avoided. The benefit-risk profile for the participation of subjects in this study is therefore considered to be acceptable.

2 STUDY OBJECTIVE(S), 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 darbepoetin alfa in the treatment of anemia in NDD-CKD subjects.

2.1.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the safety of roxadustat compared to darbepoetin alfa in the treatment of anemia in NDD-CKD subjects.
- Evaluate the HRQoL benefit of roxadustat compared to darbepoetin alfa in the treatment of anemia in NDD-CKD subjects.

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 570 subjects from approximately 200 study centers globally.

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

2.2.1.2 Study Population

The study population consists of subjects with CKD stages 3, 4, and 5 (eGFR < 60 mL/min/1.73 m^2) who are anemic and not on dialysis. Anemia is defined by mean Hb $\leq$10.5 g/dL upon repeated screening measurements. Anemia of non-renal origin is to be excluded. Washout periods of at least 12 weeks for any prior ESA, at least 6 weeks for any IV iron treatment, and at least 8 weeks for any RBC transfusion prior to randomization have been mandated in order to exclude a potential impact of these extraneous anemia treatments on the assessment of efficacy.

2.2.1.3 Description of Study

Subjects assigned to roxadustat treatment will be administered roxadustat orally as a combination of tablets of different strengths. Subjects assigned to darbepoetin alfa treatment will be administered darbepoetin alfa subcutaneously (SC) or intravenously (IV) by the investigator or a qualified member of the site staff or, after 36 weeks of treatment, by the subject themselves or caregiver, e.g., relative, if well trained and willing to self-administer. Study treatment administration is implemented in an open-label manner.

The study will consist of three study periods as follows:

- Screening period: up to 6 weeks
- Treatment period: 104 weeks
- Follow-up period: 4 weeks

Subjects that have discontinued treatment prior to their projected week 104 will continue to be followed for vital status, SAEs, cardiovascular and thromboembolic AEs in a post study follow-up period.

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 (up to 42 days duration), Hb levels will be assessed in a central laboratory for matching the inclusion criterion (mean of two Hb values must be ≤ 10.5 g/dL, see inclusion criterion 4). Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be randomized at day 1, which marks the end of screening period and start of the treatment period. If a subject fails screening, the subject may be rescreened once (immediately or later) if deemed appropriate by the investigator. The subject must be re-consented. A new rescreening period will start and all screening procedures must be repeated.

Treatment Period (Correction and Maintenance Period)

After subjects have been confirmed eligible for study participation, subjects are randomized to 1 of 2 treatment arms (1:1 ratio) as illustrated in Table 2. The randomization will occur through Interactive Response Technology (IRT). The randomization will result in a 1:1 ratio of subjects receiving roxadustat administered orally or darbepoetin alfa administered by SC or IV injection.

Table 2 Treatment Arms and Dosing Frequency

Treatment Arms	Study Treatment	Dosing Frequency in Treatment Period	
		Correction Period	Maintenance Period
1	Roxadustat	TIW	TIW
2	Darbepoetin alfa	Dosing per EU SmPC	

SmPC: Summary of Product Characteristics; TIW: three times weekly

In protocol version 1 subjects were randomized in a ratio of 2:1 receiving roxadustat versus darbepoetin alfa. The expected number of subjects randomized on protocol version 1, protocol versions 2 and 3 and the total number of randomized subjects per treatment arm are represented in the following table.

Table 3 Expected Number of Subjects Randomized

Treatment Arms	Study Treatment	Expected Number of Protocol v1 Subjects Randomized (Ratio 2:1)	Expected Number of Protocol v2 and 3 Subjects Randomized (Ratio 1:1)†	Total Expected Number of Subjects Randomized per Treatment Arm
1	Roxadustat	100	210	310
2	Darbepoetin alfa	50	210	260
Total		150	420	570

† The number of subjects under protocol v2 and v3 will depend on the number of subjects randomized under protocol v1.

During the treatment period, subjects will attend weekly study visits from day 1 to week 2, followed by every other week study visits from weeks 4 to 24. From week 24 onwards, visits will occur every four weeks until the end of treatment (EOT).

Subjects will receive study treatment (roxadustat or darbepoetin alfa) for 104 weeks.

Correction Period

The aim of the correction period is to correct Hb levels to ≥ 11.0 g/dL **and** a Hb increase from BL Hb ≥ 1.0 g/dL as measured at two consecutive study visits separated by at least 5 days (as assessed by central laboratory). Dosing and dose adjustments of roxadustat will follow prespecified dose adjustment rules. Dosing and dose adjustments of darbepoetin alfa will be per EU approved Summary of Product Characteristics (SmPC).

Once Hb is corrected the subjects will enter into the maintenance period.

Maintenance Period

The aim of the maintenance period is to treat to a Hb target level of 11.0 g/dL by maintaining the Hb levels between 10.0 g/dL and 12.0 g/dL. Dose adjustments of roxadustat will follow prespecified dose adjustment rules. Dose adjustments of darbepoetin alfa will be per EU approved Summary of Product Characteristics (SmPC).

Follow-up Period

After the end of the treatment period, subjects proceed to the 4-week follow-up period.

Post study 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 EOS visit. Thereafter, these subjects who have taken at least one dose of study drug will continue to be followed up every 6 months for vital status, SAEs, 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.

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 in outcomes assessment.

An open label design was chosen since the investigational and comparator drug are provided via different routes of administration and have a different requirement for iron supplementation.

2.2.1.5 Comparator

Darbepoetin alfa supplied as a solution for injection in a pre-filled syringe, and is administered by SC or IV injection. Once the route of administration is chosen (IV or SC), it is recommended to keep the same administration route for a subject throughout the study. It is administered in combination with IV or oral iron to maintain iron repletion.

2.2.2 Roxadustat Dose Rationale

Starting doses of roxadustat were studied in three ways in phase 2:

- using a strict weight-based dosing approach by dosing in mg/kg that was useful in the proof of concept stage
- using a tiered weight-based approach where a subject's starting dose was selected based on categorizing the subject's body weight as low (45 to 60 kg), medium (>60 to 90 kg), or high (>90 to 140 kg)
- using an absolute starting dose regardless of body weight

The tiered weight-based approach has been chosen for the development of roxadustat in the phase 3 program to provide the best opportunity for managing subjects' controlled correction to target Hb values.

Based upon simulations derived from a kinetic-pharmacodynamic model built from phase 2 data a tiered weight-based approach with starting doses of 70 mg given TIW for subjects weighing up to 70 kg and 100 mg given TIW for subjects weighing more than 70 kg has been chosen for the development of roxadustat. This approach is a variation of the tiered weight-based starting approach used in phase 2 and is expected to provide the best opportunity for managing subjects' controlled individualized correction to target Hb values by achieving a steady Hb increase associated with moderate rates of Hb overshoots.

Based on the phase 2 data, it is expected that subjects who receive these starting doses to correct anemia will require in the maintenance period a total weekly dose reduction in the order of 22% to 35% after achieving response. This dose reduction will be achieved by adjustment of the single dose. The phase 2 studies evaluated the need for dose adjustments for correcting and maintaining Hb. Dose adjustments were allowed at regular 4-week intervals to maintain, increase or decrease the dose according to prespecified rules. Prespecified dosing steps were used to correct and maintain Hb levels within treatment thresholds based on absolute Hb levels and change of Hb in the previous 4 weeks. Additional rules for dose adjustment were provided to minimize excessive hematopoiesis. These dose adjustment rules

were successful in Hb correction and Hb maintenance and will be adopted in this study with minor modifications.

The maximum allowed roxadustat dose in this study is set at 3.0 mg/kg or 300 mg per administration, whichever is lower. For randomized subjects who require chronic dialysis during the treatment period, the maximum dose step is the dose step corresponding to 3.0 mg/kg per administration or 400 mg, whichever is lower. The highest dose tested in healthy volunteers is 5 mg/kg single dose and 3.75 mg/kg TIW; the highest dose tested in phase 2 studies was 3.0 mg/kg. The doses were safe and well tolerated with transient dose dependent HR increases observed. No maximum tolerated dose (MTD) was reached in the clinical development of roxadustat based on the observed pharmacodynamic response (plasma EPO levels) and the predicted relation between EPO levels and Hb response; therefore, exploration of higher doses was not conducted. Plasma EPO levels increased in a supra-linear fashion with increasing roxadustat doses. It is expected that the majority of the subjects will show adequate Hb response (correction and maintenance) 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 anemic CKD subjects with roxadustat.

2.3 Endpoints

2.3.1 Primary Endpoints

The primary efficacy endpoint is Hb response. Hb response is defined as:

- Hb ≥ 11.0 g/dL and a Hb increase from BL Hb by ≥ 1.0 g/dL in any subject with BL Hb >8.0 g/dL, OR
- An increase from BL Hb by ≥ 2.0 g/dL in any subject with BL Hb ≤ 8.0 g/dL

as measured at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response.

2.3.2 Key Secondary Endpoints

The secondary efficacy endpoints in this study are:

- 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
- Change from BL in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol of weeks 12 to 28
- Mean monthly IV iron (mg) use per subject during weeks 1 to 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
  - Occurrence and time to occurrence of hypertension (defined as either SBP > 170 mmHg AND an increase from BL of ≥ 20 mmHg SBP or DBP > 110 mmHg AND an increase from BL of ≥ 15 mmHg DBP on 2 consecutive visits) during weeks 1 to 36

2.3.3 Additional Secondary Endpoints

2.3.3.1 Efficacy Endpoints

Hb correction and maintenance:

- Hb change from BL to the average Hb value of weeks 28 to 52 regardless of rescue therapy
- Time (weeks) to achieve the first Hb response as defined by primary endpoint.
- Hb response defined as: Hb ≥ 11.0 g/dL and a Hb increase from BL Hb by ≥ 1.0 g/dL in any subject with BL Hb > 8.0 g/dL, OR an increase from BL Hb by ≥ 2.0 g/dL in any subject with BL Hb ≤ 8.0 g/dL as measured at 2 consecutive visits separated by at least 5 days, during the first 24 weeks of treatment regardless of administration of rescue therapy prior to Hb response.
- Hb averaged over weeks 28 to 36, 44 to 52, 72 to 80, 96 to 104, without use of rescue therapy within 6 weeks prior to and during this evaluation period.
- Hb value and Hb change from BL to each post-dosing time point.
- Hb change from BL to the average Hb value of weeks 28 to 36, 44 to 52, 72 to 80, 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, 72 to 80, 96 to 104 without use of rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

Hospitalizations

- Occurrence (number) of hospitalization(s)
- Number of days of hospitalization

Rescue therapy use

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

Changes in cholesterol levels

- Change from BL to each scheduled measurement in:
  - Total cholesterol
  - LDL/High-density Lipoprotein (HDL) ratio

  - Non-HDL cholesterol
  - Apolipoproteins A1 and B, and ApoB/ApoA1 ratio
- Occurrence of mean LDL cholesterol < 100 mg/dL (mean LDL calculated over weeks 12 to 28, and weeks 36 to 52 of treatment).

Blood pressure effect
- Occurrence of achieved anti-hypertensive treatment goal (SBP < 130 mmHg and DBP < 80 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28 and 36 to 52 of treatment with study drug.

HRQoL and EQ5D 5L benefits
- Change from BL to the average value of weeks 12 to 28 and 36 to 52 in:
  - Physical Component Score (PCS) of SF-36
  - Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score
  - Total FACT-An Score
  - EQ-5D 5L VAS Score
  - WPAI:ANS Score (Work Productivity and Activity Impairment Questionnaire)
- PGIC (qualitatively by assessment)

Iron, HbA1c, and CKD progression
- Change from BL to each scheduled measurement in:
  - Serum ferritin
  - TSAT
  - HbA1c level
  - Fasting blood glucose
  - eGFR (including eGFR slope over time)
  - Urine albumin/creatinine ratio (UACR)
- Serum creatinine having doubled during the study in comparison with baseline
- Occurrence of ESRD

2.3.3.2 Safety Endpoints

Safety will be assessed by evaluating the following:

- Occurrence of Treatment Emergent AEs (TEAEs), and clinically significant changes in laboratory values from BL
- Changes from BL in vital signs, electrocardiogram (ECG) findings, and clinical laboratory values
- Occurrence of prespecified adjudicated cardiovascular and cerebrovascular events.

3 STUDY POPULATION

3.1 Selection of Study Population

The study population consists of subjects with CKD as defined by CKD stages 3, 4 and 5 (eGFR < 60 mL/min/1.73 m^2) who are anemic and not in need of dialysis.

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 has a diagnosis of CKD, with Kidney Disease Outcomes Quality Initiative (KDOQI) Stage 3, 4 or 5, not on dialysis; with an eGFR < 60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation.
4. The mean of the subject's two most recent (prior to randomization) Hb values during the screening period, obtained at least 4 days apart, must be ≤ 10.5 g/dL, with a difference of ≤ 1.0 g/dL. The last Hb value must be within 10 days prior to randomization.
5. Subject is deemed suitable by the investigator for treatment with ESA using the criteria specified in the KDIGO 2012 recommendation considering the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia.
6. This criterion has been removed.
7. This criterion has been removed.
8. Subject has a serum folate level ≥ lower limit of normal (LLN) at screening.
9. Subject has a serum vitamin B_{12} level ≥ LLN at screening.
10. 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.
11. Subject's body weight is 45.0 kg to a maximum of 160.0 kg.
12. Female subject is either:

    Of non-childbearing potential:

    - post-menopausal (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 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.

13. Female subject must not be breastfeeding at screening or throughout the study period, and for 28 days after the final study treatment administration.
14. Female subject must not donate ova starting at screening and throughout the study period and for 28 days after final study drug administration.
15. 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.
16. Male subject must not donate sperm starting from screening, throughout the study period and up to 12 weeks after final study drug administration.
17. 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 any ESA treatment within 12 weeks prior to randomization.
2. Subject has received any dose of IV iron within 6 weeks prior to randomization.

3. Subject has received a Red Blood Cell (RBC) transfusion within 8 weeks prior to randomization.
4. Subject has a known history of myelodysplastic syndrome or multiple myeloma.
5. 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.
6. Subject has a known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition.
7. 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.
8. 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.
9. Subject has active or chronic gastrointestinal bleeding.
10. Subject has received any prior treatment with roxadustat or a HIF-PHI.
11. Subject has been treated with iron-chelating agents within 4 weeks prior to randomization.
12. Subject has a history of chronic liver disease (e.g., cirrhosis or fibrosis of the liver).
13. Subject has known New York Heart Association Class III or IV congestive heart failure.
14. Subject has had a myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (e.g., deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.
15. Subject has one or more contraindications for treatment with darbepoetin alfa:
    - Uncontrolled hypertension in the opinion of the investigator, or two or more blood pressure values of SBP ≥ 160 mmHg or DBP ≥ 95 mmHg (within 2 weeks prior to randomization).
    - Known hypersensitivity to darbepoetin alfa, recombinant human erythropoietin, or any of the excipients.
16. 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 within 12 weeks prior to randomization.
17. 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.

18. 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).
19. Subject has an active clinically significant infection that is manifested by White Blood Count (WBC) > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection within one week prior to randomization.
20. Subject has a known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion.
21. Subject has had any prior organ transplant (that has not been explanted), subject is scheduled for organ transplantation, or subject is likely to initiate renal replacement therapy including dialysis within the first year of the study in the opinion of the investigator.
22. Subject will be excluded from participation if any of the following apply:
    a. subject has received investigational therapy within 30 days or 5 half lives or limit set by national law, whichever is longer, prior to initiation of screening, or
    b. any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
23. Subject has an anticipated use of dapsone in any dose amount or chronic use of acetaminophen/paracetamol > 2.0 g/day during the treatment or follow-up period of the study.
24. Subject has a history of alcohol or drug abuse within 2 years prior to randomization.
25. 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 TREATMENT(S)

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 mg).

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

4.1.2 Comparative Drug

Darbepoetin alfa is supplied as a solution for SC or IV injection in a pre-filled syringe. It is centrally provided in the following strengths 20, 30, 40, 60 and 100 µg and needs to be administered in combination with IV or oral iron to maintain iron repletion. All administrations will be performed by the investigator or a qualified member of the site staff or, after 36 weeks of treatment, by the subject themselves or caregiver, e.g., relative, if well trained and willing to self-administer. Darbepoetin alfa (Aranesp®) should be administered IV or SC according to the Package Insert or SmPC (EU SmPC for Aranesp®). Copies of this SmPC will be distributed as part of the study materials.

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 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 (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

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

A Qualified Person of Astellas Pharma Europe B.V. (APEB) or Sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

Roxadustat study drug 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.

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.

For storage and administration purposes, please refer to the EU SmPC 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 in a 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, can standard procedures for the alternative disposition of the unused study drug 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.

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 be performed via IRT prepared on behalf of the Sponsor (under the responsibility of the Global Data Science [GDS] Department of APEB). Specific procedures for randomization through the IRT are contained in the study procedures manual.

Approximately 570 subjects will be randomized to receive roxadustat TIW or darbepoetin alfa as shown in Table 9 assuming 150 subjects will be randomized pre-amendment.

Randomization will be stratified by the following four factors:

- Region: region A versus region B*
  ** Assignment to region will be determined based on health care comparability.*
- Screening Hb values (Hb ≤ 8.0 g/dL versus > 8.0 g/dL)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No)
- eGFR (< 30 mL/min/1.73 m^2 versus > 30 mL/min/1.73 m^2)

5 TREATMENTS AND EVALUATION

Subjects must be consented and registered in IRT before any screening tests or assessments are performed. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents in the eCRF.

Registration of subjects into the study, assignment of subject identification numbers, and randomization will take place using a centralized IRT. After obtaining consent, and prior to the start of screening assessments, the investigator will register the subject in IRT, which starts the screening period, and a subject identification number will be assigned. No screening tests or assessments should be performed prior to registration and assignment of a unique subject identification number by IRT. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

If a subject's laboratory results do not meet the inclusion criteria or meet the exclusion criteria at screening, any laboratory assessment may be repeated once within the 42-day screening period. This includes an additional (third) Hb value that may be collected if necessary. The mean of 2 most recent Hb values during the screening period, obtained at least 4 days apart, will be used to assess the subject's eligibility.

If a subject fails screening, they will be registered in IRT as a screen failure and considered out of the study. However, the 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, a new rescreening period starts and all screening procedures must be repeated. Subject must also be registered in IRT as re-screened under the same subject identification number as first screening.

Subjects confirmed not eligible after re-screening, should be registered in IRT as a 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 will enter the treatment period upon randomization (day 1).

Subjects will be randomized via IRT to receive roxadustat or darbepoetin alfa. The first study treatment should be on the day of randomization, i.e., day 1, after all study assessments have been completed.

All subjects will be treated for 104 weeks.

Subjects receiving roxadustat

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

The initial roxadustat dose (per dose amount) is based on the tiered, weight-based dosing scheme shown in the table below.

Table 4 Initial Dosing of Roxadustat (TIW)

Study Drug (Dose Frequency)	**Weight** (≥ 45.0 to ≤ 70.0 kg)	**Weight** (> 70.0 to ≤ 160.0 kg)
Roxadustat (TIW)	70 mg	100 mg

All subjects will administer study drug doses TIW. The period between two roxadustat administrations should be at least 36 hrs and no more than 4 days apart.

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

The roxadustat treated subjects that had entered the study under protocol v1.0, upon signing the informed consent for the amendment 1, had their dose frequency (on QW and BIW under protocol v1.0) and dose amount adjusted according to the instructions in Appendix 12.3

Section 5.1.2 describes the dose adjustment rules within this protocol to enable investigators to adjust the dose for their subjects to achieve Hb correction and to maintain their Hb levels within the predefined target range in this study.

Subjects receiving darbepoetin alfa

Darbepoetin alfa dosing is to follow the EU SmPC. The initial dosing is weight based. Darbepoetin alfa will be administered by SC or IV injection by the investigator or a qualified member of the site staff or, after 36 weeks of treatment, by the subject themselves or caregiver, e.g., relative, if well trained and willing to self-administer.

Similar to roxadustat treatment, the target of treatment is achieving Hb correction (defined as Hb values of ≥ 11.0 g/dL and Hb increase from BL Hb ≥ 1.0 g/dL at 2 consecutive study visits separated by at least 5 days [as assessed by the central laboratory]) and thereafter maintaining Hb in the target range of 10.0 to 12.0 g/dL.

5.1.2 Changes in Study Drug Dose

5.1.2.1 Dose Adjustment Rules for Subjects Receiving Roxadustat

Dose adjustments are permitted from week 4 onward, and every 4 weeks thereafter. All dose adjustments are made to maintain study subjects' Hb level within the predefined target range.

Dose adjustments will follow unique dose adjustment rules [Table 5].

Table 5 Dose Adjustment Rules for Roxadustat

	Correction Period	Maintenance Period		
Change in Hb over past 4 weeks (g/dL)[a]	(When Hb correction has not been reached)	**Hb <10.5 g/dL**	**Hb 10.5 to <12.0 g/dL**	**Hb 12.0 to <13.0 g/dL**
< -1.0	↑	↑	↑	No change
-1.0 to 1.0	↑	↑	No change	↓
>1.0	No change	No change	↓	↓

[a] Subtract 4 weeks' previous Hb value from the present Hb value to calculate the change

- All dose adjustments are made based on Hb values using HemoCue®, a point-of-care device.
- If the dose adjustment is 'No change' per Table 5 the next dose adjustment review is 4 weeks after that visit
- Dose increases by one dose step (↑) and reductions by one dose step (↓) are pre-set per the dose steps.
- The dose steps for roxadustat are as follows: 20, 40, 50, 70, 100, 150, 200, 250 and 300 mg.
- The maximum dose is the dose step corresponding to 3.0 mg/kg per administration or 300 mg, whichever is lower. The default weight is initially set as weight measured at day 1. At study visits where weight is collected, the maximum allowed dose step and the default weight for a subject will be adjusted if the weight change is ≥ 5% compared to the previous default weight collected in the study. For randomized subjects who require chronic dialysis, please refer to Appendix 12.4 The maximum allowed dose in subjects on permanent dialysis is 3.0 mg/kg or 400 mg per administration, whichever is lower.
- At week 4 only, in a subject whose baseline Hb level was < 8.0 g/dL, if the dose adjustment is to increase, then dose increase could be made with either a 1 or 2 step increase per investigator discretion to minimize the probability of requiring rescue therapy treatment.
- 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 300 mg.
- 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.

<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 two steps
- Next dose adjustment review is 4 weeks after dose resumption and in 4-weekly intervals thereafter.

Dose Adjustment for Excessive Hematopoiesis

If at any time during the treatment period Hb increases by > 2.0 g/dL at any time within 4 weeks, the dose should be reduced by one dose step.

Note: Only one dose reduction for excessive hematopoiesis is recommended within a period of 4 weeks. If a blood transfusion or ESA treatment has been performed within 2 weeks of meeting the criteria for excessive hematopoiesis, it is recommended not to perform a dose reduction for excessive hematopoiesis.

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.

5.1.2.2 Dose Adjustment Rules for Subjects Receiving Darbepoetin Alfa

The initial dose is weight-based according to the EU SmPC and either 0.45 µg/kg body weight, as a single SC or IV injection once weekly or 0.75 µg/kg body weight, as a single SC injection once every two weeks, as judged appropriate by the investigator. Dose adjustment should be made according to the EU SmPC.

If the rise in Hb is greater than 2.0 g/dL in 4 weeks, the dose is to be reduced by approximately 25%. Once the target Hb level has been achieved with once every 2-week dosing, darbepoetin alfa may be administered SC once monthly using an initial dose equal to twice the previous once every 2-week dose.

All these dose adjustments are made based on Hb values using HemoCue in both the correction and the maintenance period.

Target of treatment is achieving Hb correction (defined as Hb values of ≥ 11.0 g/dL and Hb increase from BL Hb ≥ 1.0 g/dL at 2 consecutive study visits separated by at least 5 days [as assessed by the central laboratory]) and thereafter maintaining Hb in the target range of 10.0 to 12.0 g/dL.

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 four 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 previous treatment type received for anemia (medication or procedures such as ESAs, iron (IV or oral), and RBC transfusions) within 12 months prior to randomization will 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.

Certain previous 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 informed consent to EOS visit. The medication/therapy name, start and stop date, route (if applicable), total daily dose (if applicable) and indication for each medication/therapy will be entered in the eCRF.

For all concomitant medication use, from screening visit 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 maintained in the subject's clinical study records as source documentation.

5.1.3.2.1 Supplemental Iron Use

Subjects receiving roxadustat

i. Oral iron

For subjects receiving roxadustat, oral iron is recommended for dietary supplementation to support erythropoeisis and as the first-line for prevention and treatment of 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 one hour before or one hour after oral iron.

ii. IV iron

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

- The subject has not responded adequately in terms of hemoglobin response to 2 or more consecutive dose increases of roxadustat or reached the maximum dose limit, and
- The subject has iron deficiency (either ferritin < 100 ng/mL [< 220 pmol/L] or TSAT < 20%) or the subject is intolerant of oral iron therapy.

Treatment with roxadustat may 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%.

Subjects receiving darbepoetin alfa

For subjects treated with darbepoetin alfa, oral or IV iron supplementation is required to maintain iron repletion. IV iron should only be administered if ferritin < 100 ng/mL (< 220 pmol/L) or TSAT < 20%. IV iron may be administered per local practice. Discontinuation of IV iron therapy is recommended once ferritin levels are ≥ 100 ng/mL (≥ 220 pmol/L) and TSAT ≥ 20%.

5.1.3.2.2 Statins and Other Substrates for OATP1B1

For subjects receiving roxadustat

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 6].

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 6 Proposed Maximum Daily Dose of Statins Not to Be Exceeded

Statin	Proposed maximum dose (mg/day)
Simvastatin	20 GFR < 30 mL/min: 5
Atorvastatin	40
Rosuvastatin	10 Severe renal impairment:* no recommendation as contraindicated in this case
Fluvastatin	40 GFR < 30 mL/min: 20
Pravastatin	40
Pitavastatin	2 GFR < 30 mL/min: 1

* The rosuvastatin SmPC defines severe renal impairment as GFR < 30 mL/min.

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

For subjects receiving roxadustat

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 one hour before or one hour after their phosphate binder.

It is anticipated that other multivalent cation-containing drugs and mineral supplements (e.g., iron, calcium, magnesium, aluminium), sucralfate or magnesium- or aluminium-containing antacids would produce a similar interaction; therefore, subjects should take roxadustat at least one hour before or one hour after intake of these preparations.

5.1.3.2.4 Anti-hypertensive Medications

To avoid confounding effects on study endpoints, changes to anti-hypertensive medications should be minimized, and made only if deemed medically necessary by the investigator or if prespecified changes in blood pressure are met.

5.1.3.3 Prohibited Medication

The following medications are prohibited during the period identified (see also Appendix 12.1):

- Any ESA: within 12 weeks prior to randomization until EOT
- IV iron: within 6 weeks prior to randomization.
- RBC transfusion: within 8 weeks prior to randomization.
- Any investigational drug: within 30 days or 5 half lives or limit set by national law (whichever is longer), prior to screening until EOS
- Roxadustat or another HIF-PHI: at any time prior to randomization. After randomization any HIF-PHI other than roxadustat, as allocated by randomization, until EOS
- Androgens from day of randomization until EOS
- Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy): from 4 weeks prior to randomization until EOS
- Dapsone in any dose amount or chronic use of acetaminophen/paracetamol > 2.0 g/day from the day of randomization until EOS

Use of herbal medicine is not prohibited but strongly 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 recorded from informed consent until EOT. This also includes the recording of hospitalizations until the projected date of week 108.

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 (see Section 5.1.1). If the subject is not compliant with study drug intake, the investigator should discuss this with the subject. Deviations from the prescribed dose should be entered into the eCRF and require notification to the Sponsor. All roxadustat bottles dispensed to the subject should be returned by the subject to the site, including empty bottles for reconciliation by the study monitor.

For subjects randomized to darbepoetin alfa the administration of each dose at site will be recorded in the eCRF with information on dose and route and reasons for each dose change. All administrations will be performed by the investigator or a qualified member of the site staff or, after 36 weeks of treatment, 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 and taken by the subject will be counted and recorded in the eCRF. The empty packages of darbepoetin alfa should be stored at site for reconciliation by the study monitor. In case of self-administration after 36 weeks of treatment, the empty packages of darbepoetin alfa should be returned by the subject to the site.

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. Use of rescue therapy and reason for rescue therapy should be recorded in the eCRF.

1) RBC Transfusion (for all subjects)

In the event of acute or severe blood loss, RBC transfusion is allowed if clinically indicated. In a situation where there is no obvious blood loss, RBC transfusion will be permitted if the subject has moderate to severe symptom(s) from his/her anemia, e.g., dyspnea at rest or on mild exertion, and the investigator is of the opinion that the blood transfusion is a medical necessity. Study treatment may be continued even if a blood transfusion has been administered.

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

If the investigator considers administration of ESA as a medical necessity, darbepoetin alfa may be initiated if the following criteria are met:

- the subject's Hb level is < 9.0 g/dL (HemoCue) as confirmed at two consecutive visits,

AND

- the subject's Hb level has not responded adequately despite 2 or more roxadustat dose increases in the previous 8 weeks, or the roxadustat dose reached the maximum dose limit,

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 darbepoetin alfa, 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.

The subject may continue in the study while on rescue treatment with darbepoetin alfa, however, it is not allowed to administer roxadustat during the same time period.

The course of darbepoetin alfa (i.e., the amount that may be administered) will be limited by duration of therapy and effect on Hb. The course of darbepoetin alfa rescue treatment will not exceed 4 weeks in duration, and darbepoetin alfa rescue will be stopped as soon as Hb ≥9.0 g/dL. To continue study participation, treatment with roxadustat study drug should be resumed within one week after the last administration of darbepoetin alfa at the dose level the subject was on prior to initiating darbepoetin alfa rescue therapy.

If a subject requires a second course of rescue darbepoetin alfa, the subject must be discontinued from treatment.

5.1.6 Emergency Procedures

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 Medical Monitor.

5.1.7 Restrictions During the Study

Subjects are not permitted to consume more than three alcohol-containing drinks per day during the treatment or follow-up periods.

Female subjects of childbearing potential must agree to not try to become pregnant during the study and for 28 days after the final study drug administration, AND must have a negative serum pregnancy test at screening AND, if heterosexually active, must agree to use a highly effective form of birth control as stated in the inclusion criteria. 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 5.5.7).

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, race, height, and body weight will be recorded in the eCRF.

5.2.2 Medical History

A detailed medical history, including detailed cardiovascular history, will be obtained at screening. All relevant past and present conditions as well as prior surgical procedures, and

previous and current tobacco use will be recorded in the subject's eCRF. Relevant conditions include conditions that have been treated with medication within four 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 should be performed within 12 weeks prior to randomization. This is not required if results of a previous renal ultrasound (or other renal imaging modality such as CT scan or MRI) within 12 weeks prior to randomization are available and it conclusively excludes the presence of renal cell carcinoma. Renal ultrasound findings are required prior to randomization to exclude subjects with a presence or suspicion of renal cell carcinoma (exclusion criterion 16). Sites are reminded to schedule the renal ultrasound, following the first screening visit and prior to randomization, only for those subjects that have not had a renal ultrasound, or other renal imaging modality, in the specified period. The date of the renal ultrasound examination and the assessment of the 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, CKD stage and etiology. Also the non-drug therapy history and medication history for anemia in the last 12 months prior to randomization will be obtained.

CKD stages 3, 4 and 5 is defined as eGFR < 60 mL/min/1.73 m^2 for ≥ 3 months, with or without kidney damage and not requiring dialysis. This is in line with the diagnosis criterion for CKD as defined by KDOQI. Documentation of reduced eGFR should be available in the subject's source documentation. In addition, calculation of eGFR to confirm the degree of CKD will be performed by the central laboratory at screening for eligibility and on day 1.

eGFR will be calculated using the following MDRD equation: GFR (mL/min per 1.73 m^2) = $175 \times \text{Serum Cr}^{-1.154} \times \text{age}^{-0.203} \times (0.742, \text{if female}) \times (1.212, \text{if black})$.

Anemia will be measured by repeated Hb measurements (central laboratory assessment) during screening; the mean of the 2 most recent Hb values during the screening period, obtained at least 4 days apart, must be ≤ 10.5 g/dL with a difference of ≤ 1.0 g/dL. The last Hb value must be within 10 days prior to randomization.

Exclusion of other causes of anemia should be based upon assessments of

- Complete blood count (CBC), which will include Hb concentration, RBC indices, WBC count and differential, platelet count and reticulocyte count
- Iron status
- Serum vitamin B12 and folate levels.

For more details on the laboratory tests, please see Section 5.4.3

5.2.5 Further Laboratory Testing Prior to Randomization

Other laboratory tests mandatory prior to randomization of a subject include immunoassay for HIV, Hepatitis B (HBsAg) and hepatitis C antibody (anti-HCV Ab) 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 5.4.3.3

5.3 Efficacy Assessment

5.3.1 Primary Efficacy Assessment

Efficacy assessment of treatment with study treatment 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 rescue medication (as recorded in the eCRF) will be taken into account for the evaluation of the primary efficacy assessment.

5.3.2 Additional 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. For 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 Quality of Life (QoL) questionnaires as indicated in the Schedule of Assessments (Table 1): SF-36, FACT-An, EQ-5D 5L, PGIC and WPAI:ANS (see Appendices 12.4-12.9). The QoL questionnaires are to be completed by the subject prior to any other study assessments on the study visits.

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. The SF-36 consists of eight 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 four 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 four 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 seven 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 (see Appendix 12.6). 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 by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e., state 11111). The EQ-5D-5L is shown in Appendix 12.7

5.3.3.1.4 Patient Global Impression of Change Scale (PGIC)

The PGIC (Appendix 12.8) 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.

5.3.3.1.5 Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms (WPAI:ANS)

The objective of the WPAI:ANS (version 2) is to measure work and activity impairment during the past seven days due to anemia [Reilly et al, 1993]. It is self-assessed. The 2 domains covered by the questionnaire are work and daily activities. The WPAI: ANS consists of 6 questions, including asking if the subject is working, how many hours the person missed work due to anemic symptoms, how many hours the subject actually worked and how the anemic symptoms impacted the productivity and ability to do daily activities. The WPAI:ANS is shown in Appendix 12.9

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 post-study 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).

5.3.3.3 Iron Status, HbA1c, CKD Progression and UACR

Serum iron, TSAT, ferritin, HbA1c, fasting blood glucose, eGFR and UACR will be assessed (central laboratory) according to the Schedule of Assessments, Table 1

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 may be assessed from archived serum/plasma samples and urine samples
- PGIC Score
- WPAI:ANS Score

5.4 Safety Assessment

5.4.1 Vital Signs

The vital signs blood pressure, HR and respiratory rate will be assessed at the visits as described in the Schedule of Assessments, Table 1.

See additional information in Appendix 12.4.

5.4.1.1 Blood Pressure

Blood pressure measurement will be done with the subject comfortably seated in 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.

Blood pressure (systolic and diastolic) will be measured singly on the 2 visits during the screening period, and in triplicate with a least two minute intervals for all other visits. The same arm should be used consistently for measurements throughout the study.

5.4.1.2 Heart Rate

Measurement of HR will be done at rest in a sitting position wherever possible. It can be performed with an oscillometric device as used for blood pressure measurement (see Section 5.4.1.1), by using any other suitable device or manually (wrist HR within one minute). The same methodology and device should preferably be used for the subject throughout the study, timing as indicated in the Schedule of Assessments.

HR will be measured singly on the 2 visits during the screening period, and in triplicate with at least two minute intervals for all other visits. All values will be reported in the eCRF.

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 one 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 and reported in the eCRF.

5.4.2 Adverse Events

Adverse Events (AEs) will be collected at all study visits. See Section 5.5 for detailed information regarding AE collection and data handling. 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.

The description of the collection and adjudication of prespecified cardiovascular and cerebrovascular events will be detailed in a separate adjudication charter. For submission of documentation for events that require adjudication, the ICON SQUARE system will be used. A site manual for the submission of packages for events requiring adjudication will be provided to each site and a dedicated staff member (and one back-up person) will be required to review the manual prior to getting access to the system.

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 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, 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 Sponsor/delegated CRO (Contract Research Organization) by telephone or fax immediately (i.e., within 24 hours of awareness).

5.4.3 Laboratory Assessments

5.4.3.1 HemoCue

Hb values obtained by HemoCue are used to allow "real-time" dose adjustments for all subjects. Date and results of HemoCue measurement will be collected in the eCRF at visits specified in the Schedule of Assessments [Table 1]. The HemoCue assessment of Hb will be performed on the venous blood sample collected for central laboratory Hb assessment.

5.4.3.2 Urinalysis

Dipstick analysis will be performed for protein, pH and glucose. A quantitative assessment of albuminuria (UACR) will be performed by the central laboratory. Ideally, the sample should be from the first morning void.

5.4.3.3 Central Laboratory

All safety related tests of blood specimens will be performed by a central laboratory.

Central laboratory results should be reviewed by the investigator or another qualified study staff member. Subject management is dependent upon close review of the laboratory data. Any changes in laboratory values are to be evaluated by the investigator. Clinically relevant changes will be recorded as AEs in the eCRF.

Unscheduled and repeat laboratory tests will also be performed by the central laboratory. However, in no case should prudent or necessary testing be delayed if it is not possible to send a sample to the central laboratory or if the turnaround time from the central laboratory is not sufficiently rapid for clinical management of the subject. In such emergency/urgent situations local laboratory test results may be used to make clinical judgments that affect the safety of the study subject.

A central laboratory manual with instructions on specimen collection, processing, storage and shipping to the central laboratory will be provided to all participating sites before they start the study.

In Table 7, the laboratory tests that will be performed during the conduct of the study are listed. The exact timing of all assessments can be found in [Table 1] Schedule of Assessments.

Table 7 Laboratory Tests

Lab assessment type	Parameters to be analyzed
Hematology	**CBC with WBC differential** Hemoglobin (Hb) Hematocrit (Hct) Erythrocytes (RBC) Mean corpuscular volume
	Mean corpuscular Hb Mean corpuscular Hb concentration 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 (**fasting** condition wherever possible) Creatinine Magnesium Bicarbonate Phosphorus Uric Acid Albumin Total protein Lactate dehydrogenase Blood urea nitrogen Lipase
	Liver Function Tests: • AST • ALT • Bilirubin (Total and direct) • GGT • ALP
	Lipid Panel (in **fasting** condition wherever possible): • Total Cholesterol • LDL • HDL • Triglycerides • Apolipoproteins A1, B and ApoB/ApoA1 ratio
	Serum iron Ferritin TIBC TSAT (= measured as FESAT)
	Pregnancy test (for 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 Immunoassay • HBsAg • Anti-HCV antibody
Special Laboratory Analytes	hs-CRP
Serum Biomarkers	Archival of serum samples for biomarkers
PK analysis	Level of roxadustat Covariates for PK • Albumin • α1-AGP
Whole Blood	Genotyping
Urinalysis	Qualitative • Protein • pH • Glucose Quantitative • Creatinine • Albumin • UACR
	Archival of urine samples for biomarkers

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 will include general appearance and the following body regions and systems: head, eyes, ears, neck and throat (HEENT), lungs, heart, chest and back, abdomen, genitourinary, extremities, skin, and any other, if deemed necessary.

A **targeted** physical examination (e.g., respiratory and cardiovascular) will be conducted throughout the study as described in Schedule of Assessments, 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).

Height is measured only at screening. Weight is measured at screening, day 1, weeks 24, 36, 52, 76, EOT and EOS.

5.4.5 Electrocardiogram (ECG)

Local 12-lead ECGs will be performed on all subjects at specific time points as described in Table 1, Schedule of Assessments. A single ECG will be taken with the subject in the supine position, after the subject has been lying quietly 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 visit, ECG date, HR, PR interval, QRS Interval, QT Interval, overall interpretation and relevant comments will be recorded in the eCRF. The RR interval will be calculated using the HR in the eCRF. ECG recording will be kept as source documents.

5.5 Adverse Events and Other Safety Aspects

Safety will be assessed throughout the study. A complete BL 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, complete and targeted physical assessments, laboratory tests and ECGs will be performed at several intervals. Any medically significant changes from BL will be monitored throughout the study and appropriate interventions will be taken accordingly. Clinical laboratory tests may be assessed at additional times on unscheduled visits for safety reasons.

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

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a 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 one 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 study treatment 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 of the event, severity, SAE, 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 (see Section 5.5.7). 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 week 108).

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 the BL 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.

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 one 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. Additionally, Astellas requests that all medical events listed in Appendix 12.2 (Liver Safety Monitoring and Assessment) be reported by the Investigator as SAEs, even if none of the above criteria apply.

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 interactions

Concerning other special situations: lack of efficacy 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 these events do not need to be reported. Off-label use of roxadustat can be excluded for reporting as the product is under development.

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 hours 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.

If a special situation also induces an adverse event, 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 adverse events. 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 a 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 AE (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 (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact his/her respective delegated CRO (INC Drug Safety or other CRO as specified in the Investigator Site File) by telephone 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 or email immediately (within 24 hours of awareness). If the faxing or e-mailing of an SAE Worksheet is not

possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

The SAE worksheet should be sent to the delegated CRO that is responsible for the investigator's country:

INC Drug Safety or other CRO as specified in the Investigator Site File:
Email: INCDrugSafety@INCResearch.com
Fax: toll-free numbers will be provided for each country; the specific fax number can be found on the SAE form fax cover sheet
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 questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or his/her designee or the delegated CRO that is responsible for the investigator's country (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 of the initial notification).

Full details of the SAE should also be recorded on the medical records and on the eCRF.

The following minimum information is required to be completed on the SAE Worksheet:
- The ISN/Study number 1517-CL-0610
- 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 post-study 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 Institutional Review Board (IRB)/Independent Ethics Committee (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 CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements IEC.

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 Procedure in Case of Pregnancy

If a female subject or female 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 to the delegated CRO 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. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information. Additional details should be provided in part C during the pregnancy and/or after the delivery.

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

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 a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the delegated CRO as an SAE.

5.5.8 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. The Medical Monitor should be contacted as applicable.

In the event of suspected darbepoetin alfa overdose, refer to the approved EU SmPC.

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.

5.5.9 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.

5.6 Test Drug Concentration

For the purpose of evaluation of the population PK, blood samples will be obtained from the subjects that are treated with roxadustat. 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 one visit, or over 2 to 3 visits. These 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).

The investigator is free to choose at which study visits, between week 2 and 8 of treatment, to draw the samples and in which order. The study site will agree with the subjects on timing and process of the sampling. Based on preference of the study site and the subject, there is a choice of three sampling schedules to perform the PK samples collection, see [Table 8].

During weeks 1 to 8, subjects treated with roxadustat will be instructed to record the date and time of study drug intake in the study medication diary. The information will be used to record the date and time of roxadustat intake on the dosing day prior to PK sampling and on the day

of PK sampling in the eCRF. The date and time of PK sampling and the actual study drug dose taken on the day of sampling will be recorded in the eCRF.

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

Table 8 Examples of Sampling Schedules for Population PK

Schedule#	PK Visit 1	PK Visit 2	PK Visit 3
1	Collect pre-dose sample A. Take study drug in clinic. Collect samples B to F.	None	None
2	Collect pre-dose sample A. Take study drug in clinic. Collect samples B and C.	Take study drug. Collect samples D to F.	None
3	Collect pre-dose sample A. Take study drug in clinic. Collect samples B and C.	Take study drug. Collect sample D and E.	Take study drug. Collect sample F.

The order of the PK visits for schedule 2 and 3 is a decision for the investigator.

5.6.1 Blood Samples for Roxadustat PK Analysis

Samples of venous blood for bioanalysis of roxadustat, related metabolites of roxadustat and exploratory biomarkers 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 included as covariate in the PK analysis, since both albumin and α1-AGP is involved in plasma protein binding of roxadustat. Serum albumin and α1-AGP will be analyzed by the central laboratory using a standardized assay. To perform the analysis, 2 mL blood samples will be collected on the same day as PK sampling is performed (1-3 visits). If 1 or more PK samples are taken at a visit, one α1-AGP sample should be taken at that visit as well.

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

5.7.2 Archival of Serum Samples for Biomarker Analysis

Serum samples will be drawn at the timepoints as indicated in Table 1. 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 destroyed (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 central laboratory manual.

5.7.3 Archival of Urine Samples for Biomarker Analysis

Urine samples will be drawn at the timepoints as indicated in Table 1. The processed samples will be stored and archived for potential future analysis of relevant biomarkers. These archival samples will be destroyed (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 central 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 at any time during the study. The sample will be collected into pre-labeled polypropylene collection tubes containing EDTA as anti-coagulant. 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 APEB. 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 DNA) will be managed in strictly secured condition and they will be destroyed in accordance with relevant guidelines and procedures, maximally 5 years after the last subject completed the study.

5.8 Total Amount of Blood

The total amount of blood to be collected per subject during the study, based on the subject's screening period, the 104 weeks' treatment period and the follow-up period and allowing full re-screening and unscheduled visits is estimated to be approximately 460 mL.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who 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:

- Subject no longer consents to participate in the treatment phase of the study
- Physician decision that it is in the best interest of the subject to be discontinued from the study treatment
- Significant noncompliance with study procedures, as determined by principal investigator and/or Sponsor
- Pregnancy in a study subject
- Subjects randomized to roxadustat: requirement of a second course of rescue therapy with darbepoetin alfa deemed necessary by the investigator based upon the criteria for use of rescue treatment
- Subject receives an organ transplant

Subjects that 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 one dose of study drug will continue to be followed up every 6 months for vital status, SAEs, cardiovascular and thromboembolic AEs until their projected date of completion of the follow-up period (i.e., projected week 108 date) or until consent is 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
- Death of a study subject
- The Sponsor may decide to prematurely stop the study, e.g., for safety considerations

Women of childbearing potential who discontinue from treatment and/or withdraw from this study must continue contraception for at least 28 days following the last study drug administration. Male subjects with partners of childbearing potential must agree to use a medically acceptable method of contraception during the study and for at least 12 weeks following the last study drug administration.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor.

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. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to Database Lock, a Final Review of Data and Table Listings Figures Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock

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

Approximately 570 subjects will be randomized to receive roxadustat or darbepoetin alfa as follows:

Table 9 Sample Size Calculations per Treatment Arm

Treatment Group	Protocol version 1		Protocol versions 2 and 3		Total	
	Randomized	PPS	Randomized†	PPS	Randomized	PPS
Roxadustat	100	80	210	168	310	248
Darbepoetin alfa	50	40	210	168	260	208
Total	150	120	420	336	570	456

† The number of subjects under protocol v20 and v3 will depend on the number of subjects randomized under protocol v1.

Randomization will be stratified by the following four factors:

- Region: region A versus region B*

  ** Assignment to region will be determined based on health care comparability.*

- Screening Hb values (≤ 8.0 g/dL versus > 8.0 g/dL)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No)
- eGFR (< 30 mL/min/1.73 m^2 versus > 30 mL/min/1.73 m^2)

Assuming that the PPS analysis will consist of 80% of subjects in the Full Analysis Set (FAS), 570 randomized subjects in the FAS will lead to 456 subjects in the PPS. Two hundred and forty eight (248) subjects for the roxadustat treatment group and 208 subjects for the darbepoetin alfa treatment group will provide at least 98% test power to demonstrate statistically non-inferiority of roxadustat versus darbepoetin alfa in the primary endpoint assuming that the proportion of subjects with response in both groups is the same and at least 80% and a non-inferiority margin for the difference of proportions of 15%. The power for the sensitivity analysis of post-amendment data (336 subjects) will be at least 93%.

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:

- Intent-to-Treat Set (ITT)
- Full Analysis Set (FAS)
- Per-Protocol Set (PPS)
- Safety Analysis Set (SAF)
- Pharmacokinetic Analysis Set (PKAS)

7.2.1 Intent-to-Treat Set (ITT)

All randomized subjects will be included in the ITT.

The primary and secondary efficacy endpoints will be analyzed using the ITT as a sensitivity analysis.

7.2.2 Full Analysis Set (FAS)

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

The primary and secondary efficacy endpoints will be analyzed using the FAS.

7.2.3 Per Protocol Set (PPS)

All FAS subjects who received at least 2 weeks of study treatment with valid corresponding Hb measurements 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 and secondary efficacy endpoints will also be analyzed using the PPS. Additional PPS sub-populations (e.g., PPS-36) will be described in the SAP.

7.2.4 Safety Analysis Set (SAF)

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

7.2.5 Pharmacokinetic Analysis Set (PKAS)

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

- Received at least one dose of study drug, and
- At least one 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 PK data.

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, ITT, FAS and PPS populations.

Descriptive statistics will be calculated for continuous variables (e.g., age, weight, baseline Hb, body mass index and baseline eGFR) and frequency counts and percentages will be tabulated for categorical variables (e.g., sex, race, baseline Hb category, region, baseline eGFR category and history of cardiovascular disease or cerebrovascular disease) by study treatment arm, roxadustat group and overall.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

The primary efficacy endpoint is:

Hb response defined as: Hb ≥ 11.0 g/dL and a Hb increase from BL Hb by ≥ 1.0 g/dL in any subject with BL Hb > 8.0 g/dL, or an increase from BL Hb by ≥ 2.0 g/dL in any subject with BL Hb ≤ 8.0 g/dL as measured at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response.

7.4.1.1 Primary Analysis

The primary analysis will be performed on the PPS.

The difference in the proportion of responders in the primary efficacy variable between pooled roxadustat and darbepoetin alfa will be calculated using Mattinen & Nurminen approach adjusting for the following stratification factors:

- Region: region A versus region B*
  ** Assignment to region will be determined based on health care comparability.*

- Screening Hb values (≤ 8.0 g/dL versus > 8.0 g/dL)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No)
- eGFR (< 30 mL/min/1.73 m^2 versus > 30 mL/min/1.73 m^2)

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

H_0: Hb responder rate in the pooled roxadustat group < Hb responder rate in the darbepoetin alfa group minus 15%

versus

H_1: Hb responder rate in the pooled roxadustat group ≥ Hb responder rate in the darbepoetin alfa group minus 15%

This null hypothesis will be rejected if the two-sided 95% CI for the difference of proportions lies entirely above -15%.

In addition, a 95% CI will be calculated for the proportion of responders on roxadustat and darbepoetin alfa based on the exact method of Clopper-Pearson. Sensitivity analyses will be conducted to assess the consistency of the results before and after protocol amendments 1 and 2 (e.g., protocol versions 2.0 and 3.0 respectively).

Justification of the non-inferiority margin.

In general an appropriate choice of margin should provide both:

a) Assurance that the test drug has a clinically relevant effect greater than zero (placebo). This aspect of the choice of margin is discussed in EMEA Guideline on the choice of the non-inferiority margin, section III [EMEA, 2005].

b) Assurance that the test product is not substantially inferior to the reference in EMA guideline. This aspect of the choice of margin is discussed in EMEA Guideline on the choice of the non-inferiority margin, section IV [EMEA, 2005].

Two randomized pivotal placebo controlled studies are planned in this population (FGCL-4592-060 and 1517-CL-0608) that will directly prove superiority over placebo. Since direct comparisons provide always a higher level of evidence than indirect tests, the main criterion to fix the NI-margin in the 1517-CL-0610 study is bullet b above, i.e., to prove that the difference between roxadustat and darbepoetin alfa is unimportant.

From a clinical point of view, a true response rate for roxadustat of 15% lower than the true response rate for darbepoetin alfa is regarded an unimportant loss in efficacy since roxadustat is anticipated to have a number of advantages that have been shown during the phase 2 program: no need for IV iron supplementation, no increase of blood pressure and no increase of platelet counts.

No regulatory guideline exists in this therapeutic indication recommending a non-inferiority margin. However, the selected non-inferiority margin of 15% is in line with the FDA guideline in the urinary tract infections indication, where a high responder rate was also expected and a non-inferiority margin of 15% was recommended [FDA, 1998].

7.4.1.2 Secondary Analysis

The same analysis of the primary endpoint as described in [Section 7.4.1.1] will be repeated using the FAS and ITT. A sensitivity analysis on the primary efficacy endpoint will be performed on the subgroup of subjects being randomized after the implementation of protocol v2.0 and v3.0.

7.4.1.3 Subgroup Analysis

The analysis of the primary variable will be repeated separately by gender, age group, region, BL Hb categories, iron repletion at BL, diabetes and eGFR categories. Other subgroup analyses might be added to the SAP.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Primary Analysis

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

Once the primary hypothesis has been rejected for the primary endpoint, the key secondary endpoints below (Table 10) will be tested using a fixed sequence testing procedure, as depicted in Table 10 in order to maintain the overall one-sided type I error rate at 0.025. If the one-sided p-value from a test is < 0.025, 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 Secondary Endpoints Fixed Sequence Testing Procedure

Test	Endpoint	Comparison*
1	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 (the non-inferiority margin for the difference between groups is 0.75 g/dL).	Non-inferiority of pooled roxadustat versus darbepoetin alfa
2	LDL cholesterol change from BL to the average of weeks 12 to 28	Superiority of pooled roxadustat versus darbepoetin alfa
3	Mean monthly IV iron (mg) use per subject during weeks 1 to 36	Superiority of pooled roxadustat versus darbepoetin alfa
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 pooled roxadustat versus darbepoetin alfa
5	SF-36 vitality 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 pooled roxadustat versus darbepoetin alfa
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 pooled roxadustat versus darbepoetin alfa

Table continued on next page

Test	Endpoint	Comparison*
7	Incidence of hypertension (the non-inferiority margin is fixed as a hazard ratio of 1.3)	Non-inferiority of pooled roxadustat versus darbepoetin alfa
8	MAP change from BL to the average MAP of weeks 20 to 28	Superiority of pooled roxadustat versus darbepoetin alfa
9	Incidence of hypertension	Superiority of pooled roxadustat versus pooled darbepoetin alfa

*Subjects randomized to roxadustat QW, BIW and TIW under protocol v1 will be pooled together.

1. Hb change from BL to the average Hb of weeks 28-36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period (non-inferiority) will be analyzed using a Mixed Model of Repeated Measures (MMRM) with unstructured covariance matrix model (pooled roxadustat versus darbepoetin alfa). The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment interaction and other stratification factors. The non-inferiority margin for the difference between groups is 0.75 g/dL. Non-inferiority can be concluded if the lower limit of the two-sided 95% CI of the difference between the two treatment arms is above -0.75 g/dL.
2. Change from BL in LDL cholesterol to the average value of LDL cholesterol of weeks 12-28 (superiority) will be compared (pooled roxadustat versus darbepoetin alfa) using an MMRM with unstructured covariance matrix model. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment interaction and other stratification factors.
3. Monthly IV iron use (mg) during weeks 1 to 36 (superiority) will be compared (pooled roxadustat versus darbepoetin alfa) using a MMRM with unstructured covariance matrix model. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment interaction and other stratification factors.
4. Change from BL in PF subscore of SF-36 to the average of weeks 12–28 (non-inferiority) will be compared (pooled roxadustat versus darbepoetin alfa) for all subjects, using an MMRM with unstructured covariance matrix model. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment interaction and other stratification factors. Non-inferiority can be concluded if the lower limit of the 2-sided 95% CI of the difference between the 2 treatment arms is above -3 points.
5. Change from BL in Vitality subscore of SF-36 to the average of weeks 12–28 will be compared (pooled roxadustat versus darbepoetin alfa) for all subjects, using an MMRM with unstructured covariance matrix model. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment interaction and other stratification factors. Non-inferiority can be concluded if the lower limit of the 2-sided 95% CI of the difference between the 2 treatment arms is above -3 points.
6. Change from BL in MAP to the average of weeks 20–28 (non-inferiority) will be compared (pooled roxadustat versus darbepoetin alfa) using a MMRM with unstructured covariance matrix model. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment interaction and other stratification factors.

Non-inferiority can be concluded if the lower limit of the two-sided 95% CI of the difference between the two treatment arms is below 1 mm Hg.

7. Incidence rate (per 100 subject years at risk) and cumulative risk curve of subjects with hypertension from BL will be reported and compared (pooled roxadustat versus darbepoetin alfa) using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and the two-sided 95% CI will be calculated for the frequency of pooled roxadustat as relative to darbepoetin alfa. Non-inferiority will be declared if the upper bound of the 2-sided 95% CI is below 1.3.
8. Change from BL in MAP to the average of weeks 20–28 (superiority) will be compared (pooled roxadustat versus darbepoetin alfa) using an MMRM with unstructured covariance matrix model (pooled roxadustat versus darbepoetin alfa). The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment interaction and other stratification factors.
9. Incidence rate (per 100 subject years at risk) and cumulative risk curve of subjects with hypertension from BL will be reported and compared (pooled roxadustat versus darbepoetin alfa) using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and the two-sided 95% CI will be calculated for the frequency of pooled roxadustat as relative to darbepoetin alfa.

7.4.2.2 Secondary Analysis

The analysis of the secondary endpoints as described in 7.4.2.1 will be repeated using (a) the FAS and ITT and (b) the PPS for both non-inferiority tests and superiority tests.

For all secondary variables analyzed using MMRM, an additional sensitivity analysis will be performed using an Analysis of Covariance (ANCOVA) model with Last Observation Carried Forward (LOCF) method using BL value and the stratification factors as covariates.

As an additional sensitivity analysis, the mean Hb change from BL, first secondary variable, will also be calculated using all Hb values regardless of rescue therapy (this is included among the additional endpoints). This will be analyzed using an MMRM model similar to the one described in Section 7.4.2.1

Additional sensitivity analyses will be defined in the SAP.

7.4.2.3 Subgroup Analysis

The analysis of selected secondary variables will be repeated separately by gender, age group, region, BL Hb categories, iron repletion at BL, diabetes and eGFR categories. Other subgroups analysis might be added to the SAP.

7.4.3 Analysis of Additional Endpoints

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

be concluded if the lower limit of the two-sided 95% CI of the difference between the two treatment arms (roxadustat minus darbepoetin) is above -0.75 g/dL.

Statistical analysis for the other additional 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 liver function tests [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 (pooled roxadustat and darbepoetin alfa) and by all 4 study arms, 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. The statistical method for analysis of adjudicated safety data will be detailed in a pooled cardiovascular safety 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.

7.5.1 Adverse Events

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

An AE (classified by preferred term) started during the treatment period will be considered a Treatment Emergent AE (TEAE) if it was not present prior to the first dose of study drug, or 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 one event occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study medication.

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

The proportion of subjects with TESAE, 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.

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, HR) 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 (HR, PR interval, QRS interval, QT interval and QTc interval) 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. QTc interval 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 Clinical Study Report but in a separate population PK modeling report.

7.7 Analysis of Pharmacodynamics

Pharmacodynamic data may be submitted to population pharmacodynamic or population pharmacokinetic/pharmacodynamic (PPKPD) modeling. When deemed necessary, data from this study may be combined with data from other studies. Results will be reported in a separate PPKPD 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 discontinuation criteria during the study and was not discontinued from study treatment

PD3 - Received wrong treatment or incorrect dose

PD4 - Received prohibited concomitant treatment

7.9 Interim Analysis

An interim analysis will be performed when all subjects have completed 36 weeks of treatment; efficacy and safety data will be analyzed and reported, excluding the endpoints measured after 36 weeks. Since all primary and secondary analyses have been defined over this period of time, no multiplicity adjustment is required as the information fraction at the interim analysis is 100%. Once the study is completed, efficacy and safety will be analyzed again and reported including the complete study treatment of 104 weeks.

In addition, a descriptive analysis on both safety and efficacy will be performed to provide information from this study for regulatory filings of roxadustat in case the planned interim analysis has not been reached. This will include only descriptive statistics by arm (i.e., without formal hypothesis testing).

Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be completed by an independent Data and Safety Monitoring Board (DSMB) (Section 10.1).

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

For the primary endpoint, subjects without at least two Hb values as measured at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment will be classified as non-responders.

Main analysis of the efficacy endpoints with repeated measures over time will follow the MMRM methodology. In addition, as a sensitivity analysis, an LOCF method will be fitted.

Visit time windows 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 collected using an Electronic Data Capture (EDC) 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 for correct completion while the subject is at the site. The investigator or site designee will enter only the relevant information from the medication diary (i.e., roxadustat intake data related to PK sampling) and all questionnaire data directly into the EDC 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 investigator who will print, sign and retain the laboratory results. In addition all abnormalities will be checked and documented as clinically relevant or not clinically relevant. 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:

- Demographic data (date of birth, sex, race, height and body weight)
- Inclusion and exclusion criteria details
- The identification of the participation in study
- Original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data
- Results of HemoCue Hb assessments on all visits

- Decision on study drug dosing on all visits.
- AEs and concomitant medication
- Results of relevant examinations such as ECG charts, renal ultrasound outcome.
- Central laboratory printouts
- Medication diaries (for roxadustat subjects only)
- Paper questionnaires
- Dispensing and return of study drug details
- Reason for premature discontinuation from study treatment (if applicable)
- Subject number
- Method(s) 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 GDS 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 MedDRA and World Health Organization (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
- Developed discontinuation criteria during the study and not discontinued from study treatment
- Received wrong treatment or incorrect dose
- Received prohibited concomitant treatment

When a deviation from the protocol is identified for an individual subject, the 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 Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, 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 one year. The Sponsor shall submit a summary of the final clinical study report to the IRB/IEC and the Regulatory Agency within one year after last subject out (LSO) 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. 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

1. The investigator or his/her representative will immediately inform the subject orally 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 reaction). 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.

2. 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 informed consent form. 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 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 Investigator's Brochure 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:

For EU:
• Study protocol (and amendments, as applicable) • Investigator's Brochure (and amendments, as applicable) • Investigational Medicinal Product Dossier (IMPD) • Questionnaires and SAE Report Worksheet • 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:

For EU:
• Financial disclosure in compliance with federal regulation 21CFR Part 54 • Signed and dated FDA form 1572, if conducted under a US IND • 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 • IEC/IRB 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

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, 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 approved 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 trials 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 Independent Data and Safety Monitoring Board (DSMB)

A DSMB will review prespecified safety data periodically in collaboration with the Sponsor to ensure subject safety. A separate DSMB charter will establish the process, meeting frequency and scope of responsibilities.

10.2 Independent Event Review Committee (IERC)

An Independent Event Review Committee (IERC) will adjudicate all prespecified cardiovascular and cerebrovascular events in a blinded manner to ensure a consistent safety assessment.

Details of event identification and process of adjudication will be described in an IERC charter.

10.3 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 List of Prohibited Concomitant Medication

The following medications are prohibited during the period identified:

- Any ESA: within 12 weeks prior to randomization until EOT
- IV iron: within 6 weeks prior to randomization
- RBC transfusion: within 8 weeks prior to randomization
- Any investigational drug: within 30 days or 5 half lives or limit set by national law (whichever is longer), prior to screening until EOS
- Roxadustat or another HIF-PHI: at any time prior to randomization. After randomization any HIF-PHI 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 day of randomization until EOS
- Dapsone in any dose amount from the day of randomization until EOS
- Chronic use of acetaminophen/paracetamol > 2.0 g/day from the day of randomization until EOS

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 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 has been developed globally and can be activated 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 (NASH) 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 LFT's, 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 Subjects Moving from Protocol v1.0 to Protocol v2.0

12.3.1 Visit Schedule

Subjects that have entered the study under protocol v1.0, upon signing the informed consent for the amendment 1, will have their visit frequency adjusted according to Table 1. Schedule of Assessments. For example, if subject signs informed consent for protocol v2.0 at scheduled week 3 (according to protocol v1.0), subject will attend clinic at week 4, week 6 and all subsequent visits as per Schedule of Assessments.

12.3.2 Dosing Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0

Dosing

Study drug will be dosed TIW throughout the treatment period, unless otherwise specified.

Subjects that have entered the study under protocol version 1.0, upon signing the informed consent for the amendment 1, will have their dose frequency (on QW and BIW under protocol v1.0) and dose amount adjusted. Subjects randomized to roxadustat QW or BIW who do not agree to change to TIW, should be discontinued from the study treatment and continue in the post study follow-up period.

At this visit, it is first determined if the subject would need a dose titration according to the dose adjustment rules as per Section 5.1.2.1. Once that is established subjects are converted per the below instructions. The dose assigned must not exceed the maximum allowed dose of 3.0 mg/kg bodyweight or 300 mg per administration, whichever is lower. For subjects on permanent dialysis dose assigned must not exceed 3.0 mg/kg (based on dry weight in hemodialysis subjects and weight minus abdominal fluid based on last filling in peritoneal dialysis subjects) or 400 mg per administration, whichever is lower.

a) Subjects in the correction period or maintenance period on TIW dosing, will continue on TIW dosing for the remainder of the treatment period. If needed their dose will be adjusted according to the conversion table below, at the visit when the updated informed consent is signed.

Current TIW dose (mg)	**20**	**40**	**50**	**70**	**100**	**120**	**150**	**200**	**250**	**300**	**350**	**400**
If no dose titration needed	20	40	50	70	100	100	150	200	250	300	300	300
If up titration needed*	40	50	70	100	150	150	200	250	300	300	300	300
If down titration needed*	#	20	40	50	70	100	100	150	200	250	300	300

b) Subjects in the maintenance period on BIW dosing will change to TIW dosing immediately, per conversion table below, at the visit when the informed consent for the amendment 1 is signed.

Current BIW maintenance dose (mg)	**20**	**40**	**50**	**70**	**100**	**120**	**150**	**200**	**250**	**300**	**350**	**400**
If no dose titration needed	20	20	40	50	70	70	100	150	150	200	250	250
If up titration needed*	20	40	40	70	70	100	150	150	200	250	250	300
If down titration needed*	#	20	20	40	50	70	70	100	150	150	200	200

c) Subjects in the maintenance period on QW dosing will change to TIW dosing immediately, per conversion table below, at the visit when the updated informed consent is signed.

Current QW maintenance dose (mg)	**20**	**40**	**50**	**70**	**100**	**120**	**150**	**200**	**250**	**300**	**350**	**400**
If no dose titration needed	20	20	20	20	40	40	50	70	70	100	100	150
If up titration needed*	20	20	20	40	40	50	70	70	100	100	150	150
If down titration needed*	#	#	20	20	20	40	40	50	70	70	100	100

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

[#] Contact the medical monitor if down titration is needed.

12.3.3 ESA Rescue Therapy

If, upon implementation of protocol v2.0, a subject on roxadustat has already received 1 or more ESA treatments (under protocol v1.0), they can initially continue in the study. The subject will, however, be discontinued from study treatment if a further ESA rescue treatment is required after implementation of protocol v2.0.

12.4 Instructions for Subjects Requiring Dialysis

Subjects who initiate temporary or permanent dialysis treatment are allowed to continue in the study. All modes of dialysis, i.e., hemodialysis (HD), hemodiafiltration (HDF) and peritoneal dialysis (PD) are allowed.

12.4.1 Dosing

- Subjects should continue with the same dose and dose frequency of study drug as they were on prior to dialysis initiation.
- For HD/HDF subjects, it is recommended that study drug is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day) to avoid potential bias on certain study assessments.
- For subjects treated with darbepoetin, the route of administration of darbepoetin is according to local standard of care for dialysis patients.

12.4.2 Dose Adjustment

- The dose adjustment rules remain unchanged (see Section 5.1.2.1).
- The maximum allowed dose in subjects on permanent dialysis is 3.0 mg/kg (based on post-dialysis weight in HD subjects and weight minus abdominal fluid based on last filling in PD subjects) or 400 mg per administration, whichever is lower.

12.4.3 ESA Rescue Therapy

If roxadustat subjects meet the criteria for ESA rescue therapy while on dialysis, darbepoetin alfa will be administered IV or SC according to its Package Insert or SmPC for dialysis subjects. The subject must be discontinued from study treatment if the subject requires a second course of rescue darbepoetin alfa.

12.4.4 Supplemental Iron Use

Iron supplementation rules are unchanged in subjects starting dialysis who are randomized to roxadustat (see Section 5.1.3.2.1). In subjects randomized to darbepoetin, IV iron supplementation will be given according to standard of care.

12.4.5 Health Related Quality of Life

Additional questionnaires will be completed on day of first dialysis, 4 weeks later and 12 weeks later, prior to initiation of the procedure.

12.4.6 Timing of Study Assessments

- If a study visit occurs on a dialysis day, all study assessments should be performed before start of dialysis.
- Blood pressure and HR should be measured in triplicate prior to and after end of dialysis (HD/HDF subjects only).

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

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!***

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 <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b <u>Moderate activities</u>, 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 <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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

	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 <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (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 <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 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 during the past 4 weeks. 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 past 4 weeks…

	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 past 4 weeks, how much of the time has your physical health or emotional problems 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!

12.6 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

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 <u>past 7 days</u>.

	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 <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> 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

12.7 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

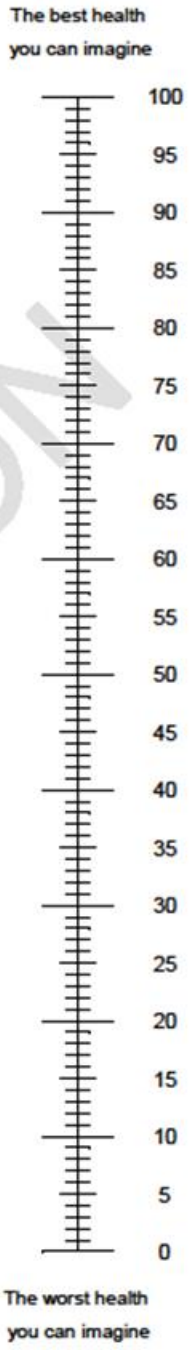
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

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 = ☐



12.8 Subjects' 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)

12.9 Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms (WPAI:ANS)

The following questions ask about the effect of your anaemic symptoms on your ability to work and perform normal daily activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO _____YES
   If NO, tick "NO" and skip to question 6.

The next questions refer to the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your anaemic symptoms? *Include hours you missed on sick days, times you went in late, left early, etc., because of your anaemic symptoms . Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS (If "0", skip to question 6)

5. During the past seven days, how much did your anaemic symptoms affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If anaemic symptoms affected your work only a little, choose a low number. Choose a high number if anaemic symptoms affected your work a great deal.

   Consider only how much anaemic symptoms affected productivity while you were working.

Anaemic symptoms had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Anaemic symptoms completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your anaemic symptoms affect your ability to perform your normal daily activities, other than work at a job?

By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If anaemic symptoms affected your activities only a little, choose a low number. Choose a high number if anaemic symptoms affected your activities a great deal.

Consider only how much <u>anaemic symptoms</u> affected your ability to do your normal daily activities, other than work at a job.

Anaemic symptoms had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Anaemic symptoms completely prevented me from doing my daily activities

CIRCLE A NUMBER

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 2

I. The purpose of this amendment is:

Substantial Changes
1. Change in hemoglobin (Hb) eligibility criteria.
DESCRIPTION OF CHANGE:
The number of Hb values assessed during the screening period is reduced from three to two and the mean Hb entry threshold is increased from ≤ 10.0 g/dL to ≤ 10.5 g/dL. This results in a change in inclusion criterion 4 and texts throughout the protocol that refer to the mean Hb entry threshold.
RATIONALE:
Reducing the number of Hb screening values required to be assessed during the screening period from three to two reduces the number of screening visits, and is likely to shorten the screening period and accelerate the decision on patient eligibility concerning the Hb inclusion criterion. The Hb stability criterion defined by a maximum allowed difference between screening values of 1.0 g/dL remains unchanged to avoid unduly unstable Hb levels at baseline. The current Hb entry criterion (mean Hb ≤ 10.0 g/dL at screening) is reconsidered. The current Hb value of ≤ 10.0 g/dL is considered too low and incongruent with contemporary clinical practice, especially in countries with high standard of care. Feedback from sites and investigators raise this criterion as the principal cause of screen failure, or alternatively, as a reason for not screening patients at all. This change will not bias or impact Hb-related endpoint assessments, nor does it affect other key elements of the trial design including the roxadustat dosing algorithm and principles for dose adjustments. The updated European Renal Best Practice (ERBP) position statement from a 2013 publication by Locatelli and colleagues provides valid support to increase the Hb threshold for inclusion: according to this statement the Hb levels should not routinely fall below 10 g/dL in all patients prior to initiation of erythropoiesis stimulating agent (ESA) therapy. Consequently, the mean Hb entry threshold is increased to ≤ 10.5 g/dL.
2. Update of the iron criteria: ferritin level ≥ 100 ng/mL and transferrin saturation (TSAT) level ≥ 20% at screening are removed.
DESCRIPTION OF CHANGE:
The iron criteria are updated to better reflect clinical practice, and as a result inclusion criteria 6 and 7 are removed.
RATIONALE:
The current iron repletion criteria do not always mimic clinical practice and are based on a paradigm which dictates the requirement of full iron repletion prior to commencing ESA therapy. The proposed changes aim to better reflect clinical practice and allow for inclusion of patients with iron indices indicative of relative or functional iron deficiency, under the condition that they are deemed eligible in the opinion of the investigator as per the 2012

Kidney Disease Improving Global Outcomes (KDIGO) anemia guidelines. These guidelines recommend to check and correct iron deficiency prior to initiation of ESA therapy, but arguably without absolute requirement to achieve the thresholds of ferritin ≥ 100 ng/mL and TSAT ≥ 20%. The KDIGO anemia guidelines further advocate individualized assessments in the clinical decision to initiate ESA therapy, and it may not always be feasible to ensure full iron repletion in individual patients. Finally, the 6 week washout period of IV iron may also limit investigators to administer sufficient iron to achieve the key ferritin and TSAT thresholds.
3. Exclusion Criterion 21 extended to exclude patients who are close to initiating renal replacement therapy including dialysis.
DESCRIPTION OF CHANGE:
Exclusion criterion 21 is extended to exclude patients that are close to initiating renal replacement therapy including dialysis (within the first year of the study).
RATIONALE:
The primary objective of this study is to assess the efficacy and safety of roxadustat in non-dialysis chronic kidney disease (CKD) patients. Currently there are no specific criteria that prevent randomization of patients who are close to initiating renal replacement therapy, including dialysis. Randomization of these patients leads to reduced exposure and less patients available for primary and key secondary endpoint assessments in the intended target population of this study. The revised exclusion criterion aims to increase awareness amongst investigators that patients predicted to undergo dialysis treatment, or be discontinued from the treatment phase due to renal transplantation during the first year of the study should not be randomized.

Non-Substantial Changes
1. Contact details of key sponsor personnel
DESCRIPTION OF CHANGE:
Medical Monitor is changed to PPD.
RATIONALE:
PPD has taken over medical monitor responsibilities from PPD.
2. Extension of the planned study period
DESCRIPTION OF CHANGE:
The planned study period is extended from 3Q2018 until 2Q2021.
RATIONALE:
Enrollment was slower than expected at the start of the study; therefore, the study duration has been increased. This increase in the duration of the trial is considered non-substantial as

exposure to the treatment with Investigational Medicinal Product (IMP) is not extended. The definition of the end of the trial for the study subjects is unchanged and the monitoring arrangements are not changed.
3. Post-study follow-up visits
DESCRIPTION OF CHANGE:
In case of premature discontinuation, subjects were to complete the end of treatment (EOT) visit and end of study (EOS) visit. This has been reworded to: 2 EOT visits and 1 EOS visit.
RATIONALE:
In the current protocol it is not clear that there are in total 3 follow-up visits for subjects that prematurely discontinue study treatment. The 3 follow-up visits are: 1. EOT visit, 2. EOT+2 week visit, 3. EOS visit. This is clarified throughout the protocol text and in Table 1: footnote c and the column EOT + 2 weeks.
4. Inclusion Criterion 5 has been extended
DESCRIPTION OF CHANGE:
Inclusion criterion 5 that addresses the suitability for treatment with ESA using the criteria specified in the KDIGO 2012 recommendation, has been further clarified.
RATIONALE:
Criteria of suitability for treatment with ESA are further explained in more detail in order to provide more clarity and guidance to the investigator. These criteria are based upon the wording used in the KDIGO 2012 anemia management guidelines. These guidelines request the treating physician to initiate the use of ESAs in non-dialysis CKD patients considering the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia.
5. Concomitant medication: Supplemental iron use
DESCRIPTION OF CHANGE:
I. Oral iron: Rewording of supplemental iron use guidance for roxadustat-treated subjects in case of intolerance to oral iron. II. Intravenous iron for all treated subjects: upon reaching iron repletion (once ferritin is $\geq$ 100 ng/mL and TSAT $\geq$ 20%) it is recommended to discontinue IV iron supplementation.
RATIONALE:
Text updates have been made to align with other phase 3 protocols in the global program for consistency throughout the roxadustat development program.
6. Prohibited medication
DESCRIPTION OF CHANGE:

The list of prohibited medications is clarified and only to summarize the prohibited medication for the identified period. In protocol version 1.0 for ESA, IV iron and red blood cell (RBC) transfusion, it was stated when these medications were prohibited, but also when these medications were allowed. The time when these medications are allowed is removed.
RATIONALE:
ESA rescue therapy, IV iron and RBC transfusion are only prohibited during the screening period. Within the treatment period these medications are restricted in use and follow certain criteria. These criteria are described under protocol sections of concomitant medication (Section 5.1.3) and rescue therapy guidelines (Section 5.1.5). Therefore to avoid confusion, the references to the treatment period are being removed from the prohibited medication lists.
7. Additional efficacy secondary endpoint
DESCRIPTION OF CHANGE:
Additional secondary endpoint has been deleted : Iron use - Monthly oral iron (mg) use per subject during weeks 1 to 36, and weeks 36 to 52 (monthly defined as a period of 4 weeks)
RATIONALE:
Use of oral iron is not considered a clinically meaningful endpoint since the study protocol recommends supplementation of oral iron to support erythropoiesis and as the first-line treatment for iron deficiency in both treatment arms.
8. Changes in reference to pre- and post-amendment
DESCRIPTION OF CHANGE:
The current tables (synopsis table 4, protocol table 3 and 10) refer to pre- and post-amendment. “Pre-amendment” are changed to “Protocol version 1” and “post-amendment” are changed to “Protocol version 2 and 3”.
RATIONALE:
With the current amendment these tables are updated to reflect the situation taking all protocol versions into account.
9. Primary Analysis: Sensitivity analyses on the primary analysis of the primary endpoint
DESCRIPTION OF CHANGE:
A sensitivity analysis on the results of the primary analysis of the primary endpoint before and after protocol amendment 1 and protocol amendment 2 is added.
RATIONALE:
This sensitivity analysis is added to evaluate the impact on the primary endpoint in both protocol amendments 1 and 2. The changes implemented following both amendments could have led to inconsistent results between those patients included before amendment 1 versus those included after amendment 1, and patients included before amendment 2 versus those

included after amendment 2.
10. Synopsis and interim analysis
DESCRIPTION OF CHANGE:
A descriptive analysis of both safety and efficacy data is added to support a regulatory submission in case the planned interim analysis is not reached. This includes only descriptive statistics.
RATIONALE:
Enrollment has been slower than expected at the start of the study. It was anticipated that at the time of submission for marketing authorization, the currently planned interim analysis would not have been reached. In order to provide full disclosure of the results, a descriptive analysis is included. Only summary data and both safety and efficacy (without inferential statistics) will be presented without any impact on the ongoing study.
11. Flow Chart
DESCRIPTION OF CHANGE:
The term “Absence of renal carcinoma per renal ultrasound” is deleted from the box describing the key selection criteria in the flow chart.
RATIONALE:
The purpose of the box in the flow chart describing key selection criteria is to inform on a high level about the most relevant criteria qualifying a subject for inclusion into the study. In this context and keeping in mind that the protocol includes approximately 40 inclusion and exclusion criteria, the criterion “Absence of renal carcinoma per renal ultrasound” is not regarded as a key selection criterion. CKD stage, Hb entry value and the suitability for treatment with ESAs are considered the key selection criteria.
12. Schedule of Assessments
DESCRIPTION OF CHANGE:
Updates to the Schedule of Assessments to reflect changes made in this Amendment and to add other clarifications.
RATIONALE:
To provide up to date and accurate information.
13. Summary of key safety information for study design: roxadustat
DESCRIPTION OF CHANGE:
Five pancreatitis events were noted during the roxadustat clinical development program, the majority of which have been associated with gallstones or biliary sludge; one was due to a pancreatic duct stricture and another case had multiple risk factors for pancreatitis.

RATIONALE:
'Phase 2' is added to make clear that the 'five pancreatitis events' refer to data from the phase 2 development program. Meanwhile the phase 3 program has been ongoing for more than 2 years
14. Three times weekly (TIW) dosing regimen of roxadustat
DESCRIPTION OF CHANGE:
The protocol described the roxadustat dosing schedule of TIW to be dosed at least 2 days apart (e.g., Monday, Wednesday, Friday). This changes into: the period between two roxadustat administrations should be at least 36 hrs.
RATIONALE:
Alignment with phase 3 dialysis protocol and providing logic to dosing regimen TIW.
15. Dose adjustment rules for subjects receiving darbepoetin alfa
DESCRIPTION OF CHANGE:
Deletion of Table 6: Recommended Dose Adjustment Rules for Darbepoetin Alfa
RATIONALE:
The principal reason for Table deletion is that the table does not fully reflect all elements of the Summary of Product Characteristics (SmPC).
16. Return of (un)used medication to site
DESCRIPTION OF CHANGE:
Clarification on the return of empty medication packages for subjects treated with darbepoetin alfa who are self-administering the medication after 36 weeks of treatment. A sentence is added with regard to treatment compliance for subjects randomized to darbepoetin: In case of self-administration after 36 weeks of treatment, the empty packages of darbepoetin alfa should be returned by the subject to the site.
RATIONALE:
To clarify that in case subjects self-inject darbepoetin alfa (only following 36 weeks of treatment with darbepoetin alfa), they need to return the empty packages to perform the check on treatment compliance.
17. Safety Assessments
DESCRIPTION OF CHANGE:
The number of visits on which vital signs are measured is reduced and an average is not derived from the 2nd and 3rd readings.

RATIONALE:
As all three readings for the vital sign parameters will be used in the statistical analysis, an average of the 2nd and 3rd readings was no longer relevant and was inconsistent with the analysis.
18. Reporting of SAEs
DESCRIPTION OF CHANGE:
Deleted the contact details of MedPace for reporting of SAEs.
RATIONALE:
Contact details of MedPace as currently stated in the protocol are not applicable.
19. Total blood volume
DESCRIPTION OF CHANGE:
The total volume of 440 mL is changed to 460 mL.
RATIONALE:
The blood volume is adjusted to better depict the total blood volume required by the current visit schedule.
20. Secondary analysis: additional sensitivity analysis
DESCRIPTION OF CHANGE:
In addition, this variable will be analyzed using the subset of subjects who have reached Hb ≥ 11.0 g/dL prior to week 28.
RATIONALE:
While subgroup analysis based on baseline characteristics are scientifically sound and well accepted by regulatory guidelines, post-baseline responses affected by the treatment are not appropriate variables to define subgroups for investigation (see graft guideline on the investigation of subgroups in confirmatory clinical trials, EMA/CHMP/539146/2013). Therefore the subgroup analysis restricted to subjects who have reached 11 g/dL during the study has been removed from the protocol.
21. Appendix 12.4 Instructions for subjects requiring dialysis
DESCRIPTION OF CHANGE:
Addition of text to Appendix 12.4 to describe that: 1. The iron supplementation rules are unchanged (Section 5.1.3.2.1) in subjects starting dialysis. 2. The route of administration of darbepoetin is according to the local standard of care for dialysis patients.
RATIONALE:
Provides alignment with the phase 3 dialysis protocol and guidance in the applicable text regarding management of subjects after having initiated dialysis. This change allows a

switch in the application route if deemed required (e.g., from subcutaneous use to intravenous use).
22. Appendix 12.10
DESCRIPTION OF CHANGE:
Appendix 12.10 has been deleted.
RATIONALE:
A general reference was added in the text to the KDIGO 2012 guideline. Appendix 12.10 did not add any further information and is therefore deleted.
23. Minor Administrative Changes
DESCRIPTION OF CHANGE:
Includes minor administrative changes, e.g., typos, format, numbering, consistency throughout the protocol following the latest Astellas document consistency guidance.
RATIONALE:
Update the protocol to correct formatting and to provide clarifications to ensure complete understanding of study procedures.

II. Amendment Summary of Changes: Substantial Changes

III List of Abbreviations and Definition of Key Terms, IV Synopsis, Study Design Overview and Inclusion Criteria, 2 Study Objective(s), Design, and Endpoints, 3 Study Population, and 5 Treatments and Evaluation *List of Key Study Terms, 2.2.1.2 Study Population, 2.2.1.3 Description of Study, 3.2 Inclusion Criteria #4 and 5.2.4 Diagnosis of the Target Disease, Severity, and Duration of Disease*
WAS:
The mean of the subject's three most recent (prior to randomization) Hb values during the screening period, obtained at least 4 days apart, must be ≤ 10.0 g/dL, with a difference of ≤ 1.0 g/dL between the highest and the lowest values. The last Hb value must be within 10 days prior to randomization.
IS AMENDED TO:
The mean of the subject's ~~three~~ **two** most recent (prior to randomization) Hb values during the screening period, obtained at least 4 days apart, must be ≤ 10.~~0~~**5** g/dL, with a difference of ≤ 1.0 g/dL ~~between the highest and the lowest values~~. The last Hb value must be within 10 days prior to randomization.

IV Synopsis, Inclusion Criteria and 3 Study Population *3.2 Inclusion criteria #6 and #7*
WAS:
6. Subject has a ferritin level ≥100 ng/mL (≥220 pmol/L) at screening. 7. Subject has a transferrin saturation (TSAT) level ≥20% at screening.
IS AMENDED TO:
6. ~~Subject has a ferritin level ≥100 ng/mL (≥220 pmol/L) at screening.~~ **This criterion has been removed.** 7. ~~Subject has a transferrin saturation (TSAT) level ≥20% at screening.~~ **This criterion has been removed.**

IV Synopsis, Exclusion Criteria and 3 Study Population *3.2 Exclusion criterion #21*
WAS:
Subject has had any prior organ transplant (that has not been explanted), or subject is scheduled for organ transplantation.
IS AMENDED TO:
Subject has had any prior organ transplant (that has not been explanted), ~~or~~ subject is scheduled for organ transplantation**, or subject is likely to initiate renal replacement therapy including dialysis within the first year of the study in the opinion of the investigator.**

V Flow Chart and Schedule of Assessments *Table 1: Schedule of Assessments*
ADDED:
i An additional (third) Hb value may be collected if necessary. Only for subjects who are switched from protocol version 2.0 to 3.0 during (re) screening can a fourth Hb value be collected, as was applicable under protocol version 2.0.

2 Study Objective(s), Design, And Endpoints *2.2.1.2 Study Population*
DELETED:
~~Subjects are iron replete; inclusion is permitted if ferritin ≥ 100 ng/mL (≥220 pmol/L) and Transferrin Saturation (TSAT) ≥ 20%.~~

IIb Amendment Summary of Changes: Non-Substantial Changes

II Contact Details of Key Sponsor's Personnel *Medical Monitor*
WAS:
PPD Global Medical Science Astellas Pharma Europe B.V. PPD
IS AMENDED TO:
PPD Global Medical Science Astellas Pharma Europe B.V. PPD

IV Synopsis, Planned Study Period
WAS:
From 1Q2014 to 3Q2018.
IS AMENDED TO:
From 1Q2014 to ~~3~~2Q20~~18~~21~~.~~

IV Synopsis, Study Design Overview and Formal Stopping Rules, V Flow Chart and Schedule of Assessments, 2 Study Objective(s), Design, and Endpoints, and 6 Discontinuation *Table 1 Schedule of Assessments Footnote c, 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 visit and end of study (EOS) visit.
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.

IV Synopsis, Inclusion Criteria, and 3 Study Population *3.2 Inclusion criteria #5*

WAS:
Subject is deemed suitable by the investigator for treatment with erythropoiesis stimulating agents (ESA) using the criteria specified in the KDIGO 2012 recommendation (see Appendix 12.10).
IS AMENDED TO:
Subject is deemed suitable by the investigator for treatment with erythropoiesis stimulating agents (ESA) using the criteria specified in the KDIGO 2012 recommendation ~~(see Appendix 12.10).~~ **considering the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia.**

IV Synopsis, Concomitant Medication Restrictions and/or Requirements, 2 Study Objective(s), Design, and Endpoints, and 5 Treatments and Evaluation

2.2.1.5 Comparator and 5.1.3.2.1 Supplemental Iron Use

WAS:

Subjects receiving roxadustat

i. Oral iron

For subjects receiving roxadustat, oral iron is recommended for dietary supplementation to support erythropoeisis and as the first-line for prevention and treatment of iron deficiency. The recommended daily dose is 200 mg of elemental iron; in case of iron intolerance or for other reasons a lower dose may be given. Subjects should be advised to take roxadustat at least one hour before or one hour after oral iron.

ii. IV iron

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

- The subject has not responded adequately in terms of hemoglobin response to 2 or more consecutive dose increases of roxadustat or reached the maximum dose limit, and
- The subject has iron deficiency (either ferritin <100 ng/mL [<220 pmol/L] or TSAT < 20%) or the subject is intolerant of oral iron therapy.

Treatment with roxadustat may continue during IV iron administration. IV iron administration should be stopped once ferritin levels are ≥100 ng/mL (≥220 pmol/L) and TSAT ≥20%.

Subjects receiving darbepoetin alfa

For subjects treated with darbepoetin alfa, oral or IV iron supplementation is required to maintain iron repletion and will be administered only if ferritin <100 ng/mL (<220 pmol/L) or TSAT < 20%. The route of iron administration is up to the investigator's discretion and follows the KDIGO 2012 recommendation for NDD-CKD subjects (see Appendix 12.10). Criteria such as the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, and subject compliance will be considered.

IS AMENDED TO:

Subjects receiving roxadustat

i. Oral iron

For subjects receiving roxadustat, oral iron is recommended for dietary supplementation to support erythropoiesis and as the first-line for prevention and treatment of iron deficiency **unless the subject is intolerant to this treatment**. The recommended daily dose is 200 mg of elemental iron~~; in case of iron intolerance or for other reasons a lower dose may be given~~. Subjects should be advised to take roxadustat at least one hour before or one hour after oral iron.

ii. IV iron

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

- The subject has not responded adequately in terms of hemoglobin response to 2 or more consecutive dose increases of roxadustat or reached the maximum dose limit, and
- The subject has iron deficiency (either ferritin <100 ng/mL [<220 pmol/L] or TSAT < 20%) or the subject is intolerant of oral iron therapy.

Treatment with roxadustat may continue during IV iron administration. **Discontinuation of** IV iron administration ~~should be stopped~~ **is recommended** once ferritin levels are ≥ 100 ng/mL (≥ 220 pmol/L) and TSAT ≥20%.

Subjects receiving darbepoetin alfa

For subjects treated with darbepoetin alfa, oral or IV iron supplementation is required to maintain iron repletion ~~and will be administered only if ferritin <100 ng/mL (<220 pmol/L) or TSAT < 20%. The route of iron administration is up to the investigator's discretion and follows the KDIGO 2012 recommendation for NDD-CKD subjects (see Appendix 12.10). Criteria such as the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, and subject compliance will be considered.~~**. IV iron should only be administered if ferritin < 100 ng/mL (< 220 pmol/L) or TSAT < 20%. IV iron may be administered per local practice. Discontinuation of IV iron therapy is recommended once ferritin levels are ≥ 100 ng/mL (≥ 220 pmol/L) and TSAT ≥ 20%.**

IV Synopsis, Prohibited Medication, 5 Treatments and Evaluation and 12 Appendices

5.1.3.3 Prohibited Medication and 12.1 List of Prohibited Concomitant Medications

WAS:

The following medications are prohibited during the period identified:

- Any ESA: within 12 weeks prior to randomization until EOT, except for darbepoetin alfa as part of randomized treatment or as rescue therapy.
- IV iron: within 6 weeks prior to randomization. From day of randomization onwards IV iron is allowed as part of supplemental iron use, if protocol-specified criteria are met.
- RBC transfusion: within 8 weeks prior to randomization. From the day of

randomization onwards RBC transfusions are allowed as part of the rescue therapy, if protocol-specified criteria are met.

IS AMENDED TO:

The following medications are prohibited during the period identified:

- Any ESA: within 12 weeks prior to randomization until EOT~~, except for darbepoetin alfa as part of randomized treatment or as rescue therapy~~.
- IV iron: within 6 weeks prior to randomization. ~~From day of randomization onwards IV iron is allowed as part of supplemental iron use, if protocol-specified criteria are met.~~
- RBC transfusion: within 8 weeks prior to randomization. ~~From the day of randomization onwards RBC transfusions are allowed as part of the rescue therapy, if protocol-specified criteria are met.~~

IV Synopsis, Additional Secondary and 2 Study Objective(s), Design, and Endpoints

2.3.3.1 Efficacy Endpoints

DELETED:

~~*Iron use*~~

- ~~Monthly oral iron (mg) use per subject during weeks 1 to 36, and weeks 36 to 52 (monthly defined as a period of 4 weeks)~~

IV Synopsis, Statistical Methods, 2 Study Objective(s), Design, and Endpoints and 7 Statistical Methodology

2.2.1.3 Description of Study, 7.1 Sample Size

WAS:

In protocol version 1.0 (pre-amendment) subjects were randomized in a ratio of 2:1 receiving roxadustat versus darbepoetin alfa. The expected number of subjects randomized pre-amendment, post-amendment and overall are represented in the following table.

Table 3 Expected Number of Subjects Randomized Pre-amendment and Post-amendment

Treatment Arms	Study Treatment	Expected Number of Pre-amendment Subjects Randomized (Ratio 2:1)*†	Expected Number of Post-amendment Subjects Randomized (Ratio 1:1)	Total Expected Number of Subjects Randomized per Treatment Arm
1	Roxadustat	100	210	310
2	Darbepoetin alfa	50	210	260
Total		150	420	570

* The number of subjects post-amendment will depend on the number of subjects randomized pre-amendment. The number of subjects randomized pre-amendment is assumed to be 150.

† Subjects pre-amendment randomized to QW and BIW will be converted to the TIW arm according to the schedule as included in Appendix 12.3

IS AMENDED TO:

In protocol version 1~~.0 (pre-amendment)~~ subjects were randomized in a ratio of 2:1 receiving roxadustat versus darbepoetin alfa. The expected number of subjects randomized **on protocol version 1, protocol versions 2 and 3 and the total number of randomized subjects per treatment arm** ~~pre-amendment, post-amendment and overall~~ are represented in the following table.

Table 3 Expected Number of Subjects Randomized~~ Pre-amendment and Post-amendment~~

Treatment Arms	Study Treatment	Expected Number of ~~Pre-amendment~~ **Protocol v1** Subjects Randomized (Ratio 2:1)~~*‡~~	Expected Number of ~~Post-amendment~~ **Protocol v2 and 3** Subjects Randomized (Ratio 1:1)†	Total Expected Number of Subjects Randomized per Treatment Arm
1	Roxadustat	100	210	310
2	Darbepoetin alfa	50	210	260
Total		150	420	570

~~*~~ † The number of subjects **under protocol v2 and v3** ~~post-amendment~~ will depend on the number of subjects randomized **under protocol v1** ~~pre-amendment. The number of subjects randomized pre-amendment is assumed to be 150.~~

~~‡ Subjects pre-amendment randomized to QW and BIW will be converted to the TIW arm according to the schedule as included in Appendix 12.3~~

IV Synopsis, Analysis of Primary Endpoint and 7 Statistical Methodology

7.4.1.1 Primary Analysis

ADDED:

Sensitivity analyses will be conducted to assess the consistency of the results before and after protocol amendments 1 and 2 (e.g., protocol versions 2.0 and 3.0 respectively).

IV Synopsis, Interim Analyses and 7 Statistical Methodology

7.9 *Interim Analysis*

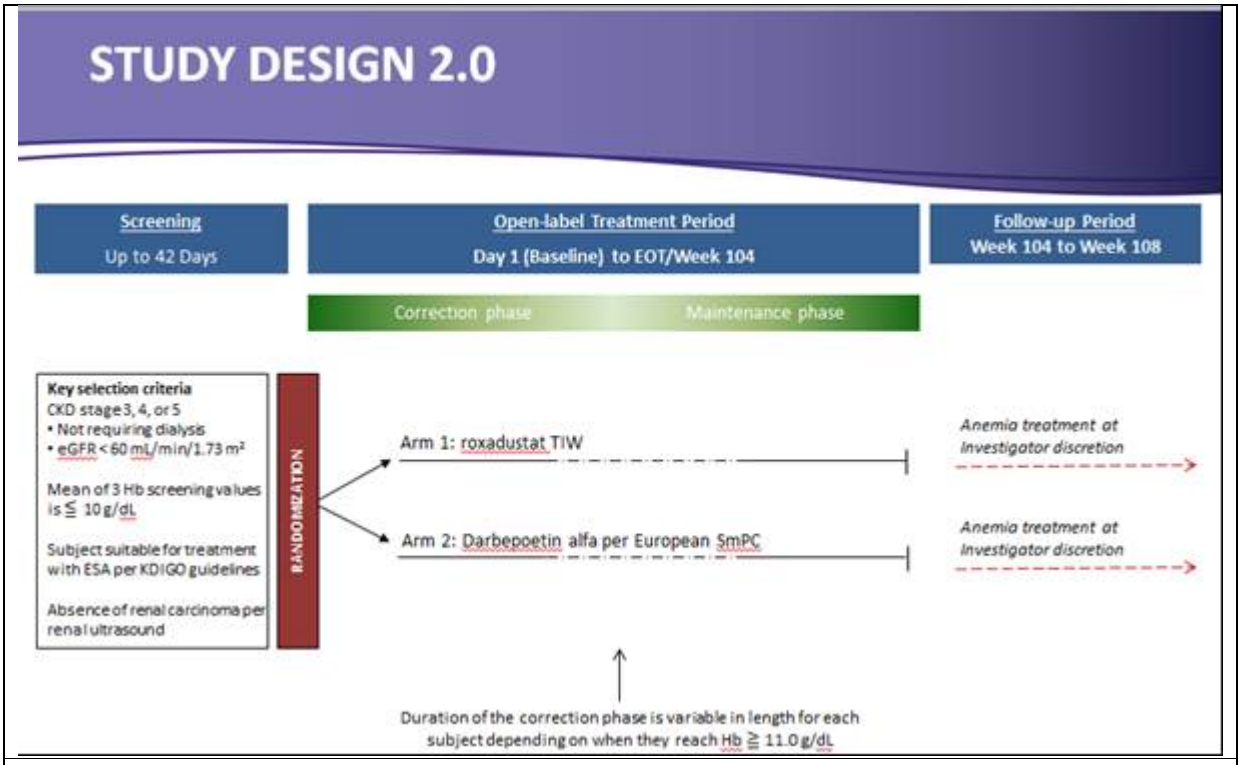
ADDED:

In addition, a descriptive analysis on both safety and efficacy will be performed to provide information from this study for regulatory filings for roxadustat in case the planned interim analysis has not been reached. This will include only descriptive statistics by arm (i.e., without formal hypothesis testing).

V Flow Chart and Schedule of Assessments

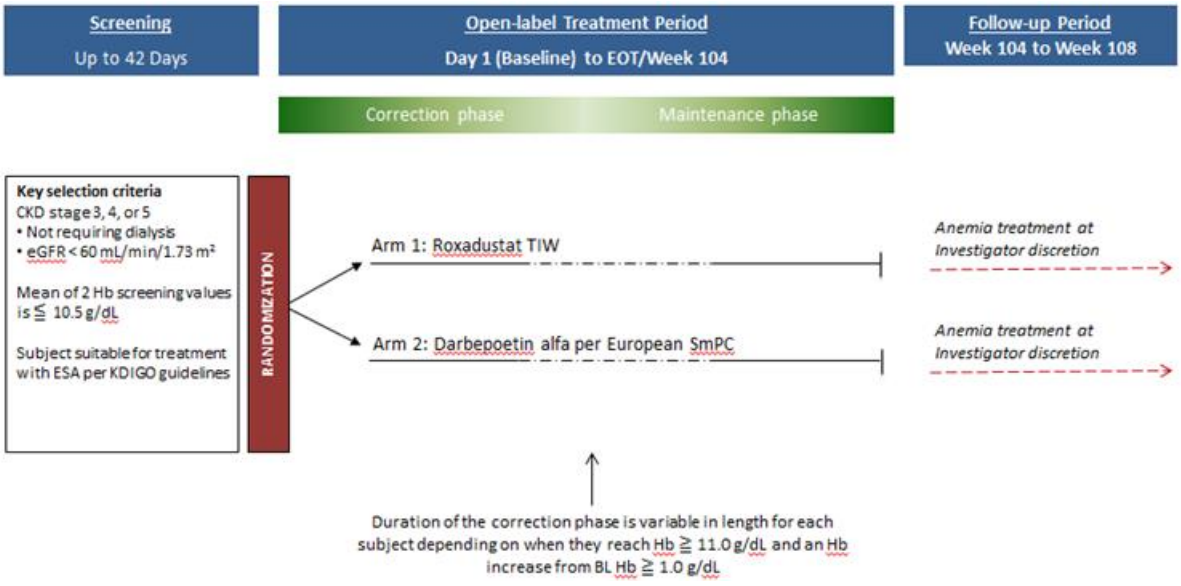
Flow Chart

WAS:



IS AMENDED TO:

STUDY DESIGN 3.0



V Flow Chart and Schedule of Assessments

Table 1: Schedule of Assessments

WAS:

Assessments	Screening Period			Treatment Period (Correction Period and Maintenance Period)					Follow-up Period		Unscheduled Visits	Post study Follow-up [c]
Visit / Week	2-6 weeks [a]			Day 1 [b]	Weekly (wks 1 - 2) ± 2 days	Every 2 Weeks (wks 4 - 24) ± 2 days	Every 4 Weeks (wks 28 - 100) ± 3 days	EOT [c] (wk 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									
Written informed consent	X											
Randomization				X								
Eligibility criteria	X			X								
Demographics	X											
Medical history	X											
Physical examination	X			X		wks 12[d], 24[d]	wks 36[d], 52[d], 76[d]	X		X[d]	O[d]	
Height[e], weight	X			X		wks 12, 24	wks 36, 52, 76	X		X	O	
Blood pressure[f], heart rate[f], respiratory rate[g]	X	X	X	X	X	X	X	X		X	X	
CBC with WBC diff, red cell indices and platelets	X			X	X	wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
Hemoglobin[h]		X	X			X	X		X		X	
HemoCue assessment[i]				X	X	X	X				X	
Reticulocyte count and Hb in reticulocytes (CHr)	X			X	X	wks 4, 6, 8, 12, 16, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
12-lead ECG	X			X		wks 12, 24	wks 36, 52, 76	X			O	
Serum chemistry	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X	X	X	O	
LFTs[j]					wk 2	wks 6, 16					O	
Renal ultrasound[k]	X							X			O	
Serum lipid panel[l]	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O	
Serum iron, ferritin, TIBC, TSAT	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
HbA1c	X			X		wk 12	wks 28, 36, 44, 60, 84	X		X	O	
Vitamin B_{12}, folate	X											
HIV immunoassay, HBsAg, anti-HCV antibody	X											

Serum pregnancy test[m]	X					wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O	
Table continued on next page												
eGFR[n]	X			X		wk 20	wks 36, 52, 68, 84	X		X	O	
hs-CRP				X		wks 4, 12, 20	wks 36, 52	X		X		
Archival serum samples for biomarkers[o]				X		wks 4, 12, 20	wks 52, 76	X		X		
Blood sample for PK[p]					wks 2 to 8							
Genotyping[q]					O							
QoL questionnaires[r]				X		wks 8, 12	wks 28, 36, 52, 76	X			O	
Urinary testing[s]				X		wks 12, 24	wks 36, 52, 64, 76, 88	X			O	
Archival urine samples for biomarkers				X		wk 24	wks 52, 76	X				
Study drug dispensing[t]				←	———	———	→				O	
Dose adjustment review[u]					X	X	X				O	
Hospitalization recording[v]	X	X	X	←	———	———	———	———	———	———	———	→ X
AE recording	X	X	X	←	———	———	———	———	———	———	———	→
Concomitant medication, procedure and non-drug therapy recording	X	X	X	←	———	———	———	———	———	———	———	→
Vital status, SAEs, cardiovascular and thromboembolic AEs[v]												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.

Note: see Appendix 12.3 Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0.

Note: see Appendix 12.4 Instructions for Subjects Requiring Dialysis.

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

[b] All study assessments are to be performed prior to first study drug administration.

[c] In case of premature treatment discontinuation or withdrawal during the treatment period, subjects will complete the EOT and EOS visits. Thereafter, subjects who have taken at least one dose of study drug will continue to be followed up at a 6-monthly frequency for vital status, SAEs, 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.

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

[e] Height measurement only required at first screening visit.

Footnotes continued on next page

[f] Blood pressure and heart rate measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period that measurements should occur prior to study drug administration if study medication is taken on same day of visit; except for visits where subjects are instructed to take study medication at home for PK sampling purpose. For subjects requiring dialysis, BP and heart rate will be recorded prior to and after dialysis (hemodialysis [HD]/hemodiafiltration [HDF] subjects only).

[g] Respiratory rate measured singly during screening period and all other visits. It is recommended during the treatment period that measurement should occur prior to study drug administration except for visits where subjects are instructed to take study medication at home for PK sampling purposes. For subjects requiring dialysis, respiratory rate will be recorded prior to dialysis (HD/HDF subjects only).

[h] Separate Hemoglobin should be collected at all the visits where Complete Blood Count (CBC) is not collected (i.e., Hb at weeks 6, 10 until the end of the study).

[i] HemoCue assessment is done on the blood sample that is collected for Hb analysis for the central laboratory.

[j] In addition to LFTs collected as part of Serum Chemistry, LFTs will separately be collected at the indicated weeks.

[k] Renal ultrasound examination within 12 weeks prior to randomization. Not required if results of a previous renal ultrasound (or other renal imaging modality such as CT scan or MRI) within 12 weeks prior to randomization is available and ruling out renal cell carcinoma. If other imaging modality, a conclusive report on the kidney should be available.

[l] Fasting whenever possible.

[m] Collect from female subjects of childbearing potential only.

[n] Using Modification of Diet in Renal Disease (MDRD) formula; calculated by the central laboratory.

[o] At day 1, week 20, 52, 76, and EOT, two equal volume samples should be collected.

[p] Sampling roxadustat will be done at 6 time points over 1 to 3 visits between weeks 2 and 8. See Section 5.6. At each pharmacokinetic visit, one additional sample will be collected for determination of Alpha 1-Acid Glycoprotein (α1-AGP) and albumin concentration.

[q] Optional assessment. A separate informed consent form must be signed before genotyping sample is collected. Sample collection can be done at any timepoint thought the treatment period of the study.

[r] Including SF-36, FACT-An, EQ-5D 5L, PGIC and WPAI:ANS. PGIC will not be performed on day 1. Questionnaires to be completed by the subject preferably prior to any study assessments. When subjects need dialysis therapy, Quality of Life (QoL) questionnaires will be completed on the day of first dialysis (preferably before the dialysis is started), 4 weeks later and 12 weeks later.

[s] Ideally, the sample should be from the first morning void. Urinary testing includes qualitative testing with dipstick testing (for protein, pH, glucose) and quantitative assessment of albumin and creatinine for calculation of albumin/creatinine ratio.

[t] Dosing of darbepoetin alfa per EU SmPC.

[u] Subjects randomized to roxadustat: dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (wks 4, 8, 12 etc), except in the event 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 visit.

[v] Telephone or in-person follow-up call with subject.

IS AMENDED TO:

Assessments	**Screening Period**		**Treatment Period** (Correction Period and Maintenance Period)					**Follow-up Period**		**Unscheduled Visits**	**Post study Follow-up [c]**
Visit / Week	**Up to ~~2~~ 6 weeks [a]**		**Day 1[b]**	**Weekly (wks 1 - 2) ± 2 days**	**Every 2 Weeks (wks 4 - 24) ± 2 days**	**Every 4 Weeks (wks 28 - 100) ± 3 days**	**EOT [c] (wk 104) ± 3 days**	**EOT[c] + 2 wks ± 3 days**	**EOS [c] (EOT + 4 wks) ± 3 days**		**Every 6 months until projected wk 108**
	S1	**S2 ~~S3~~**									
Written informed consent	X										
Randomization			X								
Eligibility criteria	X		X								
Demographics	X										
Medical history	X										
Physical examination	X		X		wks 12[d], 24[d]	wks 36[d], 52[d], 76[d]	X		X[d]	O[d]	
Height[e], weight	X		X		wks 12, 24	wks 36, 52, 76	X		X	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	X	wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
Hemoglobin[h]		X[i]			X	X		X		**~~X~~ O[il]**	
HemoCue assessment[ji]			X	X	X	X				**~~X~~O**	
Reticulocyte count and Hb in reticulocytes (CHr)	X		X	X	wks 4, 6, 8, 12, 16, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
12-lead ECG	X		X		wks 12, 24	wks 36, 52, 76	X			O	
Serum chemistry	X		X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X	X	X	O	
LFTs[kj]				wk 2	wks 6, 16					O	
Renal ultrasound[lk]	X						**~~X~~**			O	
Serum lipid panel[mi]	X		X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O	
Serum iron, ferritin, TIBC, TSAT	X		X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 60, 68, 76, 84, 92, 100	X		X	O	
HbA1c	X		X		wk 12	wks 28, 36, 44, 60, 84	X		X	O	
Vitamin B_{12}, folate	X										
HIV immunoassay, HBsAg, anti-HCV antibody	X										
Serum pregnancy test[nm]	X				wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O	

Table continued on next page

Assessments	Screening Period		Treatment Period (Correction Period and Maintenance Period)					Follow-up Period		Unscheduled Visits	Post study Follow-up [c]
Visit / Week	Up to ~~2~~ 6 weeks [a]		Day 1 [b]	Weekly (wks 1 - 2) ± 2 days	Every 2 Weeks (wks 4 - 24) ± 2 days	Every 4 Weeks (wks 28 - 100) ± 3 days	EOT [c] (wk 104) ± 3 days	EOT [c] + 2 wks ± 3 days	EOS [c] (EOT + 4 wks) ± 3 days		Every 6 months until projected wk 108
	S1	S2 ~~S3~~									
eGFR[on]	X		X		wk 20	wks 36, 52, 68, 84	X		X	O	
hs-CRP			X		wks 4, 12, 20	wks 36, 52	X		X		
Archival serum samples for biomarkers[po]			X		wks 4, 12, 20	wks 52, 76	~~X~~		~~X~~		
Blood sample for PK[qp]				wks 2 to 8							
Genotyping[rq]				O							
QoL questionnaires[sr]			X		wks 8, 12	wks 28, 36, 52, 76	X			O	
Urinary testing[ts]			X		wks 12, 24	wks 36, 52, 64, 76, 88	X			O	
Archival urine samples for biomarkers			X		wk 24	wks 52, 76	~~X~~				
Study drug dispensing[ut]			←	—	—	—	→			O	
Dose adjustment review[vu]				X	X	X				O	
Hospitalization recording[wv]	X	X	←	—	—	—	—	—	→		X
AE recording	X	X	←	—	—	—	—	—	→		
Concomitant medication, procedure and non-drug therapy recording	X	X	←	—	—	—	—	—	→		
Vital status, SAEs, cardiovascular and thromboembolic AEs[wv]											X

S1/S2~~/S3~~ = Screening visit 1~~,~~**and** 2 ~~and 3~~; EOT = End of Treatment; EOS = End of Study; Wk(s) = Week(s); X = mandatory test/assessment; O = optional test/assessment.

~~Note: see Appendix 12.3 Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0.~~

Note: see Appendix 12.4 Instructions for Subjects Requiring Dialysis.

[a] **a** ~~Due to t~~**T**he requirement of **a** 4-day separation between the screening Hb values, **defines the minimum duration of** the screening period. ~~will last a minimum of 2 weeks but is allowed to be a~~ **The** maximum **duration of the screening period is** 6 weeks. Sites are recommended to schedule the ~~three~~ **two** screening visits in the shortest time span possible.

[b] **b** All study assessments are to be performed prior to first study drug administration.

[c] **c** In case of premature treatment discontinuation or withdrawal during the treatment period, subjects will complete the EOT **visits (EOT visit and EOT + 2 weeks visit)** and EOS visit~~s~~. Thereafter, subjects who have taken at least one dose of study drug will continue to be followed up at a 6-monthly frequency for vital status, SAEs, 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.

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

[e] **e** Height measurement only required at first screening visit.

Footnotes continued on next page

[f] **f** Blood pressure and heart rate measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period that measurements should occur prior to study drug administration if study medication is taken on same day of visit; except for visits where subjects are instructed to take study medication at home for PK sampling purpose. For subjects requiring dialysis, BP and heart rate will be recorded prior to and after dialysis (hemodialysis [HD]/hemodiafiltration [HDF] subjects only).

[g] **g** Respiratory rate measured singly during screening period and all other visits. It is recommended during the treatment period that measurement should occur prior to study drug administration except for visits where subjects are instructed to take study medication at home for PK sampling purposes. For subjects requiring dialysis, respiratory rate will be recorded prior to dialysis (HD/HDF subjects only).

[h] **h** Separate Hemoglobin should be collected at all the visits where Complete Blood Count (CBC) is not collected (i.e., Hb at weeks 6, 10 until the end of the study).

i An additional (third) Hb value may be collected if necessary. Only for subjects who are switched from protocol version 2 to 3 during (re) screening can a fourth Hb value be collected, as was applicable under protocol version 2.

i1 If during an unscheduled visit, Hb needs to be assessed, this should always be done with the HemoCue AND a central laboratory Hb assessment.

[i] **j If during an unscheduled visit Hb needs to be assessed, this should always be done with the HemoCue AND a central laboratory Hb assessment. The HemoCue assessment should be** ~~is~~ done on the blood sample that is collected for Hb analysis for the central laboratory.

[j] **k** In addition to LFTs collected as part of Serum Chemistry, LFTs will separately be collected at the indicated weeks.

[k] **l** Renal ultrasound examination within 12 weeks prior to randomization. Not required if results of a previous renal ultrasound (or other renal imaging modality such as CT scan or MRI) within 12 weeks prior to randomization is available and ruling out renal cell carcinoma. If other imaging modality, a conclusive report on the kidney should be available.

[l] **m** Fasting whenever possible.

[m] **n** Collect from female subjects of childbearing potential only.

[n] **o** Using Modification of Diet in Renal Disease (MDRD) formula; calculated by the central laboratory.

[o] **p** At day 1, week 20, 52, **and** 76~~, and EOT~~, two equal volume samples should be collected.

[p] **q** Sampling roxadustat will be done at 6 time points over 1 to 3 visits between weeks 2 and 8. See Section 5.6. At each pharmacokinetic visit, one additional sample will be collected for determination of Alpha 1-Acid Glycoprotein (α1-AGP) and albumin concentration.

[q] **r** Optional assessment for **subjects treated with roxadustat**. A separate informed consent form must be signed before genotyping sample is collected. Sample collection can be done at any timepoint th**r**ough**ou**t the treatment period of the study.

[r] **s** Including SF-36, FACT-An, EQ-5D 5L, PGIC and WPAI:ANS. PGIC will not be performed on day 1. Questionnaires to be completed by the subject preferably prior to any study assessments. When subjects need dialysis therapy, Quality of Life (QoL) questionnaires will be completed on the day of first dialysis (preferably before the dialysis is started), 4 weeks later and 12 weeks later.

[s] **t** Ideally, the sample should be from the first morning void. Urinary testing includes qualitative testing with dipstick testing (for protein, pH, glucose) and quantitative assessment of albumin and creatinine for calculation of albumin/creatinine ratio.

[t] **u** Dosing of darbepoetin alfa per EU SmPC.

[u] **v** Subjects randomized to roxadustat: dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (wks 4, 8, 12 etc), except in the event 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 visit.

[v] **w** Telephone or in-person follow-up call with subject.

1 Introduction

1.3.1 Roxadustat

WAS:

Five pancreatitis events were noted during the roxadustat clinical development program, the majority of which have been associated with gallstones or biliary sludge; one of which was due to a pancreatic duct stricture, and another case had multiple risk factors for pancreatitis.

IS AMENDED TO:

Five pancreatitis events were noted during the roxadustat **phase 2** clinical development program, the majority of which have been associated with gallstones or biliary sludge; one of which was due to a pancreatic duct stricture, and another case had multiple risk factors for pancreatitis.

5 Treatments and Evaluation

Section 5.1.1 Dose/Dose Regimen and Administration Period

WAS:

All subjects will administer study drug doses TIW and study drug doses must be at least 2 days apart (e.g., Monday Wednesday, Friday) and no more than 4 days apart.

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

The roxadustat treated subjects that have entered the study under protocol v1.0, upon signing the informed consent for the amendment 1, will have their dose frequency (on QW and BIW under protocol v1.0) and dose amount adjusted according to the instructions in Appendix 12.3. Subjects randomized to roxadustat QW or BIW who do not agree to change to TIW, should be discontinued from the study treatment and continue in the post study follow-up period.

IS AMENDED TO:

All subjects will administer study drug doses TIW ~~and study drug doses must be at least 2 days apart (e.g., Monday Wednesday, Friday)~~. **The period between two roxadustat administrations should be at least 36 hrs** and no more than 4 days apart.

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

The roxadustat treated subjects that ~~have~~ **had** entered the study under protocol v1.0, upon signing the informed consent for the amendment 1, ~~will have~~ **had** their dose frequency (on QW and BIW under protocol v1.0) and dose amount adjusted according to the instructions in Appendix 12.3. ~~Subjects randomized to roxadustat QW or BIW who do not agree to change to TIW, should be discontinued from the study treatment and continue in the post study follow-up period.~~

5 Treatments and Evaluation *5.1.2.2 Dose Adjustment Rules for Subjects receiving Darbepoetin alfa*
DELETED: Table 6: Dose Adjustment Rules for Darbepoetin Alfa

5 Treatments and Evaluation *5.1.4 Treatment Compliance*
ADDED:
In case of self-administration after 36 weeks of treatment, the empty packages of darbepoetin alfa should be returned by the subject to the site.

5 Treatments and Evaluation *5.4 1.1 Blood Pressure*
WAS:
Blood pressure (systolic and diastolic) will be measured singly on the three visits during the screening period, and in triplicate with a least two minute intervals for all other visits. An average of the SBP and DBP will be calculated from the 2nd and 3rd readings automatically within the eCRF. The same arm should be used consistently for measurements throughout the study.
IS AMENDED TO:
Blood pressure (systolic and diastolic) will be measured singly on the ~~three~~ **2** visits during the screening period, and in triplicate with a least two minute intervals for all other visits. ~~An average of the SBP and DBP will be calculated from the 2nd and 3rd readings automatically within the eCRF.~~ The same arm should be used consistently for measurements throughout the study.

5 Treatments and Evaluation *5.4 1.2 Heart Rate*
WAS:
HR will be measured singly on the three visits during the screening period, and in triplicate with at least two minute intervals for all other visits. All values will be reported in the eCRF. An average will be calculated from the 2nd and 3rd readings automatically within the eCRF.
IS AMENDED TO:
HR will be measured singly on the ~~three~~ **2** visits during the screening period, and in triplicate with at least two minute intervals for all other visits. All values will be reported in the eCRF. ~~An average will be calculated from the 2nd and 3rd readings automatically within the eCRF.~~

5 Treatments and Evaluation *5.5.2 Definition of Serious Adverse Events (SAEs)*
WAS:
All of the events of interest noted above should be recorded on a SAE worksheet and within the timelines of reporting SAEs, thus within 24 hours of becoming aware of this event. 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.
IS AMENDED TO:
All of the events of interest noted above should be recorded on ~~a~~ **the** SAE **and/or Special Situation** worksheet and within the timelines of reporting SAEs, thus within 24 hours 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.

5 Treatments and Evaluation *5.5.5 Reporting of Serious Adverse Events (SAEs)*
WAS:
In the case of a Serious Adverse Event (SAE), the investigator must contact his/her respective delegated CRO (INC Drug Safety or Medpace Clinical Safety) by telephone or fax immediately (within 24 hours of awareness). The investigator should complete and submit a SAE worksheet containing all information that is required by the Regulatory Authorities to the delegated CRO by fax or email immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone. The SAE worksheet should be sent to the delegated CRO that is responsible for the investigator's country: INC Drug Safety and as specified in the Investigator Site File: Email: INCDrugSafety@INCResearch.com Fax: toll-free numbers will be provided for each country; the specific fax number can be found on the SAE form fax cover sheet Tel: +49 89 99 39 13 198 Medpace Clinical Safety and as specified in the Investigator Site File: Medpace SAE hotline – USA: Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999 Fax: +1-866-336-5320 or +1-513-579-0444 Email: medpace-safetynotification@medpace.com Or Medpace SAE hotline – Europe: Telephone: +49 89 89 55 718 44 Fax: +49 89 89 55 718 104 Email: medpace-safetynotification@medpace.com

IS AMENDED TO:
In the case of a ~~S~~**s**erious ~~A~~**a**dverse ~~E~~**e**vent (SAE), the investigator must contact his/her respective delegated CRO (INC Drug Safety or ~~Medpace Clinical Safety~~ **or other CRO as specified in the Investigator Site File**) by telephone or fax immediately (within 24 hours of awareness). The investigator should complete and submit a**n** SAE worksheet containing all information that is required by the Regulatory Authorities to the delegated CRO by fax or email immediately (within 24 hours of awareness). If the faxing **or e-mailing** of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone. The SAE worksheet should be sent to the delegated CRO that is responsible for the investigator's country: INC Drug Safety ~~and~~ **or another CRO** as specified in the Investigator Site File: Email: INCDrugSafety@INCResearch.com Fax: toll-free numbers will be provided for each country; the specific fax number can be found on the SAE form fax cover sheet Tel: +49 89 99 39 13 198 ~~Medpace Clinical Safety and as specified in the Investigator Site File:~~ ~~Medpace SAE hotline – USA:~~ ~~Telephone: +1 800 730 5779, ext. 2999 or +1 513 579 9911, ext. 2999~~ ~~Fax: +1 866 336 5320 or +1 513 579 0444~~ ~~Email: medpace-safetynotification@medpace.com~~ ~~Or~~ ~~Medpace SAE hotline – Europe:~~ ~~Telephone: +49 89 89 55 718 44~~ ~~Fax: +49 89 89 55 718 104~~ ~~Email: medpace-safetynotification@medpace.com~~

5 Treatments and Evaluation *5.8 Total Amount of Blood*
WAS:
The total amount of blood to be collected per subject during the study, based on the subject's screening period, the 104 weeks' treatment period and the follow-up period and allowing full re-screening and unscheduled visits is estimated to be approximately 440 mL.
IS AMENDED TO:
The total amount of blood to be collected per subject during the study, based on the subject's screening period, the 104 weeks' treatment period and the follow-up period and allowing full re-screening and unscheduled visits is estimated to be approximately 4**46**0 mL.

7 Statistical Methodology
7.4.2.2 Secondary Analyses

DELETED:

~~In addition, this variable will be analyzed using the subset of subjects who have reached Hb ≥11.0 g/dL prior to week 28.~~

11 References

WAS:

EMEA. Aranesp – Procedural steps taken and scientific information after the authorization http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000332/WC500026145.pdf

EMEA. Aranesp European Public Assessment Report [EPAR] 2004; EMEA. Aranesp Procedural steps taken and scientific information after the authorisation. Changes made after 2003).

EMEA, EPAR Aranesp 2004

IS AMENDED TO:

EMEA. Aranesp –Procedural steps taken and scientific information after the authori~~z~~sation. **Changes made after 2003**. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000332/WC500026145.pdf**.**

EMEA. Aranesp European Public Assessment Report [EPAR]**.** 2004**.**~~; EMEA. Aranesp Procedural steps taken and scientific information after the authorisation. Changes made after 2003).~~

~~EMEA, EPAR Aranesp 2004~~

12 Appendices
12.4 Instructions for Subjects Requiring Dialysis

WAS:

Subjects who initiate temporary or permanent dialysis treatment are allowed to continue in the study. All modes of dialysis, i.e., hemodialysis (HD), hemodiafiltration (HDF) and peritoneal dialysis (PD), are allowed.

12.4.1 Dosing

- Subjects should continue with the same dose and dose frequency of study drug as they were on prior to dialysis initiation.
- For HD/HDF subjects, it is recommended that study drug is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day) to avoid potential bias on certain study assessments.

12.4.2 Dose Adjustment

- The dose adjustment rules remain unchanged (see Section 5.1.2.1).
- The maximum allowed dose in subjects on permanent dialysis is 3.0 mg/kg (based on dry weight in HD subjects and weight minus abdominal fluid based on last filling in PD subjects) or 400 mg per administration, whichever is lower.

12.4.3 ESA Rescue Therapy

If roxadustat subjects meet the criteria for ESA rescue therapy while on dialysis, darbepoetin alfa will be administered IV or SC according to its Package Insert or SmPC for dialysis subjects. The subject must be discontinued from study treatment if the subject requires a second course of rescue darbepoetin alfa.

IS AMENDED TO:

Subjects who initiate temporary or permanent dialysis treatment are allowed to continue in the study. All modes of dialysis, i.e., hemodialysis (HD), hemodiafiltration (HDF) and peritoneal dialysis (PD)~~,~~ are allowed.

12.4.1 Dosing

- Subjects should continue with the same dose and dose frequency of study drug as they were on prior to dialysis initiation.
- For HD/HDF subjects it is recommended that study drug is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day) to avoid potential bias on certain study assessments.
- **For subjects treated with darbepoetin, the route of administration of darbepoetin is according to local standard of care for dialysis patients.**

12.4.2 Dose Adjustment

- The dose adjustment rules remain unchanged (see Section 5.1.2.1).
- The maximum allowed dose in subjects on permanent dialysis is 3.0 mg/kg (based on ~~dry weight~~ **post-dialysis weight** in HD subjects and weight minus abdominal fluid based on last filling in PD subjects) or 400 mg per administration, whichever is lower.

12.4.3 ESA Rescue Therapy

If roxadustat subjects meet the criteria for ESA rescue therapy while on dialysis, darbepoetin alfa will be administered IV or SC according to its Package Insert or SmPC for dialysis subjects. The subject must be discontinued from study treatment if the subject requires a second course of rescue darbepoetin alfa.

12.4.4 Supplemental Iron Use

Iron supplementation rules are unchanged in subjects starting dialysis who are randomized to roxadustat (see Section 5.1.3.2.1). In subjects randomized to darbepoetin, IV iron supplementation will be given according to standard of care.

12 Appendices

12.10 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease 2012 (KDIGO 2012)

DELETED:

~~12.10 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease 2012 (KDIGO 2012)~~

~~Please refer for the KDIGO 2012 guidelines to:~~
~~VOLUME 2 | ISSUE 4 | AUGUST 2 2012~~
~~http://www.kidney-international.org~~

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