A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

ISN/Protocol 1517-CL-0608

ClinicalTrials.gov Identifier: NCT01887600

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Sponsor: Astellas Pharma Europe B.V.

Sylviusweg 62

2333 BE Leiden

The Netherlands

A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for 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-0608

Version 2.1

Incorporating Non-substantial Amendment 1 [See Attachment 1]

21 June 2016

EudraCT No: 2012-005180-27

Sponsor:

Astellas Pharma Europe B.V.

Sylviusweg 62

2333 BE Leiden

The Netherlands

Protocol History:
Version 1.0 [11 Dec 2012]
Version 2.0 Incorporating Substantial Amendment 1 [17 Dec 2014]

[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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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. INVESTIGATOR'S SIGNATURE

A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

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Version 2.1/ Incorporating Non-substantial Amendment 1

21 June 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

SAE Fax number	**See SAE form**
Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	**Astellas Pharma Europe B.V.** [redacted]
Medical Monitor:	[redacted] Astellas Pharma Europe B.V. [redacted]
Clinical Research Contact:	[redacted] Astellas Pharma Europe B.V. [redacted]

III. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANOVA	Analysis of variance
AnS	Anemia Subscale
anti-HCV Ab	Anti-hepatitis C virus antibody
APEB	Astellas Pharma Europe BV
ASP1517	= FG-4592 (codename of investigational product) or roxadustat (international nonproprietary name)
AST	Aspartate Aminotransferase (GOT)
AT	Aminotransferases
BL	Baseline
BP	Blood Pressure
CA	Competent Authority
CBC	Complete Blood Count
CHr	Hemoglobin content of reticulocytes
CI	Confidence Interval
CKD	Chronic Kidney Disease
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
Cr	Creatinine
CRF	Case Report Form
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
EOS	End of Study
EPO	Erythropoietin
EQ-5D 5L	Health Related Quality of Life Questionnaire consisting of Five Levels
ESA	Erythropoiesis-Stimulating Agent
ESRD	End Stage Renal Disease
EOT	End of Treatment
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full Analysis Set
FG-4592	= ASP1517 (codename of investigational product) or roxadustat (international nonproprietary name)
GCP	Good Clinical Practice

Abbreviations	Description of abbreviations
GDS	Global Data Science
Hb	Hemoglobin
HbA1c	Hemoglobin A1c Glycated hemoglobin
HBsAg	Hepatitis B Surface Antigen
HD	Hemodialysis
HDF	Hemodiafiltration
HDL	High density lipoprotein
HIF	Hypoxia-inducible Factor
HIF-PH	Prolyl Hydroxylase
HIF-PHI	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 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IERC	Independent Event Review Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Study Number
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low density lipoprotein
LA-CRF	Liver Abnormality Case Report Form
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MACE	Major cardiovascular adverse events: myocardial infarction, stroke, death from all causes
MACE+	Myocardial infarction, stroke, death from all causes, chronic heart failure requiring hospitalization, unstable angina requiring hospitalization
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
MMRM	Mixed Model of Repeated Measures
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NDD-CKD	Non dialysis-dependent chronic kidney disease
PF	Physical Functioning
PGIC	Patients' Global Impression of Change
PKAS	Pharmacokinetic Analysis Set
PPD	Population pharmacodynamic
PPK	Population pharmacokinetics
PPK/PD	Population pharmacokinetic/pharmacodynamic
PPS	Per Protocol Set

Abbreviations	Description of abbreviations
PWB	Physical Wellbeing
QoL	Quality of Life
QTc	QT Interval corrected for heart rate
RBC	Red Blood Cell
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SF-36	Short Form 36
SMD	Study Medication Diary
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SST	Serum Separator Tube
sTfR	Soluble Transferrin Receptor
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWB	Social Wellbeing
$t_{½}$	Apparent Terminal Elimination Half-life
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TIBC	Total Iron-Binding Capacity
TIW	Thrice Weekly
TSAT	Transferrin Saturation (also known as FeSAT, iron saturation)
ULN	Upper Limit of Normal
USRDS	United States Renal Data System
VAS	Visual Analogue Scale
VT	Vitality
WBC	White Blood Cell
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 the study drug, roxadustat or placebo, or who has undergone study procedures and which does not necessarily have a causal relationship with this treatment. AE collection starts after obtaining signed informed consent and continues until the End of Study visit. AEs will not be collected during the period between first screen where subject has failed screening and first rescreening visit.
Baseline	1) Observed values/findings which are regarded as calibrated zero status in the present study; 2) Time when 'Baseline' is observed.
Baseline Hemoglobin (Hb) value	Mean of 4 Hb values: the last 3 Hb values during screening and the Hb value at the day of randomization, all assessed by the central laboratory.
Discontinuation	The act of concluding participation in either the study treatment or the study, prior to completion of all protocol-required elements, in a trial by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard.
Enroll	To register or enter into a clinical trial; transitive and intransitive. Informed consent precedes enrollment, which precedes or is contemporaneous with randomization.
Extended treatment period	Period of time that patient is treated from end of primary treatment period (52 weeks) up to 104 weeks
Hb response	• Hb ≥ 11.0 g/dL and a Hb increase from baseline (BL) by ≥ 1.0 g/dL in any subject with BL Hb> 8.0 g/dL, OR • an increase from BL by ≥ 2.0 g/dL in any subject with BL Hb ≤ 8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., red blood cell [RBC] transfusion, erythropoiesis-stimulating agent (ESA), or IV iron) prior to Hb response.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or placebo (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or placebo.
Post study follow-up	Period of time from end of study (EOS) visit to projected week 108 or until the last subject randomized reaches EOS, whichever comes first. This period is only applicable to subjects who prematurely discontinued treatment. These subjects will be followed up on a 6-monthly frequency for vital status, SAEs, cardiovascular and thromboembolic AEs.

Terms	Definition of terms
Primary treatment period	Period of time that subject is treated from first treatment up to 52 weeks
Randomization	Action to allocate a subject to the treatment group or treatment cohort. Subjects will be randomized to roxadustat or placebo at day 1.
Rescreening	Process of repeating screening. If a subject fails screening they may be re-screened once if deemed appropriate; all screening procedures will be repeated. Renal ultrasound only to be repeated if not within 12 weeks prior to randomization.
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, 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"
Screening failure	Screened subject, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive randomized treatment, or decided not to participate anymore (withdrew consent) prior to the treatment period.
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, either as a recipient of the investigational product(s) or as a control.
Treatment Period	Period of time from first study drug intake until last study drug intake. Minimum 52 weeks to a maximum of 104 weeks or until the last subject randomized to treatment has completed 40 weeks of treatment (or at the forecasted week 40 date if this subject discontinues treatment early)
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Title of Study	A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis [ISN/Protocol 1571-CL-0608]
Planned Study Period	From 1Q2013 to 4Q2017
Study Objective(s)	The primary objective of this study is to evaluate the efficacy of roxadustat in the treatment of anemia in non-dialysis Chronic Kidney Disease (CKD) subjects. The secondary objectives in this study are to: • Evaluate the safety of roxadustat in the treatment of anemia in non-dialysis CKD subjects. • Evaluate health-related quality of life (HRQoL) benefit of treatment with roxadustat in subjects with CKD anemia. • Evaluate the need for anemia rescue therapy with roxadustat treatment in subjects with CKD anemia: red blood cell (RBC) transfusion, or erythropoiesis-stimulating agent (ESA), or IV iron.
Planned Total Number of Study Centers and Location	Approximately 200 centers globally
Design and Methodology	This is a phase 3, multi-center, randomized, double-blind, placebo-controlled study. The study population consists of subjects with CKD as defined by CKD stages 3, 4, and 5 (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) who are anemic and not receiving dialysis. The study will consist of 3 study periods as follows: • Screening period: up to 6 weeks. • Treatment period: minimum 52 weeks (primary treatment period) up to a maximum of 104 weeks (extended treatment period) or until the last subject randomized to treatment has completed 40 weeks of treatment (or at the forecasted week 40 date if this subject discontinues treatment early). Treatment period for last patient randomized is 52 weeks. • Post-Treatment Follow-Up period: 4 weeks. Subjects that have discontinued treatment prior to their projected week 104 will continue to be followed for vital status and serious adverse events (SAEs), cardiovascular and thromboembolic adverse events (AEs) in post study follow up. Subjects are randomized to 1 of 2 treatment arms. The randomization will result in a 2:1 ratio of subjects receiving roxadustat or placebo, respectively. Study treatment administration is implemented in a double-blind, placebo controlled manner. Neither the subjects nor the investigators and their staff can distinguish the roxadustat tablets from the matching placebo tablets. Both will be identical in appearance, packaging, and labeling in order to maintain the blind. Proper randomization of treatments and preserving the treatment blind are maintained by Interactive Response Technology (IRT). The initial study drug dose (per dose amount) is based on the tiered, weight-based dosing scheme shown in Table 1.

Table 1 Initial Study Drug (Roxadustat/Placebo) Dosing

Study Drug (Dose Frequency)	**Weight** (≥ 45 to ≤ 70 kg)	**Weight** (> 70 to ≤ 160 kg)
Roxadustat/ Placebo (TIW)	70 mg	100 mg

Study drug will be dosed thrice weekly (TIW) during the treatment period. Initially subjects will be dosed for hemoglobin (Hb) correction, until subjects achieve central Hb values of ≥ 11.0 g/dL and Hb increase from BL ≥ 1.0 g/dL at 2 consecutive study visits, separated by at least 5 days (correction period).

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 4 weeks until end of treatment (EOT).

Subjects will be treated with roxadustat or placebo for at least 52 weeks and will continue taking the double-blind treatment as they were assigned until a maximum of 104 weeks. Depending on the rate of recruitment, the maximum treatment period will be 104 weeks for subjects who were randomized early into the study.

- The last subject randomized will stop treatment at the minimum of 52 weeks.
- When the last subject randomized reaches 40 weeks of treatment (or the forecasted week 40 date, if the last subject randomized discontinues treatment early)
    - Subjects beyond 52 weeks treatment will stop treatment at this point.
    - Subjects that have not yet reached 52 weeks treatment will continue until they reach 52 weeks treatment

Correction Period

The aim of the Correction period is to correct Hb levels to ≥ 11.0 g/dL with an increase from BL ≥ 1.0 g/dL at 2 consecutive visits. This period is variable in length for each subject, depending on when a subject achieves central Hb ≥ 11.0 g/dL and an Hb increase from BL ≥ 1.0 g/dL as measured by Hb values at 2 consecutive study visits separated by at least 5 days. Once 2 consecutive Hb values reach 11.0 g/dL or higher, the subject 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 Hb 10.0 g/dL and 12.0 g/dL.

Dose Adjustments

All dose adjustments will follow pre-specified dose adjustment rules, see Table 2, and are made based on Hb values using the HemoCue® device, a point-of-care device.

Table 2 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 2, the next dose adjustment review is 4 weeks after that visit.
- Dose increases by 1 dose step (↑) and reductions by 1 dose step (↓) are pre-set per the dose steps.
- The dose steps 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 BL 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. This should be discussed with the Medical Monitor and documented in the source documentation.

At any time when Hb ≥ 13.0 g/dL

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

	Dose Adjustment for Excessive Hematopoiesis At any time during the Treatment Period: • If Hb increases by > 2.0 g/dL within 4 weeks, the dose should be reduced by 1 dose step **Note**: Only 1 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. **Follow up Period** After the Treatment Period, subjects proceed to the 4-week Post-Treatment Follow-up period. **Post Study Follow-up** Subjects that have discontinued treatment prior to their projected week 104 will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the EOS visit. Thereafter, these subjects will continue to be followed up on a 6-monthly frequency for vital status and SAEs, cardiovascular and thromboembolic AEs until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent withdrawn. **Data Safety Monitoring Board/Independent Event Review Committee** A Data Safety Monitoring Board (DSMB) will review pre-specified safety data periodically in collaboration with the sponsor to ensure subject safety. The DSMB will review safety data in a blinded and unblinded manner while the sponsor remains blinded. An Independent Event Review Committee (IERC) will adjudicate all pre-specified cardiovascular and cerebrovascular events in a blinded manner to ensure consistent safety assessment. Details will be specified in an IERC charter. **Population Pharmacokinetic Analysis** Blood samples for population pharmacokinetics (PPK) will be collected at 6 different time points and can be collected over 1 to 3 visits in weeks 2 to 8 of treatment.
Number of Subjects Planned	450-600 subjects will be randomized.

Selection Criteria	**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 must be 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 chronic kidney disease, with Kidney Disease Outcomes Quality Initiative (KDOQI) Stage 3, 4 or 5, not receiving 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 three most recent 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. 5. Subject has a ferritin level ≥ 30 ng/mL (≥ 67.4 pmol/L) at screening. 6. Subject has a transferrin saturation (TSAT) level ≥5% at screening. 7. Subject has a serum folate level ≥ lower limit of normal at screening. 8. Subject has a serum vitamin B_{12} level ≥ lower limit of normal at screening. 9. Subject's alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels are ≤ 3 x upper limit of normal (ULN), and total bilirubin (TBL) ≤ 1.5 x ULN. 10. Subject's body weight is 45.0 kg up to a maximum of 160.0 kg. 11. Female subject is either: • Of non-child bearing potential: • post-menopausal (defined as at least 1 year without any menses) prior to screening, or • documented surgically sterile • or if of child bearing 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 continued for 28 days after the last study treatment administration. 12. Male subject and their female spouse/partner(s) who are of childbearing potential must be using highly effective contraception starting at screening and continue throughout the study period, and for 12 weeks after final study treatment administration. * 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.

13. Subject agrees not to participate in another interventional study from the time of signing informed consent until the End of Study visit (EOS).

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 had more than one dose of IV iron within 12 weeks prior to randomization.
3. Subject has received a 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 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 have elective surgery that is expected to lead to significant blood loss 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 a 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., pulmonary embolism) within 12 weeks prior to randomization. 15. Uncontrolled hypertension in the opinion of the investigator or two or more blood pressure values of systolic BP (SBP) ≥ 160 mmHg or diastolic BP (DPB) ≥ 95 mmHg confirmed by repeat measurement within 2 weeks prior to randomization. 16. Subject has a diagnosis or suspicion (e.g., complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma on renal ultrasound within 12 weeks prior to randomization. 17. Subject has a history of malignancy, except the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps. 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 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 and retinal vein occlusion. 21. Subject has had any prior organ transplant (that has not been explanted), or a scheduled organ transplantation. 22. Subject has participated in any interventional clinical study or has been treated with any investigational drugs within 30 days or 5 half lives or limit set by national law, whichever is longer, prior to the initiation of Screening. 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. Female subject • must agree not to breastfeed starting at screening or during the study period, and continued for 28 days after the final study treatment administration. • must not donate ova starting at screening and throughout the study period and continued for 28 days after final study drug administration. 26. Male subject • must not donate sperm starting at screening and throughout the study period and for 12 weeks after final study drug administration. 27. 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.

Discontinuation Criteria	Subjects should be discontinued from study treatment for any of the following reasons: • Subject no longer consents to participate in the treatment period 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. • Subject requires a third course of ESA rescue therapy. • Subject receives an organ transplant If a subject has discontinued treatment prior to their projected week 104 the subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the EOS visit. Thereafter, this subject will continue to be followed up on a 6-monthly frequency for vital status and SAEs, cardiovascular and thromboembolic AEs until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent withdrawn. Subjects should be withdrawn from the study for any of the following reasons: • Subject no longer consents to participate in the study. • Subject is lost to follow-up despite reasonable efforts by the investigator to contact the subject. • Death of the study subject The Sponsor may decide to prematurely stop the study, e.g., for safety considerations.
Test Drug Dose: **Mode of Administration:** **Duration of Treatment:**	Roxadustat (=ASP1517 / FG-4592) Tablets for oral administration Strengths of 20, 50 and 100 mg Maximum of 104 weeks of treatment
Reference Therapy Dose: **Mode of Administration:** **Duration of Treatment:**	Placebo Tablets for oral administration matching the roxadustat tablets in appearance and size Strengths of 20, 50 and 100 mg Maximum of 104 weeks of treatment
Prohibited Medication	The intake or administration of the following previous medication is prohibited: • Any ESA within 12 weeks prior to randomization. • IV iron (more than 1 dose) within 12 weeks prior to randomization.

	• RBC transfusion within 8 weeks prior to randomization. • Iron-chelating drugs within 4 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 the initiation of Screening. Roxadustat or another HIF-PHI at any time. The following medications are prohibited during the period identified: • Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to randomization until EOS visit. • Androgens from randomization until EOS visit. • Dapsone in any dose amount or chronic use of acetaminophen (paracetamol) > 2.0 g/day from randomization until EOS visit. Any HIF-PHIother than roxadustat, as allocated by randomization, until EOS visit. Rescue therapy guidelines (Section 5.5.5) are provided to optimize standardization of the use of rescue therapy by investigators and to ensure safety of the individual study subjects. Rescue medication or procedures include RBC transfusion, ESA, and IV iron.
Efficacy	There are 2 separate regionally based primary efficacy endpoints in this study depending upon whether the data are being filed to support submission to the US FDA or to Ex-US health authorities, such as the EMA. The EU (EMA) primary efficacy endpoint is Hb response. Hb response is defined as: • Hb ≥ 11.0 g/dL and a Hb increase from BL by ≥ 1.0 g/dL in any subject with BL Hb > 8.0 g/dL, **OR** • an increase from BL by ≥ 2.0 g/dL in any subject with BL Hb ≤ 8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or IV iron) prior to Hb response. The US (FDA) primary efficacy endpoint is the change in Hb from BL to the average level during the evaluation period (defined as Week 28 until Week 52) regardless of rescue therapy. The key secondary efficacy endpoints in this study are: • Hb maintenance: 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. • Change from BL in low–density lipoprotein (LDL) cholesterol to the average value of LDL cholesterol in weeks 12-28. • Use and time to use of rescue therapy (composite of RBC transfusions, ESA use, and IV iron) in the first 24 weeks of treatment. • Change from BL in Short Form (SF)-36 Physical Functioning (PF) subscore to the average SF-36 PF subscore in weeks 12-28.

	• Change from BL in SF-36 Vitality (VT) subscore to the average SF-36 VT subscore in weeks 12-28.
	• Blood pressure effect
	  • Change from BL in Mean Arterial Pressure (MAP) to the average MAP in weeks 20-28.
	  • Occurrence, and time to occurrence of hypertension (defined as either SBP > 170 mmHg AND an increase from BL ≥ 20 mmHg or as DBP > 110 mmHg, AND an increase from BL ≥ 15 mmHg).
	Additional secondary endpoints for assessment of efficacy include endpoints for Hb correction and maintenance, hospitalizations, rescue therapy use, change in cholesterol levels, BP effect, HRQoL, hepcidin, iron, hemoglobin A1c glycated hemoglobin (HbA1c) and rate of eGFR decline.

Safety	Safety will be assessed by evaluating the following: • Occurrence of AEs, SAEs, and clinically significant changes in laboratory values from BL. • Changes from BL in vital signs, electrocardiogram (ECG) findings, and clinical laboratory values. • Various region-specific pooled analyses of pre-specified adjudicated cardiovascular and cerebrovascular events (such as major cardiovascular adverse events [MACE; i.e., myocardial infarction, stroke, death from all causes], MACE+ [i.e., MACE, hospitalization for chronic heart failure, hospitalization for unstable angina] and other events) will be conducted; these analyses will be detailed in region-specific pooled safety analysis plans.
Statistical Methods **Sample Size**	A total of 450-600 planned subjects will be randomized to receive roxadustat or placebo in a double-blind fashion in a 2:1 ratio. **EU (EMA)** Three hundred subjects for the roxadustat treatment group and 150 subjects for the placebo treatment group will provide > 95% test power to demonstrate a statistical significant difference between roxadustat and placebo in the EU (EMA) primary endpoint, assuming that the proportion of subjects with response in the roxadustat group is at least 65% and in the placebo group is at most 25%. **USA (FDA)** A sample size of 450 will have > 99% power to detect a 1.0 g/dL difference in mean Hb values between the 2 treatment groups, assuming that the common standard deviation is 1.2 g/dL using an analysis of variance (ANOVA) test with a 0.05 2-sided significance level. Most importantly, this sample size is required for a meta-analysis of pre-specified cardiovascular and cerebrovascular events pooling studies. Four hundred and fifty subjects is the minimum number of subjects that will be randomized. In case this sample size is not sufficient to achieve the required number of pre-specified cardiovascular and cerebrovascular events, then the number of randomized subjects will be increased up to 600. The justification of the required number of events for this safety endpoint will be detailed in a pooled cardiovascular safety analysis plan.

Analysis Sets	The following analysis sets are defined and will be used for the statistical analysis: • Full Analysis Set (FAS) • Per Protocol Set (PPS) • Safety Analysis Set (SAF) • Pharmacokinetic Analysis Set (PKAS).
Efficacy	**EU (EMA)** The proportion of responders in the EU (EMA) primary efficacy endpoint will be compared using a Cochran–Mantel–Haenszel (CMH) test adjusting for the stratification factors comparing pooled roxadustat to pooled placebo. The EU (EMA) primary hypothesis to be tested for the primary efficacy analysis is: H_0: Hb responder rate in the roxadustat group = Hb responder rate in the Placebo group versus H_1: Hb responder rate in the roxadustat group ≠ Hb responder rate in the Placebo group. H_0 tested at the alpha = 0.05 level of significance and will be rejected if the $P < 0.05$ from the test. The CMH adjusted odds ratio (pooled roxadustat versus pooled placebo) and its 95% confidence interval (CI) will be provided. In addition, a 95% CI will be calculated for the proportion of each roxadustat and placebo based on the exact method of Clopper-Pearson. **US (FDA)** The Hb change from BL to the average Hb of weeks 28-52 will be analyzed using a Mixed Model of Repeated Measurements (MMRM) with unstructured covariance matrix model. The model will contain terms for treatment arm, BL measurement, visit, visit x treatment arm, and other stratification factors. The primary hypothesis to be tested for the US FDA primary efficacy analysis is: H_0: Hb mean change from BL to the average level from week 28 to week 52 in the roxadustat group = Hb mean change from BL in the placebo group versus H_1: Hb mean change from BL to the average level of week 28 to week 52 in the roxadustat group ≠ Hb mean change from BL in the placebo group.

Secondary	Once the primary hypothesis has been rejected for the EU (EMA) primary endpoint, the key secondary endpoints will be tested using a fixed sequence testing procedure as follows. 1. Change from BL in Hb to the average Hb in weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period (superiority of pooled roxadustat versus pooled placebo). 2. Change from BL in LDL cholesterol to the average value of LDL cholesterol in weeks 12-28 (superiority of pooled roxadustat versus pooled placebo). 3. Use and time to use of rescue therapy within the first 24 weeks of treatment (noninferiority of pooled roxadustat versus pooled placebo). 4. Change from BL in SF-36 PF subscore to the average SF-36 PF subscore in weeks 12–28 (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subgroup with BL PF subscore < 35. 5. Change from BL in SF-36 vitality subscore to the average SF-36 VT subscore in weeks 12–28 (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subgroup with BL vitality PF subscore < 50. 6. Change from BL in MAP to the average MAP in weeks 20–28 (noninferiority of pooled roxadustat versus pooled placebo). 7. Occurrence and time to occurrence of hypertension (noninferiority of pooled roxadustat versus pooled placebo).
Safety	Safety analyses will be performed using the Safety Analysis Set (SAF). Safety parameters include AEs, laboratory parameters (with special emphasis on excessive Hb response and Liver Function Tests (LFTs), vital signs, renal ultrasound findings and ECG parameters. The number and percentage of subjects reporting Treatment-Emergent Adverse Events (TEAEs) in each treatment group will be tabulated. Descriptive statistics will be presented for laboratory, vital signs values and ECG parameters by visit and for the changes from BL to each visit. The statistical method for analysis of the CSE pooling studies will be detailed in a pooled cardiovascular safety analysis plan.
Pharmacokinetics	Population pharmacokinetic data will be generated for roxadustat from a timed blood sampling scheme. All details of the 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 (PPD) or population pharmacokinetic/pharmacodynamic (PPK/PD) modeling. When deemed necessary, data from this study may be combined with data from other studies. Results will be reported in a separate PPK/PD modeling report.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Figure 1 Flow Chart

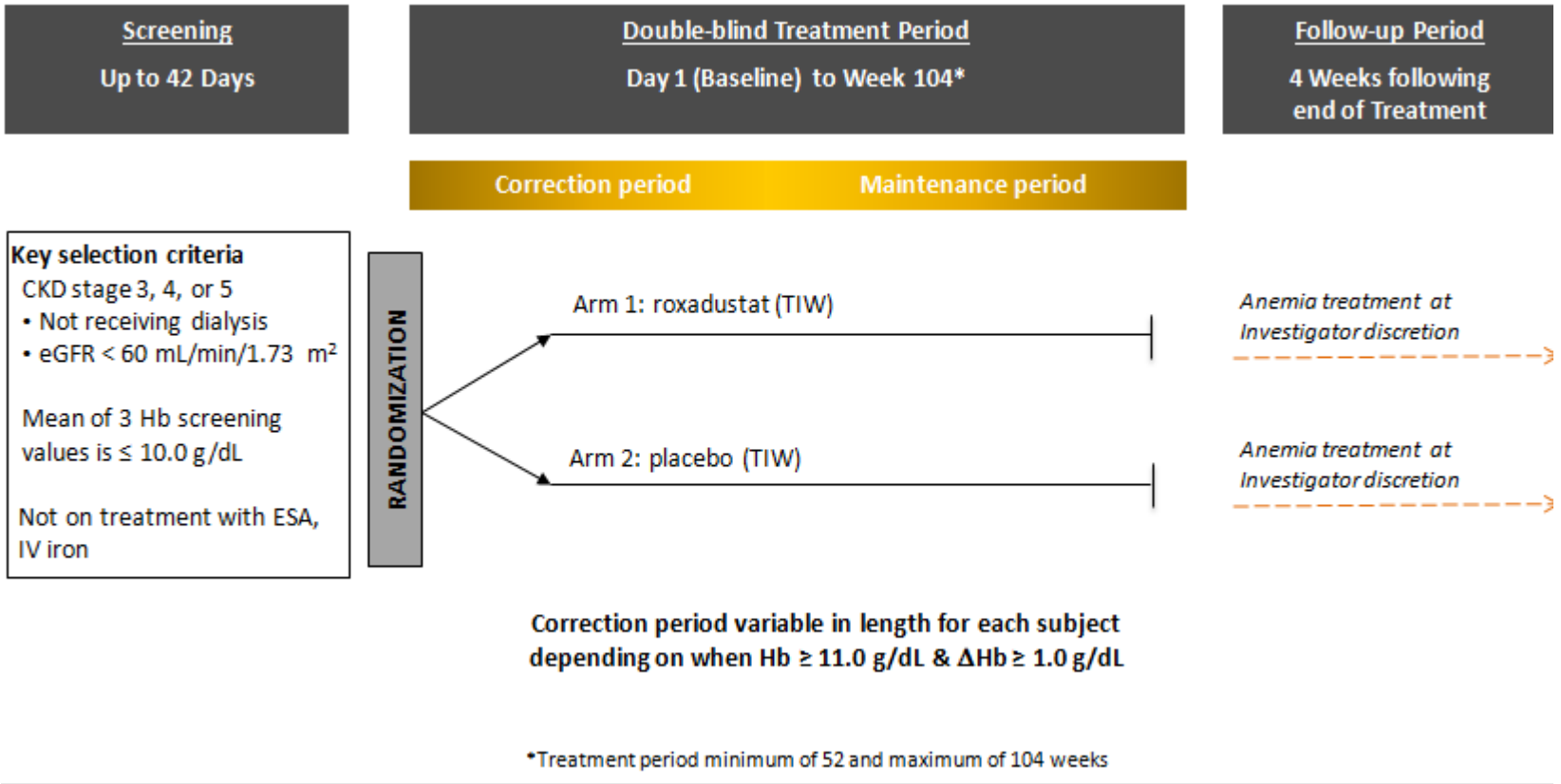


Table 1 Schedule of Assessments

Study Period:	**Screening**			**Treatment**[a]				**Follow-up**				**Post study Follow-up**
Visit / Week:	**Up to 6 Weeks** **S1**	**S2**	**S3**	**Day 1**[b]	**Weekly** (wks 1 to 2) ± 2 days	**Every 2 Weeks** (wks 4 to 24) ± 2 days	**Every 4 Weeks** (wks 28 to 100) ± 3 days	**EOT** (wk 104) ± 3 days	**EOT + 2 wks** ± 3 days	**EOS** (EOT + **4 wks**) ± 3 days	**Unscheduled Visits**	Every 6 months until projected wk 108
Written informed consent	X											
Randomization				X								
Eligibility criteria	X			X								
Demographics and medical history including tobacco use	X											
Weight	X			X		wks 12, 24	wks 36, 52, 76	X		X	O[c]	
Physical examination	X			X		wks 12[d] 24[d]	wks 36[d], 52[d], 76[d]	X		X[c]	O[c, d]	
Blood pressure[e], heart rate[e], respiratory rate[g]	X	X	X	X	X	X	X	X		X	O[c]	
CBC with WBC differential, red cell indices and platelet count	X			X	X	wks 4, 8, 12, 20	wk 28 and every following 8 wks	X		X	O[c]	
Reticulocyte count, Hemoglobin content of reticulocytes (CHr)	X			X	X	wks 4, 6, 8, 12, 16, 20	wk 28 and every following 8 wks	X		X	O[c]	
Hemoglobin[h]		X	X			X	X		X		O[c]	
HemoCue® assessment[i]				X	X	X	X				O[c]	
Serum chemistry (incl LFT)	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X	X	X	O[c]	
LFTs[j]					wk 2	wks 6, 16					O[c]	
Serum Lipid panel (fasting whenever possible)	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O[c]	
Serum iron, ferritin, TIBC, TSAT	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X		X	O[c]	
HbA1c	X			X		wk 12	wks 28, 36, 44, 60, 84	X		X	O[c]	
Vitamin B_{12}, folate	X											
HIV Immunoassay, HBsAg, anti-HCV antibody	X											

Table continued on next page

Study Period:	**Screening**			**Treatment**[a]				**Follow-up**				**Post study Follow-up**
Visit / Week:	**Up to 6 Weeks**			**Day 1**[b]	**Weekly** (wks 1 to 2) ± 2 days	**Every 2 Weeks** (wks 4 to 24) ± 2 days	**Every 4 Weeks** (wks 28 to 100) ± 3 days	**EOT** (wk 104) ± 3 days	**EOT + 2 wks** ± 3 days	**EOS** (EOT + **4 wks**) ± 3 days	**Unscheduled Visits**	Every 6 months until projected wk 108
	S1	**S2**	**S3**									
Serum Pregnancy test[k]	X					wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O[c]	
eGFR (Cr Clear Modified Diet Abbreviated)[l]	X			X		wk 20	wks 36, 52, 68, 84	X		X	O[c]	
Special laboratory analytes (hepcidin, sTfR, hs-CRP)				X		wks 4, 12, 20	wks 36, 52	X		X		
Archival serum/plasma samples for biomarkers				X		wks 4, 12, 20	wks 52, 76	X		X		
Blood sample for population pharmacokinetics					wks 2 to 8[m]							
Genotyping[n]					X							
Urinary testing[o]				X		wks 12, 24	wks 36, 52, 64, 76, 88	X			O[c]	
Quality of Life Questionnaires[p]				X		wks 8, 12	wks 28, 36, 52, 76	X			O[c]	
12-lead ECG	X			X		wks 12, 24	wks 36, 52, 76	X			O[c]	
Renal ultrasound[q]	X										O[c]	
Dose adjustment review[r]						X	X				O[c]	
Hospitalization recording[s]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	
Procedure and non-drug therapy recording	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensing[t]				X[u]	X	X	X				O[c]	
Vital Status, SAEs, cardiovascular and thromboembolic AEs												X

AE: adverse events; CBC: complete blood count; CHr: hemoglobin content of reticulocytes; Cr: creatinine; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOT: End of Treatment; EOS: End of Study; HbA1c: hemoglobin A1c glycated hemoglobin; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: Human Immunodeficiency Virus; hs-CRP: high sensitivity C-reactive protein; LFT: liver function test; O: optional test/assessment (see below for footnotes); S1/S2/S3: screening visit 1, 2 and 3; SAE: serious adverse event; sTfR: soluble transferrin receptor; TIBC: total iron binding capacity; TSAT: Transferrin Saturation (also known as FeSAT, iron saturation); WBC: white blood cell; wk(s): week(s); X: mandatory test/assessment.

Note: see Appendix 3 Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0

Note: see Appendix 4 Instructions for Subjects Requiring Dialysis

Table footnotes continued on next page

[a] In case of premature discontinuation or withdrawal during the treatment period, the subject should complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the EOS visit. Thereafter, this subject will continue to be followed up at a 6-monthly frequency for vital status and SAEs, cardiovascular and thromboembolic AEs until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent is withdrawn.

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

[c] The study drug dosing is to be reviewed and if needed new or additional study drug is to be dispensed.

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

[e] Blood pressure (BP) measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period, BP measurement 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 pharmacokinetic sampling purpose. For subjects requiring dialysis, BP will be recorded prior to, and after dialysis (hemodialysis [HD]/hemodiafiltration [HDF] subjects only).

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

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

[h] Hemoglobin (Hb) should be collected at all the visits where CBC is not collected.

[i] If during an unscheduled visit Hb needs to be assessed, this should always be done with the HemoCue AND central laboratory Hb assessment. Hb will be assessed by HemoCue on the blood sample collected for central laboratory Hb assessment.

[j] Liver Function Tests (LFTs) to be collected at visits where full Serum Chemistry is not collected

[k] Collect from female subjects of child bearing potential only.

[l] Calculated by the Central Laboratory

[m] Sampling roxadustat will be done at 6 time points over 1 to 3 visits (see Section 5.6). At each pharmacokinetic visit, an additional sample will be collected for albumin and alpha-acid glycoprotein determination.

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

[o] 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 Cr for calculation of albumin/Cr ratio. At day 1, weeks 24, 52 and 76 and EOT a urine sample will be archived for potential future biomarker analysis.

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

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

Table footnotes continued on next page

[r] Dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (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.

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

[t] For subjects requiring dialysis, it is recommended for HD/HDF subjects that study drug is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day).

[u] Intake of initial study drug on day of randomization.

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 (RRT) (kidney transplant or dialysis). In 2007, CKD affected 13% of the US adult population (approximately 29 million U.S. 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 patients suffering from End Stage Renal Disease (ESRD) also continues to increase worldwide. The US has 1 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 (point prevalence Dec 31), there were approximately 570,000 ESRD patients in the US, of whom 370,000 were receiving hemodialysis (HD), 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 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 5-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 is first seen 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. Half of new dialysis patients (50.1%) 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 (Cr) 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 studies in the FDA briefing document for the October 2007 Cardiovascular and Renal 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 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 IV). 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 EPO (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 et al, 1989; Winearls et al, 1986], 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 CKD non-dialysis 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; Drueke 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 HD usually requires concomitant IV iron supplementation.

There is currently an unmet medical need for an oral treatment that will correct anemia in CKD non-dialysis and dialysis patients to a target Hb level that is safe and well tolerated.

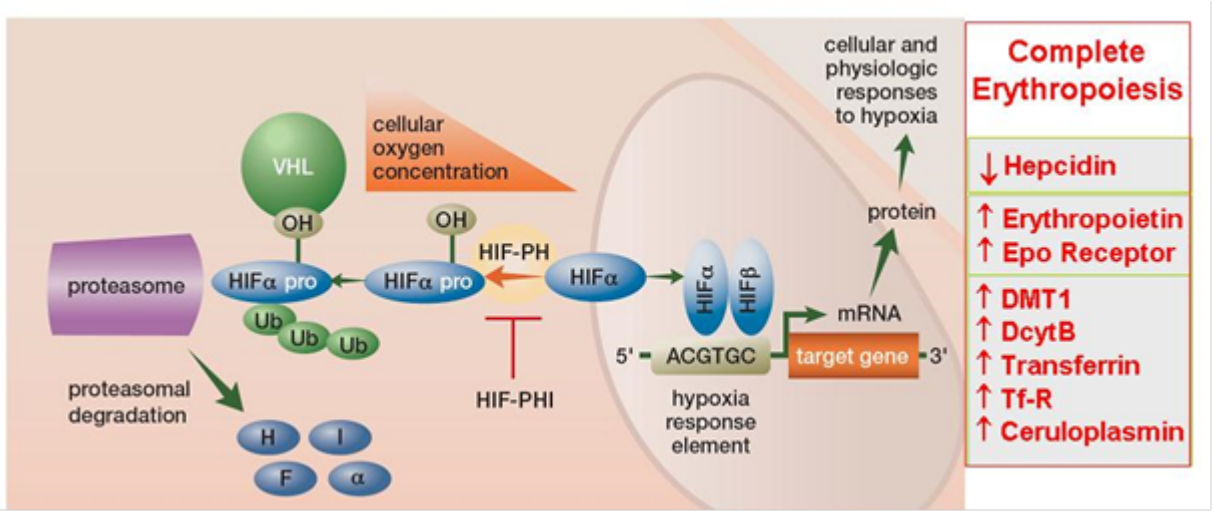
Roxadustat is an oral medication that could potentially deliver effective treatment for CKD-related anemia with less need for iron supplementation and without producing supraphysiologic levels of circulating EPO.

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

Figure 2 HIF-PHI Mechanism of Action



Source: Epstein, et al. Cell, 2001 Oct 5; 107(1)

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 HIF prolyl hydroxylases (HIF-PH) that utilize molecular oxygen as the substrate for hydroxylation. Thus, HIF-PH constitutes the body's main oxygen sensor by regulating the prevalence and activity of nuclear HIF protein. Under hypoxic conditions, HIF-PHs are inactive and lead to initiation of the HIF-responsive transcriptional cascade [Wang et al, 1995; Semenza, 1998].

Roxadustat is a potent and reversible HIF-PH inhibitor that transiently induces HIF stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure 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-PH inhibitors such as roxadustat alter expression not only of the EPO gene but also of genes regulating iron metabolism, it is postulated that roxadustat may be effective in treating these anemias as well [Langsetmo et al, 2005].

Chronic hypoxia and intermittent hypoxia induce different sets of genes associated with HIF transcriptional activity, presumably because intermittent stimulation allows the restoration of HIF degradation, turnover, and inactivation. Transient activation of HIF thereby precludes sustained gene expression and the induction of genes that are expressed late after HIF activation, as well as expression of additional genes that are secondary to activation of HIF-dependent genes. Both 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 dialysis and non dialysis 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 14 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 non dialysis-dependent chronic kidney disease (NDD-CKD) and 431 subjects with dialysis-dependent chronic kidney disease (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 3 times a week for 4 weeks. In a completed thorough QT study in healthy subjects, single doses up to 5 mg/kg were administered, without evidence of QT prolongation. The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in healthy adult subjects, and in 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 and pharmacodynamics of roxadustat were characterized in studies in healthy subjects and in dialysis and non-dialysis CKD patients. Roxadustat showed generally dose proportional pharmacokinetics (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 patients (after single doses of 1 and 2 mg/kg). The exposure was higher in dialysis patients compared to healthy subjects.

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

Additional drug-drug interaction studies were performed with statins and phosphate binders. Roxadustat increases the AUCinf of simvastatin 1.9-fold, of rosuvastatin 2.9-fold and of atorvastatin 2.0-fold. The AUCinf 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 subjects (Study [redacted]), 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 pharmacodynamic studies conducted with roxadustat in CKD patients not on dialysis (Study [redacted]), the mean maximum EPO increase from baseline (BL) ranged from 82-443 and 492-554 mIU/mL after a single 1 and 2 mg/kg dose, respectively. In dialysis patients (Study [redacted]), 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 patients, 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 patients not on dialysis (Study [redacted]) showed that roxadustat promoted erythropoiesis at lower doses in CKD patients than in healthy subjects. In contrast to the classical paradigm suggesting that anemia

in CKD patients is caused by the inability of these patients 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 patients 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. Hb responder (Hb increase of ≥1.0 g/dL) rates were 62%, 60%, 91%, and 100% in the roxadustat0.7, 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 achieve a level of ≥11.0 g/dL as well as increasing by ≥1.0 g/dL, the Hb responder rate with roxadustat2.0 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 (BP), as has been reported with ESA treatment [Eschbach et al, 1989].

Data from a 16- to 24-week treatment study in CKD patients 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 patients. For cohorts that have completed treatment, corrected Hb levels were maintained within target range for the 16- or 24-week treatment period. 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. 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 non-dialysis CKD patients. 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 patients on dialysis showed the feasibility of converting patients 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. 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's 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 dialysis and non-dialysis CKD patients with anemia who have been enrolled and treated in completed and ongoing clinical studies. Roxadustat leads to a robust dose-related erythropoietic response in patients 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.

1.3 Summary of Key Safety Information for Study Drugs

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 patients. The most commonly reported adverse events (AEs) in healthy subjects were headache, pharyngolaryngeal pain, and nasal congestion. The most commonly reported AEs (> 5%) in CKD patients not on dialysis were diarrhea, nausea, urinary tract infection, nasopharyngitis, peripheral edema, hyperkalemia, headache, and hypertension. The most commonly reported AEs (> 3%) in CKD patients on dialysis were diarrhea, nausea, hypertension, and upper respiratory tract infection. The only expected non-serious adverse drug reaction is 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 adverse event 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 [redacted], and 6.9% in Study FGCL-4592-041) and thrombosis (overall incidence < 1 %). No increased cancer risk has been noted with roxadustat treatment. However, the study program was not powered to detect absence of cancer risk.

Liver enzymes were monitored closely throughout the phase 2 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.

A number of pancreatitis events were noted during the phase 2 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. Only 1 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 patients with type 2 diabetes mellitus, and CKD, has been well described in the literature.

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

1.4 Risk-Benefit Assessment

Based upon the results of the studies described above the benefit of roxadustat is the correction of anemia and relief of signs and symptoms of anemia resulting in an increased QoL, 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.

Patients treated with placebo may be at risk of achieving insufficient efficacy as expressed by Hb levels not improving significantly or worsening as compared to BL. As a result they may have no improvement in QoL, impairment of physical functioning and performance.

An established dose adjustment algorithm, very similar to the one used in phase 2, will be used during the study to titrate roxadustat doses to enable patients 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 (placebo or roxadustat) rules for the use of rescue medication/procedures such as IV iron, ESAs or red blood cell transfusion are in place in order to assure safety of the affected study subjects.

In pharmacokinetic studies there was no evidence of drug accumulation with the proposed clinical regimen of up to 3 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 dialysis and non-dialysis 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. There is a potential risk that the drug interaction between phosphate-binders and roxadustat could decrease the efficacy of roxadustat, which will be mitigated by Hb-based dose adjustments. There is also a potential risk that a subject who suddenly discontinues or decreases the dose of a phosphate binder might be exposed to increased concentrations of roxadustat, although there are no data evaluating this potential effect. Although drug interaction of roxadustat with phosphate binders is an identified effect, it is unclear whether this interaction poses a true risk to subjects since the pharmacokinetics of discontinuing phosphate binder or changing the phosphate binder dose has not been investigated. Subjects who suddenly discontinue or decrease the dose of a phosphate-binder are advised to discuss changes in their use of phosphate binders with the investigator. As a further risk mitigation, this study protocol includes a recommendation that roxadustat be taken separately from a phosphate binder.

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

Based on the clinical and non-clinical experimental results to date, it can be expected that the orally administered roxadustat will be efficacious and safe 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 patient can be avoided. The benefit-risk for the participation of patients 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 in the treatment of anemia in non-dialysis CKD subjects.

2.1.2 Secondary Objectives

The secondary objectives in this study are to:

- Evaluate the safety of roxadustat in the treatment of anemia in non-dialysis CKD subjects.
- Evaluate HRQoL benefit of roxadustat treatment in subjects with CKD anemia.
- Evaluate the need for anemia rescue therapy with roxadustat in subjects with CKD anemia: RBC transfusion, ESA, or IV iron.

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, double-blind, placebo controlled study in anemic subjects with Stage 3, 4 or 5 CKD who are not on dialysis. This study is planned to recruit 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. Another study with similar design will be conducted by FibroGen Inc, in study centers across North America, Latin America and Asia Pacific.

2.2.1.2 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 receiving dialysis. Anemia is defined by mean Hb ≤ 10.0 g/dL upon repeated screening measurements. Subjects do not need to be iron replete at BL; inclusion is permitted if ferritin ≥30 ng/mL (≥ 67.4 pmol/L) and Transferrin Saturation (TSAT) ≥ 5%. Anemia of non-renal origin is to be excluded. Washout periods of at least 12 weeks for any prior ESA or IV iron treatment or 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 will take roxadustat or placebo orally as a combination of tablets of different strengths. All tablets for subjects receiving roxadustat will contain active ingredient whereas all tablets for subjects receiving placebo will contain just placebo. The study will consist of 3 study periods as follows:

- Screening period: up to 6 weeks.
- Treatment period: minimum 52 weeks (primary treatment period) up to a maximum of 104 weeks (extended treatment period) or until the last subject randomized to treatment has completed 40 weeks of treatment (or at the forecasted week 40 date if this subject discontinues treatment early). Treatment period for last patient randomized is 52 weeks.
- Post-treatment follow-up period: 4 weeks.

Refer to the study schema in [Figure 1].

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

2.2.1.3.1 Screening Period

During the screening period, subjects' eligibility for study participation will be assessed.

2.2.1.3.2 Treatment Period

After subjects have been confirmed eligible for study participation, they will be randomized to receive 1 of 2 treatment arms. The randomization will result in a 2:1 ratio of subjects receiving roxadustat or placebo, respectively.

The initial study drug dose (per dose amount) is based on a tiered, weight-based dosing scheme shown in [Table 2].

Table 2 Initial Study Drug (Roxadustat/ Placebo) Dosing

Study Drug (Dose Frequency)	**Weight** (≥ 45 to ≤ 70 kg)	**Weight** (> 70 to ≤ 160 kg)
Roxadustat/Placebo (TIW)	70 mg	100 mg

Study drug will be dosed initially for Hb correction, until subjects achieve central Hb value of ≥ 11.0 g/dL and Hb increase from BL of ≥ 1.0 g/dL at 2 consecutive study visits separated by at least 5 days (correction period).

Once Hb correction is reached the subject will enter the maintenance period. The aim of the maintenance period is to treat to a Hb level of 11.0 g/dL by maintaining the Hb levels between 10.0 g/dL and 12.0 g/dL. 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 4 weeks until the end of treatment (EOT). Subjects will be treated with roxadustat or placebo for at least 52 weeks and will continue taking the double-blind treatment as they were assigned until a maximum of 104 weeks. Depending on the rate of recruitment, the maximum treatment period will be 104 weeks for subjects who were randomized early into the study.

- The last subject randomized will stop treatment at the minimum of 52 weeks.
- When the last subject randomized reaches 40 weeks of treatment (or the forecasted week 40 date, if the last subject randomized discontinues treatment early)
    - Subjects beyond 52 weeks treatment will stop treatment at this point.
    - Subjects that have not yet reached 52 weeks treatment will continue until they reach 52 weeks treatment.

For details on study drug dosing, see [Section 5.1].

2.2.1.3.3 Follow-up Period

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

2.2.1.3.4 Post-study Follow-up Period (Only for Subjects Prematurely Discontinued from Treatment)

Subjects that have stopped treatment prior to their projected week 104 will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the end of study (EOS) visit. Thereafter, these subjects will continue to be followed up on a 6-monthly frequency for vital status and SAEs, cardiovascular and thromboembolic AEs until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent withdrawn.

2.2.1.4 Randomization and Blinding

A randomized double-blind 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. For more details on blinding, please refer to [Section 4.4].

2.2.1.5 Comparator

Placebo 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. Scientifically, efficacy and benefit of a new investigational medicinal product is most convincingly established by demonstrating superiority in a placebo-controlled trial.

2.2.2 Dose Rationale

Starting doses of roxadustat in the correction setting were studied in 3 ways in the phase 2 program:

- 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);
- and using an absolute starting dose regardless of body weight.

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

Based upon simulations derived from a pharmacokinetic-pharmacodynamic model built from phase 2 data a tiered weight-based approach with starting doses of 70 mg given 3 times a week (TIW) for patients weighing up to 70 kg and 100 mg given TIW for patients 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 provides 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 can be 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 pre-specified 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 dose in this study is set at 3.0 mg/kg or 300 mg, 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 subjects 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 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 a minimum of 52 weeks, will provide sufficient data on the long term treatment of anemic CKD subjects with roxadustat.

2.3 Endpoints

2.3.1 Primary Endpoint

For EU (EMA) the primary efficacy endpoint is Hb response.

Hb response is defined as:

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

at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or IV iron) prior to Hb response.

For US (FDA) the primary efficacy endpoint is the change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 52) regardless of rescue therapy.

2.3.2 Secondary Endpoints

The key secondary efficacy endpoints in this study are:

- Hb maintenance: 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
    - Change from BL in low–density lipoprotein (LDL) cholesterol to the average value of LDL cholesterol in weeks 12-28
- Use and time to use of rescue therapy (composite of RBC transfusions, ESA use, and IV iron) in the first 24 weeks of treatment.
- Change from BL in Short Form (SF)-36 Physical Functioning (PF) subscore to the average SF-36 PF subscore in weeks 12-28
- Change from BL in SF-36 Vitality (VT) subscore to the average SF-36 VT subscore in weeks 12-28
- Blood pressure effect
    - Change from BL in Mean Arterial Pressure (MAP) to the average MAP in weeks 20-28
    - Occurrence and time to occurrence of hypertension (defined as either systolic blood pressure [SBP] > 170 mmHg AND an increase from BL ≥ 20 mmHg or as DBP > 110 mmHg, AND an increase from BL of ≥ 15 mmHg)

2.3.3 Other Endpoints

2.3.3.1 Additional Secondary Evaluation of Efficacy

Hb correction and maintenance:

- Hb averaged over weeks 28-36, without use of rescue therapy within 6 weeks prior to and during this evaluation period
- Time to achieve the first Hb response as defined by primary endpoint
- Hb change from BL to each post-dosing time point
- Hb level averaged over weeks 44-52, without use of rescue therapy within 6 weeks prior to and during this evaluation period
- Hb change from BL to the average Hb value of weeks 28-36 and weeks 44-52, regardless of the use of rescue therapy
- Proportion of Hb values within 10.0-12.0 g/dL in weeks 28-36, without use of rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

Hospitalizations

- Occurrence of hospitalization
- Number of days of hospitalization.

Rescue therapy use

- Having received RBC transfusions
- Number of RBC packs per subject
- Volume of RBC transfused per subject
- Having received IV iron therapy
- Number of ESA-week dose per subject: 1-3 doses of epoetin alfa or beta or biosimilar thereof (in EU) administered within 1 week = 1 ESA-week; 1 darbepoetin SQ or IV dose = 2 ESA-week; 1 Mircera IV or SQ dose = 4 ESA-week.

Changes in cholesterol levels

- Change from BL to each post-dosing study visit 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 12-28 of treatment).

Blood pressure effect

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

HRQoL and Euroqol Questionnaire – 5 Dimensions 5 Levels (EQ-5D 5L) benefits of roxadustat in subjects with CKD anemia

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

Hepcidin and Iron, Hemoglobin A1c glycated hemoglobin (HbA1c), and CKD progression

- Changes from BL to each study visit in:
  - Serum hepcidin
  - Serum ferritin
  - TSAT
  - HbA1c level
  - Fasting blood glucose
  - eGFR (including eGFR slope over time)
  - Urine albumin/Cr ratio
- Serum Cr having doubled during the study
- Occurrence of ESRD, i.e., dialysis initiation

2.3.3.2 Safety Endpoints

Safety will be assessed by evaluating the following:

- Occurrence of AEs, SAEs and clinically significant changes in laboratory values from BL
- Changes from BL in vital signs, electrocardiogram (ECG) findings and clinical laboratory values
- For the purpose of EU regulatory filing and other submissions: Adjudicated MACE+ events (i.e., myocardial infarction, stroke, death from all causes, hospitalization for chronic heart failure, hospitalization for unstable angina) and other pre-specified events will be pooled and analyzed across multiple studies in the global phase 3 program. This analysis will be described in a separate pooled safety statistical analysis plan.
- For the purpose of US FDA regulatory filing: Adjudicated MACE i.e., myocardial infarction, stroke, death from all causes, will be pooled across multiple studies in the global phase 3 program to serve as primary safety endpoint.

The adjudicated MACE events in this study will be part of this pooled analysis, but will not be a self-contained endpoint within this individual study.

3 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 receiving dialysis.

Waivers to the selection criteria will not be allowed.

3.1 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 must be 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 chronic kidney disease, with Kidney Disease Outcomes Quality Initiative (KDOQI) Stage 3, 4 or 5, not receiving 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 three most recent 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.
5. Subject has a ferritin level ≥ 30 ng/mL (≥ 67.4 pmol/L) at screening.
6. Subject has a transferrin saturation (TSAT) level ≥5% at screening.
7. Subject has a serum folate level ≥ lower limit of normal at screening.
8. Subject has a serum vitamin B_{12} level ≥ lower limit of normal at screening.
9. Subject's alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels are ≤ 3 x upper limit of normal (ULN), and total bilirubin (TBL) is ≤ 1.5 x ULN.
10. Subject's body weight is 45.0 kg up to a maximum of 160.0 kg.
11. Female subject is either:
    - Of non-child bearing potential:
      - post-menopausal (defined as at least 1 year without any menses) prior to screening, or
      - documented surgically sterile
    - or if of child bearing 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 continued for 28 days after the last study treatment administration.

12. Male subject and their female spouse/partner(s) who are of childbearing potential must be using highly effective contraception starting at screening and continue throughout the study period, and for 12 weeks after final study treatment administration.

    * 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.
13. Subject agrees not to participate in another interventional study from the time of signing informed consent until the End of Study visit (EOS).

3.2 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 had more than one dose of IV iron within 12 weeks prior to randomization.
3. Subject has received a 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 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 have elective surgery that is expected to lead to significant blood loss 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 a 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., pulmonary embolism) within 12 weeks prior to randomization.
15. Uncontrolled hypertension in the opinion of the investigator or two or more blood pressure values of systolic BP (SBP) ≥ 160 mmHg or diastolic BP (DBP) ≥ 95 mmHg confirmed by repeat measurement within 2 weeks prior to randomization.
16. Subject has a diagnosis or suspicion (e.g., complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma on renal ultrasound within 12 weeks prior to randomization.
17. Subject has a history of malignancy, except the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps.
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 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 and retinal vein occlusion.
21. Subject has had any prior organ transplant (that has not been explanted) or a scheduled organ transplantation.
22. Subject has participated in any interventional clinical study or has been treated with any investigational drugs within 30 days or 5 half lives or limit set by national law, whichever is longer, prior to the initiation of Screening.
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. Female subject:
    - must agree not to breastfeed starting at screening or during the study period, and continued for 28 days after the final study treatment administration.
    - must not donate ova starting at screening and throughout the study period and continued for 28 days after final study drug administration.

26. Male subject must not donate sperm starting at screening and throughout the study period and for 12 weeks after final study drug administration.
27. 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.

3.3 Discontinuation Criteria for Individual Subjects

Discontinuation is the act of concluding participation in either the study treatment or the study, prior to completion of all protocol-required elements, in a trial by an enrolled subject.

The subject is free to withdraw from the study treatment and/or 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. Subjects should be discontinued from the 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
- Subject requires a third course of ESA rescue therapy (for details, see [Section 5.1.5])
- Subject receives an organ transplant

If a subject has discontinued treatment prior to their projected week 104, subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the EOS visit. Thereafter, this subject will continue to be followed up on a 6-monthly frequency for vital status and SAEs, cardiovascular and thromboembolic AEs until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent withdrawn.

- Subjects should be withdrawn from the study for any of the following reasons:
- Subject no longer consents to participate in the study
- Subject is lost to follow-up despite reasonable efforts by the investigator to contact the subject
- Death of the study subject
- The Sponsor may decide to prematurely stop the study, e.g., for safety considerations

Discontinued and withdrawn subjects will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the end of study (EOS) visit procedures. The appropriate documentation must be entered on the electronic case report form (eCRF).

Women of childbearing potential who 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.

4 STUDY DRUGS

4.1 Description of Study Drugs

4.1.1 Test Drug(s)

Roxadustat is supplied as red 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.

More details can be found in the Investigator's Brochure.

4.1.2 Comparative Drug

Placebo tablets are identical in appearance to roxadustat tablets.

The matching placebo drug product is supplied as red coated, oval tablets for oral administration marked as 20, 50 and 100 mg. All ingredients used for manufacture of the placebo tablets comply with US and EU compendial or regulatory standards. Size and debossing are identical to roxadustat, matching the appearance of the different strengths (i.e., 20, 50 or 100 mg) of the roxadustat tablets.

More details can be found in the Investigator's Brochure.

4.1.3 Drug(s) for Pre-investigational Period

Not applicable.

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged and labelled under the responsibility of a qualified person at Astellas Pharma Europe BV (APEB) or sponsor's designee in accordance with APEB or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice guidelines, International Conference on Harmonization for Good Clinical Practice (ICH GCP) guidelines, and applicable local laws/regulations. A Qualified Person of APEB or sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC Annex 13.

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.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person at the study site (e.g., pharmacist), and that:

- such deliveries are recorded
- study drug is handled and stored safely and properly
- study drug is only dispensed to study subjects in accordance with the protocol
- any unused study drug is returned to the sponsor or designee standard procedures for the alternative disposition of unused study drug are followed if agreed by the sponsor.

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

- The investigator agrees not to supply study drug to any persons except the subjects randomized in this study.
- The investigator/pharmacist will keep the study drug in a pharmacy or other locked and secure storage facility under controlled storage conditions, where access is limited to appropriately qualified staff and authorized by the investigator to dispense this study drug.
- A study drug inventory will be maintained by the investigator/pharmacist. 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 this study, the investigator/pharmacist 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 returned medication. Any discrepancies must be accounted for. Appropriate forms for deliveries and returns must be signed by the person responsible.
- Used or unused study drug is returned 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

4.4.1 Blinding Method

Study drug administration is implemented in a double-blind, placebo-controlled manner. Neither the subjects nor the investigators and their staff can distinguish the roxadustat tablets from the matching placebo tablets. Both will be identical in appearance, packaging and labeling in order to maintain the blind.

Randomization of treatments and preservation of the treatment blind are maintained by an Interactive Response Technology (IRT). The randomization code will remain confidential until completion of the study.

4.4.2 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization schedule will be generated under the responsibility of the Global Data Science (GDS) Department, Astellas Pharma Europe B.V. (see Section 4.5). The vendor of the IRT used in this study will receive the randomization schedule and perform the random assignments of medication numbers to study treatments. These files will be held securely and will be released to the study biostatistician only after database hard lock has taken place and a decision has been taken to unblind the study.

Procedures for emergency unblinding of individual subjects, in the event that knowledge of the treatment assigned is required for the correct management of a medical emergency, are described in [Section 4.4.3]. Emergency unblinding of a few individual subjects does not, in general, affect the continued blinding of other subjects in the study or the scientific integrity of the study.

The Independent DSMB see [Section 10.1], will have access to group-unblinded and/or fully unblinded DSMB reports. They will also be authorized to access the unblinded treatment for single subjects or for single treatment groups via the IRT. The DSMB will not disclose this information to any other staff involved in this study.

4.4.3 Breaking the Treatment Code for Emergency

For each randomized subject, individual code breaks will be accessible in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The code is accessible through the IRT. The time and date of any code break will automatically be documented in the IRT.

Only the responsible investigator or delegates duly registered in the study file as sub-investigators can break the code via the IRT. Subjects or other study personnel will not be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure. Any breaking of the treatment code by the investigational staff must be reported immediately to the 24-hour contact for SAEs [see Section II] and must include an explanation for breaking the code. The sponsor should be contacted to discuss the case, if possible, prior to unblinding. The date of breaking the blind, person who requested the blind

to be broken, person who broke the blind, the reason for breaking the blind, and the person informed at the sponsor will be captured in the eCRF.

Unplanned unblinding may result in the discontinuation of subject participation from the study.

4.4.4 Breaking the Treatment Code by the Sponsor

The sponsor's personnel from the Drug Safety and Pharmacovigilance Department may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Code will be provided to the limited staff who are empowered to break the codes for all SUSAR cases for reporting purposes.

4.5 Assignment and Allocation

Assignment to treatment groups will be done using the randomization scheme prospectively prepared by [redacted] on behalf of the sponsor, under the responsibility of the GDS Department of APEB. Automated randomization and treatment assignments will be provided by an IRT.

A total of 450-600 planned subjects will be randomized to receive 1 of the 2 treatment arms in a 2:1 ratio as follows:

- Roxadustat (planned 300-400 subjects)
- Placebo (planned 150-200 subjects)

Randomization will be stratified by the following 4 factors:

- Region (region A versus region B)*
  * assignment to region will be determined based on health care system comparability
- Screening Hb values ($\leq$ 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 $\geq$ 30 mL/min/1.73 m^2)

5 TREATMENTS AND EVALUATION

Subjects must provide a signed Informed Consent Form (ICF) and be registered in IRT before any screening tests or assessments are performed. Participating study sites are required to document all screened candidates who provided Informed Consent. If a subject is later 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 technology. After obtaining consent, and prior to the start of screening assessments, the investigator will register the subject in IRT, which starts the 42 day 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 parameter results do not meet the inclusion criteria or meet the exclusion criteria at Screening, the laboratory parameter assessment may be repeated once within the 42-day screening period. This includes an additional (4^{th}) Hb value that may be collected if necessary. The mean of 3 most recent Hb values during the 42-day 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 42-day screening period starts and all screening procedures must be repeated. Subject must also be registered in IRT as re-screened under the same subject number as first screening.

Subjects confirmed not eligible after screening or, if applicable, after re-screening, should be registered in IRT as a screen/re-screen failure.

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Administration Period

Following the screening period, eligible subjects will enter the treatment period upon randomization. Subjects will be randomized via IRT to receive roxadustat or placebo. The initial study drug dose is based on the tiered, weight-based dosing scheme [refer to Table 2]. The first study drug administration should be on the day of randomization, i.e., day 1, after all study assessments have been completed.

Scheduled Visits

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 4 weeks until the EOT.

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

All subjects will administer study drug TIW and study drug doses must be administered at least 2 days apart, 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.

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

Subjects who entered the study under protocol v1.0 should, upon signing the updated informed consent, adapted their dose frequency and dose amount according to the instructions in Appendix 3 Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0.

There were no adaptations to dose frequency or dose amount for subjects moving from Protocol v2.0 to Protocol v2.1.

5.1.2 Changes in Study Drug Dose

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 and are based on Hb values using the HemoCue® device, a point-of-care device.

Dose adjustments will follow unique dose adjustment rules [Table 3].

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 1 dose step (↑) and reductions by 1 dose step (↓) are pre-set per the dose steps.
- The dose steps 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 BL 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. This should be discussed with the Medical Monitor and documented in the source documentation.

At Any Time when Hb ≥ 13.0 g/dL

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

Dose Adjustment for Excessive Hematopoiesis

At any time during the Treatment Period:

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

Note: Only 1 dose reduction for excessive hematopoiesis is recommended within a period of 4 weeks. If a blood transfusion or ESA rescue 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. If the dose adjustment interval falls on a non-visit study week, the dose adjustment review should be performed at the next scheduled clinic visit.

5.1.3 Previous and Concomitant Medication (Drugs and Therapies)

5.1.3.1 Previous Medication (Drugs and Therapies)

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 previous medication within 4 months prior to randomization should be documented in the eCRF. The medication name, start and stop date, route, dose, 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, frequency and indication for each medication will be entered in the eCRF.

The following previous medication is not permitted:

- Any ESA within 12 weeks prior to randomization
- IV iron (more than 1 dose) within 12 weeks prior to randomization
- RBC transfusion within 8 weeks prior to randomization
- Iron-chelating drugs within 4 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 the initiation of Screening
- Roxadustat or another HIF-PHI at any time.

5.1.3.2 Concomitant Medication (Drugs and Therapies)

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), dose and frequency 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.

Statins and Other Substrates for OATP 1B1

There is a risk that roxadustat will increase the plasma levels of statins and other drugs that are substrates of OATP 1B1, 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 4].

The investigator is also advised to consider this potential interaction between roxadustat and other drugs that are substrates for OATP 1B1 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 Summary of Product Characteristics (SmPC) of these drugs for further details and guidance.

Table 4 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

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

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

Subjects should take roxadustat in a consistent manner relative to their phosphate binder intakes, 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 be advised that roxadustat be taken at least 1 hour before or 1 hour after their phosphate binder.

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

Anti-hypertensive Medications

To avoid confounding effects on study endpoints, changes to anti-hypertensive medications should be kept to a minimum during the course of the study, and only if deemed medically necessary by the investigator. Changes to anti-hypertensive medications will be documented in the eCRF.

Supplemental Vitamin B12, Folate

Vitamin B12 and folate can be taken without restriction at any time during the study.

Supplemental Iron and ESA Use

Oral iron is recommended as the first-line treatment for iron supplementation and can be taken without any restriction. However, IV iron and ESA use is restricted to use as rescue therapy, see rescue therapy guidelines, [Section 5.1.5]. Administration of roxadustat between -1 hour and +1 hour of intake of oral iron is not recommended.

Prohibited Medications

The following medications are prohibited during the period identified:

- Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to randomization until EOS visit
- Androgens from randomization until EOS visit
- Dapsone in any dose amount or chronic use of acetaminophen (paracetamol) > 2.0 g/day from randomization until EOS visit
- Any hypoxia-inducible factor HIF-PHI other than roxadustat, as allocated by randomization, until EOS visit.

Use of herbal medicine is not prohibited but strongly discouraged during the course of the study.

5.1.4 Treatment Compliance

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 (see Sections 7.8 and 8.1.6).

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. If subjects meet the criteria for ESA rescue therapy whilst on dialysis, ESAs will be administered IV or SC according to the Package Insert or SmPC of the respective ESA for dialysis patients.

RBC Transfusion

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 drug may be continued even if a blood transfusion had been administered.

ESA

If a subject's Hb level has not sufficiently responded to 2 or more dose increases or maximum dose (by body weight) of the study drug and the investigator considers the initiation of an ESA (i.e., EPO analogue) rescue as a medical necessity, the investigator should consider initiating the use of an approved ESA only if all of the following criteria are met:

- The subject's Hb level has not sufficiently responded to 2 or more dose increases in previous 8 weeks or maximum dose (by body weight) of the study drug; **and**
- The subject's Hb is < 8.0 g/dL; **and**
- Reducing the risk of alloimmunization in transplant eligible subjects and/or reduction of other RBC transfusion-related risks is a goal.

The subject may continue on study, however, the subject is not allowed to be administered both ESA and study drug during the same time period. The course of ESA (i.e., the amount that may be administered) will be limited by duration of therapy and effect on Hb, including that 1 course of ESA treatment will not exceed 4 weeks in duration, and that ESA rescue will be stopped as soon as Hb ≥ 9 g/dL. Treatment with study drug may be resumed as soon as possible after the following intervals:

- At least 2 days after stop of Epoetin alfa or Epoetin beta, or biosimilar thereof
- At least 1 week after stop of darbepoetin alfa
- At least 2 weeks after stop of methoxy polyethylene glycol-epoetin beta.

If a subject requires a third course of rescue with ESAs, the subject must be discontinued. The subject will complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the EOS visit, and will continue to be followed up on 6-monthly frequency for vital status and SAEs, cardiovascular and thromboembolic AEs until their projected date of completion or, if earlier, until the last subject randomized reaches EOS.

For instructions on ESA rescue treatments for subjects moving from protocol v1.0 to protocol v2.0, see Appendix 3

Intravenous Iron

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 route of treatment. The recommended daily oral dose is 200 mg of elemental iron.

The investigator may initiate the use of IV iron supplement if:

- The subject's Hb level has not sufficiently responded to 2 or more dose increases of study drug while taking oral iron (unless not tolerated), and
- Hb < 8.5 g/dL, and
- Ferritin < 100 ng/mL, or TSAT < 20%.

If IV iron rescue criteria are met, the dose in a single administration (day) should be no more than 250 mg. Study treatment may continue during IV iron administration. At 4 to 8 weeks after the single dose of IV iron, a repeat dose of IV iron can be administered if the Hb remains < 9.0 g/dL and the subject still meets iron deficiency criteria (ferritin < 100 ng/mL or TSAT < 20%). After this 8-week period, full IV iron rescue criteria would need to be met again in order to qualify a subject for a second course of IV iron at a later point in the trial.

In Case of Excessive Hematopoiesis

If a blood transfusion or ESA has been performed within 2 weeks of meeting the criteria for Excessive Hematopoiesis, it is recommended not to perform a dose reduction of the study drug for excessive hematopoiesis.

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 dose hold. This should be documented and discussed with the study medical monitor.

5.1.7 Restrictions During the Study

Subjects are not permitted to consume more than 3 alcohol-containing drinks per day during the treatment or follow-up periods.

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 highly effective contraception as stated in the inclusion criteria.

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 drug. If a subject discontinues prematurely, contraception must be practiced for 28 days (female subjects) and 12 weeks (male subjects) following final administration of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported [see Section 5.5.8 Procedure in Case of Pregnancy].

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic data recorded during Screening, including date of birth or age (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, other than the target disease for each subject 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. 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 must be performed within 12 weeks prior to randomization. This can be replaced by a pre-existing examination (or other renal imaging modality such as CT or magnetic resonance imaging (MRI) scan if conducted within 12 weeks prior to randomization and it conclusively excludes the presence of renal cell carcinoma). Examination results must be available prior to randomization. Sites are reminded to schedule the renal ultrasound, following the screening visit, once the subjects are confirmed eligible for the study, for subjects only that have not had a renal ultrasound in the specified period. The date and assessment of presence of 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 for anemia, date of diagnosis, CKD stage and etiology for CKD and non-drug therapy history and medication history for anemia in the last 12 months prior to randomization.

Chronic Kidney Disease 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. A reduction in kidney function to this

level or lower represents loss of half or more of the adult level of normal kidney function, which may be associated with a number of complications. Documentation of reduced eGFR should be available in the subject's source documentation. In addition, calculation of eGFR will be performed by the central laboratory on day 1 to confirm the degree of CKD.

eGFR will be calculated using the following MDRD equation: eGFR (mL/min per 1.73 m^2) = 175 × Serum Cr $^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.21 if black).

Anemia will be measured by repeated Hb measurements (central laboratory assessment) during screening; the mean of the 3 most recent Hb values during the Screening period, obtained at least 4 days apart, must be ≤ 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.

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

- Complete blood count (CBC), which will include Hb concentration, red cell indices, white blood cell count and differential, platelet count and reticulocyte count
- Serum ferritin level
- TSAT
- Serum vitamin B12 and folate levels.

For more details on the laboratory tests please refer to [Section 5.4.3.4 Central Laboratory].

5.2.5 Further Laboratory Testing Prior to Randomization

Other laboratory tests mandatory prior to randomization of a subject include enzyme-linked immunosorbent assay for HIV, HBsAg and 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 5.4.3.4 Central Laboratory].

5.3 Efficacy Assessment

5.3.1 Primary Efficacy Assessment

Efficacy assessment of treatment with study drug will be based primarily upon Hb as assessed by central laboratory from intravenous blood sampling.

For the exact timing of Hb assessments refer to the Schedule of Assessments [Table 1]. For further details on central laboratory assessments, refer to [Section 5.4.3.4].

The use of rescue medication (as recorded in the eCRF) will be utilized for the evaluation of the primary efficacy assessment.

5.3.2 Additional Efficacy Assessment

See additional information in Appendix 4 Instructions for Subjects Requiring Dialysis.

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 BP, refer to [Section 5.4.1.1].

5.3.2.2 Serum Lipid Panel

Blood sampling for serum lipids should be done in a fasted condition, wherever possible. The following parameters will be assessed (central laboratory): Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apolipoproteins A1 and B and ApoB/ApoA1 ratio.

5.3.3 Additional Assessments

See additional information in Appendix 4 Instructions for Subjects Requiring Dialysis.

5.3.3.1 Health Related Quality of Life

All study subjects will be required to complete QoL questionnaires as indicated in the Schedule of Assessments [Table 1]: SF-36, FACT-An, EQ-5D 5L, PGIC and Work Productivity and Activity Impairment questionnaire Anemic Symptoms (WPAI:ANS). See Appendices 5, 6, 7, 8 and 9.

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

The SF-36 is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. It is aimed at both adults and adolescents aged 18 years and older. The SF-36 consists of 8 domains of health status: Physical functioning (10 items), Role-physical (4 items), Bodily pain (2 items), General health (5 items), Vitality (4 items), Social functioning (2 items), Role emotional (3 items) and Mental health (5 items). Two component scores, the Physical Component Summary and the Mental Component Summary can also be calculated. For both the SF-36 domain scores and summary scores, higher scores indicate better health status. The SF-36 has a recall period of the 'past 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 4 dimensions of well-being: physical (PWB)—7 items, functional well-being (FWB)—7 items, social/family (SWB)—7 items each, and emotional well-being (EWB)—6 items. A subscale of 13 fatigue specific items (the Fatigue Subscale) plus 7 additional items related to anemia were developed for use in conjunction with the FACT-G (Cella, 1997). The 13 fatigue items plus the 7 additional items related to anemia comprise the Anemia Subscale (AnS). Administration of the FACT-G plus the AnS is referred to as the FACT-An. 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 EQ-5D 5L is a self-reported questionnaire. The EQ-5D is being used as a measure of respondents' HRQoLand utility values. The EQ- 5D consists of the EQ-5D descriptive system and the EQ 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).

5.3.3.1.4 Patients' Global Impression of Change (PGIC) Scale

The PGIC 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).

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 7 days due to anemia. 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.

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 1 dose of study drug), until the projected date of the EOS visit (week 108) or, if earlier, until the last subject randomized reaches EOS.

5.4 Safety Assessment

See [Section 5.5 Adverse Events and other Safety Aspects].

Please review the requirements related to the evaluation, reporting and analysis of liver abnormalities information found in Appendix 2 Liver Safety Monitoring and Assessment. In the event of a confirmed, severe hepatic abnormality as defined in Appendix 2 Liver Safety Monitoring and Assessment, it is the investigators responsibility to ensure contact with the sponsor/delegated contract research organization (CRO) by telephone or fax immediately (i.e., within 24 hours of awareness).

5.4.1 Vital Signs

See additional information in Appendix 4 Instructions for Subjects Requiring Dialysis.

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 each of the 3 visits during the screening period, and in triplicate with at least 2 minute intervals for all other visits. The same arm should be used consistently for measurements throughout the study. All values will be reported in the eCRF.

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 BP measurement [see Section 5.4.1.1], by using any other suitable device or manually (wrist HR within 1 minute). The same methodology and device should preferably be used for the subject throughout the study, timing as indicated in the schedule of assessments.

HR will be measured singly on each of the 3 visits during the screening period, and in triplicate with at least 2 minute intervals for all other 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 1 minute). The same methodology and device should preferably be used for the subject throughout the study, timing as indicated in the schedule of assessments. Respiratory rate will be measured singly during all visits 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 1 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 2 (Liver Safety Monitoring and Assessment) for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in the study and receiving study drug is accompanied by increases in LFTs (e.g., AST, ALT, bilirubin) or is suspected to be due to hepatic dysfunction.

In the event of a confirmed, severe hepatic abnormality as defined in Appendix 2 (Liver Safety Monitoring and Assessment) it is the investigator's responsibility to ensure contact with the Medical Monitor of the Sponsor/delegated Contract Research Organization by telephone or fax immediately (i.e., within 24 hours of awareness) for further follow-up.

5.4.3 Laboratory Assessments

5.4.3.1 Abnormal Liver Function Tests

If laboratory testing for a subject enrolled in a study and receiving study drug reveals an increase of serum aminotransferases (AT) to > 3 x ULN, or bilirubin > 2 x ULN, at least all 4 of the usual serum measures (ALT, AST, alkaline phosphatase [ALP], and TBL) should be repeated within 48 - 72 hours of notification of the test results. See Appendix 2 (Liver Safety Monitoring and Assessment) for additional information on monitoring and assessment of abnormal LFTs.

5.4.3.2 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.

5.4.3.3 Urinalysis

Dipstick analysis will be performed for protein, pH and glucose. A quantitative assessment of albumin and Cr for the calculation of albumin/Cr ratio will be performed by the Central Laboratory. Ideally, the sample should be from the first morning void.

5.4.3.4 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.

To maintain a blinded allocation to study treatment, the results of hepcidin, the level of hemoglobin content of reticulocytes (CHr) and the quantity of Soluble Transferrin Receptor (sTfR) will be reported to sites and the Sponsor after completion of the study.

Below is a table of the laboratory tests that will be performed during the conduct of the study [Table 5]. The exact timing of all assessments can be found in the Schedule of Assessments [Table 1].

Table 5 Laboratory Tests

	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 CHr
Table continued on next page	

	Parameters to be analyzed
Biochemistry Serum Chemistry	Sodium Potassium Calcium Chloride Glucose (fasted condition wherever possible) Cr Magnesium Bicarbonate Phosphorus Uric Acid Albumin Total protein Lactate dehydrogenase Blood urea nitrogen Lipase Pregnancy test (for females of child bearing potential only) Liver Function Tests: • AST • ALT • Bilirubin (Total and direct) • Gamma Glutamyl Transferase ALP Lipid Panel (in fasted condition wherever possible): • Total Cholesterol • LDL • HDL • Triglyceride • Apolipoprotiens A1 and B and ApoB/ApoA1 ratio Iron Ferritin Total Iron-Binding Capacity (TIBC) TSAT (=FESAT) Covariate for pharmacokinetic markers • Albumin • α1-AGP HbA1c Vitamin B_{12}Folate
Serology (Immunology):	HIV Immunoassay HBsAg Anti-HCV Antibody Tests
Special Laboratory Analytes:	Hepcidin sTfR (blinded) High sensitivity C-reactive protein (hs-CRP) (blinded)
Table continued on next page	

	Parameters to be analyzed
Serum	Archival Serum samples for biomarkers
Plasma	Level of roxadustat and potentially metabolites
Whole Blood	Genotyping
Urinalysis	Qualitative • Protein • pH • Glucose Quantitative • Cr • Albumin 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 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, lungs, heart, chest and back, abdomen, genitourinary, extremities, skin, and any other, if deemed necessary.

A targeted 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].

5.4.5 Electrocardiogram (ECG)

Local 12-lead ECGs will be performed on all subjects at specific time points as described in 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 in the eCRF using the HR. ECG recording will be kept as source documents.

5.4.6 Exploratory Assessments

Exploratory assessments in this study include the following parameters:

- hs-CRP
- Relevant selected biomarkers may be assessed from archived serum/plasma samples
- WPAI

- PGIC

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 adverse event (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 1 of the following criteria:

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

AEs present prior to study drug administration will be considered as 'non-treatment emergent'. Baseline conditions that worsen during the study will be recorded as adverse events. Adverse events 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.

Data to be recorded in the eCRF include a description of the event, date of onset, onset status (onset before/after first dose of double-blind medication), end of the event, severity, SAE, seriousness criteria, action with respect to study medication, treatment required, relationship to study drug 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 drug or through to EOS, except for pregnancy reporting [see Section 5.5.8]. For subjects that continue into the post study follow-up period, SAEs, cardiovascular and thromboembolic AEs will be captured until their projected date of completion of the follow-up period (i.e., projected week 108) or until the last subject randomized reaches EOS, whichever comes first.

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 drug 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 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 (an adverse event 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 adverse event that, had it occurred in a more severe form, might have caused death),
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly or birth defect,

- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).
- Other medically important events.

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

If 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 adverse event is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

If a subject becomes pregnant during treatment, this should be reported as if it were a SAE. Refer to Section 5.5.8 Procedure in Case of Pregnancy.

5.5.3 Criteria for Causal Relationship to the Study Drug

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

Table 6 Criteria for Causal Relationship to Study Drug

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

Severity of AEs will be graded according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. For terms not specified as part of NCI-CTCAE Version 4.03, the following guideline should be used to determine grade:

Table 7 Criteria for Defining the Severity of an Adverse Event

Grade	Description
1 - Mild	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
2 - Moderate	Moderate; minimal, local or non-invasive intervention indicated.
3 - Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
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 SAE, the investigator must contact the delegated CRO 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 delegated CRO by fax immediately (within 24 hours of awareness). Toll free fax number for each country is provided on the fax coversheet of the SAE Worksheet. In case of fax failure the SAE Worksheet should be emailed to the delegated CRO.

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

The contact details of the delegated CROs are:

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

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.

Follow-up information for the event should be sent promptly (preferable within 7 days of the initial notification).

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

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

- ISN/Study number
- Subject number, sex and age
- Date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

All SAEs, including death, should be reported up to EOS visit or up to 28 days after the last intake of study medication, whichever is last. Any hospitalizations 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 (i.e., IND Safety Reports) to the regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (i.e., EU). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

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

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

You may contact the sponsor's Medical Monitor for any other problem related to the safety, welfare, or rights of the study subject.

For SUSARs from a blinded trial, unblinded Council for International Organizations of Medical Sciences-I report will be submitted to the authorities and IRB/IEC where required.

5.5.6 Follow-up to Adverse Events

All adverse events 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 adverse event follow-up, the adverse event 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 2 (Liver Safety Monitoring and Assessment) for detailed instructions on liver abnormality follow-up responsibilities related to history of symptoms, concomitant drug use, alcohol use, and recreational drug use.

5.5.7 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are progression to end stage renal disease. This does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.5.5 Reporting of Serious Adverse Events (SAEs).

5.5.8 Procedure in Case of Pregnancy

If a female subject or female partner of a male subject becomes pregnant during the subject's treatment 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 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.
- ″Normality″ of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

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, as applicable/needed. Investigators should inform the IRB/IEC of such information when needed.

5.5.10 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 will be performed [see Section 5.1.5]. The Sponsor's Medical Monitor should be contacted as applicable.

5.6 Test Drug Concentration

For purpose of evaluation of population pharmacokinetics, blood samples will be obtained from all subjects. The intention is to collect 6 blood samples per subject at the following time points:

A: up to 2 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 over 1 to 3 visits, 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 pharmacokinetic visit (last assessment of the visit)
- The investigator is free to choose at which study visits, between weeks 2 and 8 of treatment, to draw the samples and in which order. The study site will inform the subjects on timing and process of the sampling. Based on preference of the study site, there is a choice of 3 sampling schedules to perform the pharmacokinetic samples collection, see [Table 8].
- During weeks 1 to 8 subjects will be instructed to record the date and time of study drug intake in the Study Medication Diary (SMD), except for the visit(s) when the study drug is taken in the clinic. The information will be used to record the date and time of roxadustat intake on the day prior to pharmacokinetic sampling and on the day of pharmacokinetic sampling in the eCRF. The date and time of each pharmacokinetic sample and the actual study drug dose taken on the day of sampling will be recorded in the eCRF.

Table 8 Example of Sampling Schedules for Population Pharmacokinetics

Schedule[a]	Pharmacokinetic Visit 1	Pharmacokinetic Visit 2	Pharmacokinetic Visit 3
1	Collect sample A Take study drug in clinic Collect samples B to F	None	None
2[a]	Collect sample A Take study drug in clinic Collect samples B and C	Take study drug at home Collect samples D to F	None
3[a]	Collect sample A Take study drug in clinic Collect samples B and C	Take study drug at home Collect sample D and E	Take study drug at home Collect sample F

[a] The order of the pharmacokinetic visits for schedule 2 and 3 is a decision for the investigator

5.6.1 Blood Sample for Roxadustat Pharmacokinetic Analysis

Samples of venous blood (3 mL) for bioanalysis of roxadustat will be collected into appropriately labeled tubes containing sodium-heparin as anticoagulant. Immediately after collection, blood samples will be kept on melting ice until ready for centrifugation, which must be done within 30 minutes of collection. Blood samples will be centrifuged at 1500 g for 10 minutes at room temperature in order to obtain plasma. Plasma will be harvested and transferred into an appropriately labeled 3.6 mL polypropylene storage tube and stored at -20°C or below, within 30 minutes of centrifugation.

Samples will be stored frozen at the site until shipment.

Samples will be sent to the central laboratory packed with sufficient dry ice to keep the samples frozen. Further details will be provided in the laboratory manual.

5.7 Other Measurements, Assessments, or Methods

Serum levels of albumin and α1-AGP will be included as covariate in the pharmacokinetic 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 pharmacokinetic sampling is performed (1-3 visits). If 1 or more pharmacokinetic samples are taken at a visit, 1 α1-AGP sample should be taken at that visit as well.

After blood sampling, serum separator tube (SST), samples should be kept in an upright position for at least 30 minutes at room temperature to allow blood clotting. The tubes should not be refrigerated or opened during this time. After this clotting period, the SST will be centrifuged for 10 minutes at 1500 g at room temperature within the next 30 minutes (i.e., within 1 hour of sampling). Serum from each tube will be harvested and transferred into a properly labeled polypropylene tube and stored at –20°C or below until shipment to the central laboratory where they will be analyzed.

5.7.1 Hepcidin in Serum

For the determination of hepcidin, serum samples will be drawn at the visits as indicated in [Table 1]. All details on the processing of the samples, storage and shipment conditions will be provided in the laboratory manual. Results will be blinded to site personnel and the Sponsor.

5.7.2 Archival of Serum Samples for Biomarker Analysis

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

5.7.4 Optional Genotyping Sample

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

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 ethylenediaminetetraacetic acid (anticoagulant) 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 after completion of the study according to relevant guidance and procedures.

5.8 Total Amount of Blood

The maximum total amount of blood to be collected per subject during the study period, if subject completes 104 weeks of treatment, allowing full rescreening and unscheduled visits is estimated to be 420 mL.

6 TERMINATION OF THE CLINICAL STUDY

1. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the investigator.
2. If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor of the discontinuation and the reason for it.

7 STATISTICAL METHODOLOGY

7.1 Sample Size

The study is sufficiently powered for both regionally-based primary efficacy endpoints. A minimum of 450 subjects are planned to be randomized to receive roxadustat or placebo (2:1 with approximately 300 roxadustat versus 150 placebo) in a double-blind manner in order to support the primary endpoint(s) of the study.

EU (EMA)

Three hundred subjects for the roxadustat treatment group and 150 subjects for the placebo treatment group will provide > 95% test power to demonstrate a statistically significant difference between roxadustat and placebo in the primary endpoint assuming that the proportion of subjects with response in the roxadustat group is at least 65% and in the placebo group is at most 25%.

USA (FDA)

A sample size of 450 will have > 99% power to detect a 1.0 g/dL difference in mean Hb values between the 2 treatment groups, assuming that the common standard deviation is 1.2 g/dL using an analysis of variance (ANOVA) test with a 0.05 2-sided significance level.

Most importantly, this sample size is required for a meta-analysis of composite safety endpoint by pooling studies. Four hundred and fifty subjects is the minimum number of subjects that will be randomized. In case this sample size is not sufficient to achieve the required number of MACE/MACE+ events, then the number of randomized subjects will be increased up to 600. The justification of the required number of events for this safety endpoint will be detailed in the pooled cardiovascular safety analysis plan.

7.2 Analysis Set

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

- Full Analysis Set (FAS)
- Per Protocol Set (PPS)
- Safety Analysis Set (SAF)
- Pharmacokinetic Analysis Set (PKAS).

7.2.1 Full Analysis Set (FAS)

All randomized subjects who received at least 1 dose of study drug and have at least 1 post-dose Hb assessment. All efficacy data will be analyzed using the full analysis set.

7.2.2 Per Protocol Set (PPS)

All FAS subjects who received at least 2 weeks of study treatment with valid corresponding Hb measurements and without major protocol deviations. Criteria for PPS exclusion will be defined in the Statistical Analysis Plan (SAP). The primary and secondary efficacy endpoints will also be analyzed using the per protocol set.

7.2.3 Safety Analysis Set (SAF)

All subjects that received any dose of study drug will be included in the safety population. All safety data will be analyzed using the safety population.

7.2.4 Pharmacokinetic Analysis Set (PKAS)

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

- Received at least 1 dose of study drug, and
- At least 1 quantifiable plasma concentration of roxadustat was obtained and dosing and sampling history has been recorded.

Additional details of the population pharmacokinetics (PPK) analysis set will be described in a separate document.

The PKAS will be used for all tables and graphical summaries of the pharmacokinetic data.

7.3 Demographics and Other Baseline Characteristics

Demographic (age, race, sex) and BL characteristics, including stratification factors, and subject disease characteristics will be summarized for the Safety, FAS and PPS populations.

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

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

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

EU (EMA)

The primary efficacy endpoint for EU (EMA) is a binary response endpoint (Hb response) defined as:

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

at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without having received rescue therapy (i.e., RBC transfusion, ESA, or IV iron) prior to Hb response.

Subjects in FAS who either discontinue or receive rescue therapy before Hb response will be regarded as non-responders.

US (FDA)

The primary efficacy endpoint for US (FDA) is a quantitative endpoint defined as:

The change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 52)

Hb results obtained from the central laboratory will be used for all efficacy analyses. Baseline Hb is defined as the mean of the 4 central laboratory Hb values prior to the first dose of study drug.

7.4.1.1 Primary Analysis

EU (EMA)

The EU (EMA) primary efficacy endpoint will be analyzed using the FAS.

The proportion of responders in the EU (EMA) primary efficacy endpoint will be compared using a Cochran–Mantel–Haenszel (CMH) test adjusting for the stratification factors comparing pooled roxadustat to pooled placebo. The EU (EMA) primary hypothesis to be tested for the primary efficacy analysis is:

> H_0: Hb responder rate in the roxadustat group = Hb responder rate in the Placebo group
>
> versus
>
> H_1: Hb responder rate in the roxadustat group ≠ Hb responder rate in the Placebo group

H_0 tested at the alpha=0.05 level of significance and will be rejected if the $p<0.05$ from the test.

The CMH adjusted odds ratio (pooled roxadustat versus pooled placebo) and its 95% confidence interval (CI) will be provided. In addition, a 95% CI will be calculated for the proportion of each roxadustat and placebo based on the exact method of Clopper-Pearson.

US (FDA)

The US (FDA) primary efficacy endpoint will be analyzed using all randomized subjects (intent-to-treat principle).

The Hb change from BL to the average Hb of weeks 28-52 will be analyzed using a Mixed Model of Repeated Measurements (MMRM) with unstructured covariance matrix model. The model will contain terms for treatment arm, BL measurement, visit, visit x treatment arm, and other stratification factors.

The primary hypothesis to be tested for the US (FDA) primary efficacy analysis is:

> H_0: Hb mean change from BL to the average level from Week 28 to Week 52 in the roxadustat group = Hb mean change from BL in the placebo group
>
> versus:
>
> H_1: Hb mean change from BL to the average level of Week 28 to Week 52 in the roxadustat group ≠ Hb mean change from BL in the placebo group.

7.4.1.2 Secondary Analysis

The 2 primary efficacy analyses will be repeated using the PPS.

As a sensitivity analysis, the analysis of the EU (EMA) primary endpoint will be repeated using all Hb values during the first 24 weeks regardless of whether rescue therapy was used.

A sensitivity analysis on the 2 primary efficacy endpoints will be performed on the subgroup of patients being randomized after the implementation of protocol v2.0.

7.4.1.3 Subgroup Analysis

The analysis of the primary endpoint and selected secondary endpoints 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.

7.4.2 Secondary Endpoints

7.4.2.1 Primary Analysis

Once the primary hypothesis has been rejected for the EU (EMA) primary efficacy endpoint [see Section 7.4.1.1], the key secondary endpoints below will be tested using a fixed sequence testing procedure, as depicted in [Table 9], in order to maintain the overall 2-sided type I error rate at 0.05. If P-value from a test is < 0.05, the claim of superiority (or noninferiority for tests 6 and 7) will be considered successful and the test will progress to the next comparison in sequence. The analysis set for the analysis of the secondary endpoints will be the PPS for the noninferiority tests and the FAS for the superiority tests.

Table 9 Secondary Endpoints Fixed Sequence Testing Procedure

Test	Endpoint	Test (superiority unless otherwise specified)
1	Hb change from BL	*Pooled roxadustat versus pooled placebo
2	LDL change from BL	*Pooled roxadustat versus pooled placebo
3	Use and time to use of rescue therapy	*Pooled roxadustat versus pooled placebo
4	SF-36 PF subscore change from BL	*Pooled roxadustat versus pooled placebo
5	SF-36 vitality subscore change from BL	*Pooled roxadustat versus pooled placebo
6	MAP change from BL	Noninferiority of pooled roxadustat versus pooled placebo
7	Occurrence and time to occurrence of hypertension	Noninferiority of pooled roxadustat versus pooled placebo

*Subjects randomized to roxadustat QW, BIW and TIW prior to implementation of protocol v2.0 will be pooled together. Subjects randomized to placebo will also be pooled together.

- Change from BL in the average Hb of weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period (superiority of pooled roxadustat versus pooled placebo) will be analyzed using a MMRM with unstructured covariance matrix model. The model will contain terms for treatment arm, BL measurement, visit, visit x treatment arm and other stratification factors.
- Change from BL in LDL cholesterol to the average value of LDL cholesterol of weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) using a MMRM model with unstructured covariance containing terms for treatment arm, BL measurement, visit, visit x treatment arm, and other stratification factors.
- Use and time to use of rescue therapy (composite of RBC transfusion, ESA use and IV iron) in the first 24 weeks of treatment will be reported and compared using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and its 95% will be calculated for the frequency of pooled roxadustat as relative to pooled placebo. Superiority will be declared if the lower bound of the 2-sided 95% CI is higher than 1.0.
- Change from BL in SF-36 PF subscore to the average in weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subset of subjects with BL PF subscore below 35, using a MMRM model with unstructured covariance containing terms for treatment arm, BL measurement, visit, visit x treatment arm, and other stratification factors.
- Change from BL in SF-36 vitality subscore to the average SF-36 vitality subscore in weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subset of subjects with BL vitality subscore below 50, using a MMRM model with unstructured covariance containing terms for treatment arm, BL measurement, visit, visit x treatment arm, and other stratification factors.

- Change from BL in MAP to the average MAP in weeks 20–28 will be compared (noniferiority of pooled roxadustat versus pooled placebo) using a MMRM model with unstructured covariance containing terms for treatment arm, BL measurement, visit, visit x treatment arm, and other stratification factors. Noninferiority will be declared if the upper bound of the 2-sided 95% CI of the difference between roxadustat and placebo is below 2 mmHg.
- Occurrence and time to occurrence of hypertension will be reported and compared (noninferiority of pooled roxadustat versus pooled placebo) using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and its 95% will be calculated for the frequency of pooled roxadustat as relative to pooled placebo. Noninferiority will be declared if the upper bound of the 2-sided 95% CI does not exceed 1.3. Once this hypothesis is rejected, superiority will be checked but not as part of the sequence testing procedure.

7.4.2.2 Secondary Analysis

Each of the key secondary endpoints will be repeated separately by gender, age group, region, BL Hb categories, iron repletion at BL, diabetes and eGFR categories. Subgroup analyses will be detailed in the SAP.

7.4.3 Analysis of Additional Efficacy Endpoints

Statistical methods for the additional endpoints detailed in [Section 2.3.3.1] will be detailed in the SAP.

7.5 Analysis of Safety

Safety analyses will be performed using the SAF. Safety parameters include AEs, laboratory parameters (with special emphasis on excessive Hb response and LFTs), vital signs, renal ultrasound findings 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 BL for all analyses. All safety analyses will be presented by treatment group; roxadustat and placebo. Further details will be described in the SAP.

7.5.1 Adverse Events

AEs will be coded using MedDRA.

An AE (classified by preferred term) started during the double-blind treatment period will be considered a 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 double-blind 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 SOC and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to study medication. If more than 1 event occurs with the same preferred term for the same subject, the subject will be counted only once for that

preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study medication.

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

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

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

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

Adjudicated safety data will be reported in a separate report.

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

7.5.2 Clinical Laboratory Parameters

Descriptive statistics for laboratory values (in International System of Units [SI]) and changes from BL at each assessment time point and for the maximum and minimum value on treatment will be presented by treatment group for all laboratory parameters. Presence of Potentially Clinically Significant laboratory values will be reported using similar statistics as mentioned for TEAEs.

7.5.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic BP, 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 ECG

Descriptive statistics for ECG parameters (Heart Rate, PR interval, QRS interval, QT interval and QTc [QT interval corrected for heart rate] 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; and if RR is not available, it

will be replaced with 60/HR in the correction formula. Presence of Potentially Clinically Significant ECG values will be reported using similar statistics as mentioned for TEAEs.

7.5.5 ESA

A variety of sensitivity analyses may be performed to evaluate subjects who did or did not receive rescue with ESAs, and excluding CV events occurring during the interval after receipt of rescue.

7.6 Analysis of Pharmacokinetics

Plasma concentration data of roxadustat will be subjected to population pharmacokinetic analysis. The aim of this analysis is to describe the pharmacokinetic behavior of roxadustat in the target population and to evaluate the effects of selected covariates on the pharmacokinetics of roxadustat. The results of the population pharmacokinetic analysis will not be reported in the Clinical Study Report but in a separate population pharmacokinetic modeling report.

7.7 Analysis of Pharmacodynamics

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

7.8 Protocol Deviations and Other Analyses

Protocol deviations requiring notification to the Sponsor as defined in Section 8.1.6 Protocol Deviations 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 (and Early Discontinuation of the Clinical Study)

The study will have no interim analysis with statistical inference. Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be completed by an independent DSMB [see Section 10.1].

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

Main analysis of the efficacy endpoints with repeated measures over time will follow the MMRM methodology. In addition, as a sensitivity analysis, a Last Observation Carried Forward (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 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.

The investigator or site designee will enter data into an eCRF 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 onto the eCRF as soon as possible after the subject visit. The SMD and the questionnaires will be completed by the subject. The investigator or designee should review the diaries and questionnaires for correct completion whilst the subject is at the site. The investigator or site designee will enter only the relevant information from the medication diary (i.e., study medication intake data related to pharmacokinetic sampling) and all questionnaire date directly into the EDC system. (e)CRFs, 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 the central laboratory and specialist laboratory.

Laboratory results will be provided to the investigator who will print and retain the laboratory results and sign abnormalities for their clinical relevance. Laboratory data will be transferred electronically to the Data Management Center at predefined intervals during the study.

The laboratory may provide the Data Manager 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 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
- Participation in study and signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data
- Adverse events and concomitant medication
- Results of HemoCue device Hb assessments on all visits
- Decision on study drug dosage on all visitsResults of relevant examinations (e.g., ECG charts, Ultrasound reports)
- Laboratory printouts (such as Central Laboratory assessments, including certification by the investigator of abnormal laboratory data being clinically relevant or not)
- Dispensing and return of study drug details
- Reason for premature discontinuation from study treatment (if applicable)
- Subject number
- Method of contraception for subjects or subject's partner of childbearing potential.

8.1.3 Clinical Study Monitoring

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

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents [refer to Section 8.1.2 "Specification of Source Documents"] 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 Drug Reference list 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 was 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.

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)

The clinical study may only begin after receipt of a written approval from the IRB/ IEC. Documents to be submitted to the IRB/IEC may differ per committee but should at least

include the final study protocol, subject information, informed consent and the Investigator's Brochure, containing information on the study drug.

This protocol and the required supporting documents will be submitted to the Competent Authority (CA) according to the national laws. Prior to starting the study, approval must be obtained in writing, where applicable. The original or at least a photocopy of this statement must be forwarded to the sponsor.

The investigator shall make accurate and adequate written progress reports to the IRB/IEC/CA at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB/IEC/CA for APEB sponsored studies within 1 year after last subject out or termination of the study.

8.2.2 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to ICH GCP Guidelines and the applicable laws and regulations.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

Prior to execution of the clinical study, the investigator should prepare the written informed consent form and other written information in collaboration with the delegated CRO/sponsor and revise the information whenever necessary. The written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the IRB/IEC.

- The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will.
- The investigator or delegate who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the written information, or write down his/her name, and date the form.
- Informed consent must be obtained by the time that the first observations / examinations of the screening period are performed. Guardian consent should be obtained from the proxy consenter, before start of pre-investigational period.
- The investigator or other responsible personnel must give a copy of the signed consent form to the subject and store the original appropriately in accordance with the rules at the study site concerned.
- The investigator or other responsible personnel should note the following when obtaining consent from subjects:
    - No subject may be subjected to undue influence, such as compulsory enrollment into a study.

- The language and expressions used in the written information should be as plain and understandable as possible. Subjects should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor 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/sub-investigator 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 participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented in the subject's medical records, and it should be confirmed whether the subject is willing to remain in the study or not.
2. If the investigator recognizes the necessity to revise the written information in the terms and conditions applicable to paragraph 1, the written information should be revised immediately based upon the newly available information, and be re-approved by the IRB/IEC.
3. The investigator/sub-investigator must obtain written informed consent to continue participation with the revised written information defined in paragraph 2, even if subjects are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the informed consent form, or write down his/her name and date the form. The investigator or other responsible personnel should give a copy of the signed informed consent form to the subject who had given consent with the written information and store the original appropriately as done for the previous informed consent.

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, its board members, and its personnel shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

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 federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

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 discussed 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 (IEC only if applicable per local regulations) ● CRFs and SAE Worksheet ● Investigator’s File ● Study drug with all necessary documentation ● Study contract ● 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 U.S. IND ● If the investigator submits to the IEC: Submission letter to the 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.) ● Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee) ● 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, and Investigator's File) and relevant correspondence. Essential documents should be retained until at least 2 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 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution when these documents no longer need to be retained. 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 ICH GCP.

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 eCRFs supplied for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented to 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 Investigator Indemnity

The sponsor agrees to, and does hereby, indemnify, defend and hold the investigator harmless from and against all claims, demands, actions, and proceedings which may be brought or asserted against the investigator to recover damages and losses for or attributable to bodily injury, sickness, disease, or death arising from or alleged to arise from or be reasonably attributable to this study.

Notwithstanding the foregoing, the sponsor does not, however, agree to indemnify, defend or hold the investigator harmless from claims, demands, actions, proceedings or damages resulting or claimed to have resulted from:

- Failure of the investigator to evaluate or properly interpret available information that is relevant to this study, and for independent decisions made as the result of such failure;
- Failure of the investigator to adhere to all provisions of the protocol for this study and to written recommendations and written instructions delivered to the investigator by the sponsor concerning the administration and use of drug substances, including the placebo, involved in this study;
- Failure of the investigator to render professional service or to conduct this study in a normal, prudent manner.

A condition of this indemnity obligation is that, whenever the investigator has information from which it may be reasonably concluded that an incident of bodily injury, sickness, disease or death has occurred, the investigator shall immediately give notice to the sponsor of all pertinent data surrounding any such incident, and, in the event a claim is made or a suit is brought, the investigator shall assist the sponsor and cooperate in the gathering of information with respect to the time, place, and circumstances and in obtaining the names and addresses of the injured parties and available witnesses. The investigator shall not, except at his own cost, voluntarily make any payment or incur any expense in connection with any such claim or suit without the prior written consent of the sponsor.

8.3.6 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 a Coordinating (principal) Investigator. The Coordinating Investigator 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. A Coordinating Investigator will be selected from the participating investigators by Astellas 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 (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The sponsor or sponsor's designee may arrange to inspect/audit the clinical study at any or all investigational sites. The auditor is independent from the clinical monitoring and project management team at the sponsor. 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 pre-specified safety data periodically in collaboration with the sponsor to ensure subject safety. The DSMB will review safety data in a blinded and unblinded manner while the sponsor remains blinded.

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

10.2 Independent Event Review Committee (IERC)

An IERC will adjudicate all relevant cardiovascular and cerebrovascular events in a blinded manner to ensure consistent safety assessment. Details will be specified in an IERC Charter.

10.3 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 Appendix 1: List of Prohibited Concomitant Medication

- Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to randomization until EOS visit.
- Androgens from the day of randomization until EOS visit.
- Dapsone in any dose amount from the day of randomization until EOS visit.
- Chronic use of acetaminophen (paracetamol) > 2.0 g/day from the day of randomization until EOS visit.
- Any hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) other than roxadustat, as allocated by randomization, until EOS visit.

12.2 Appendix 2: Liver Safety Monitoring and Assessment

If laboratory testing for a subject randomized in study and receiving study drug reveals an increase of serum AT to > 3× ULN, or bilirubin > 2× ULN, at least all 4 of the usual serum hepatic measures (ALT, AST, ALP, and TBL) should be repeated. Testing should be repeated within 48 – 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality, to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

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

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

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

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

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

Follow-up Procedures

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

Study Discontinuation

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

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

*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 2 "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocelluary-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 too be discriminating"). 2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x 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. Pharmacoepidermiol Drug Saf 2006 Apr;15(4):241-3.]"

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

Reference

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

12.3 Appendix 3: Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0

Visit Schedule

Subjects who have entered the study under protocol v1.0, upon signing the updated informed consent, adapted their visit frequency according to Table 1. Schedule of Assessments. For example, if the subject signs the 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.

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 who have entered the study under protocol version 1.0 should, upon signing the updated informed consent, adapt their dose frequency and dose amount. 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. Once that is established, patients 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 HD 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 the conversion table below, at the visit when the updated informed consent 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 the 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 were only applicable when the criteria for dose adjustment has been met

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

Note: There are no adaptations to dose frequency or dose amount for subjects moving from Protocol v2.0 to Protocol v2.1.

ESA Rescue Therapy

Protocol v2.0 allows subjects to receive ESA rescue treatment twice. If a third ESA treatment is required the subject will be discontinued from the study treatment.

If, upon implementation of protocol v2.0, a subject has already received 3 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.

12.4 Appendix 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., HD, hemodiafiltration (HDF) and peritoneal dialysis 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).
- 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 peritoneal dialysis subjects) or 400 mg per administration, whichever is lower.

12.4.3 Rescue Therapy – ESA Use

If subjects meet the criteria for ESA rescue therapy whilst on dialysis, ESAs will be administered IV or SC according to the Package Insert or SmPC of the respective ESA for dialysis patients.

12.4.4 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.

12.4.5 Timing of Study Assessments

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

12.5 Appendix 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!***

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for completing these questions!

12.6 Appendix 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

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FACT-An (Version 4)

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

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

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

FACT-An (Version 4)

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

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

12.7 Appendix 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)*

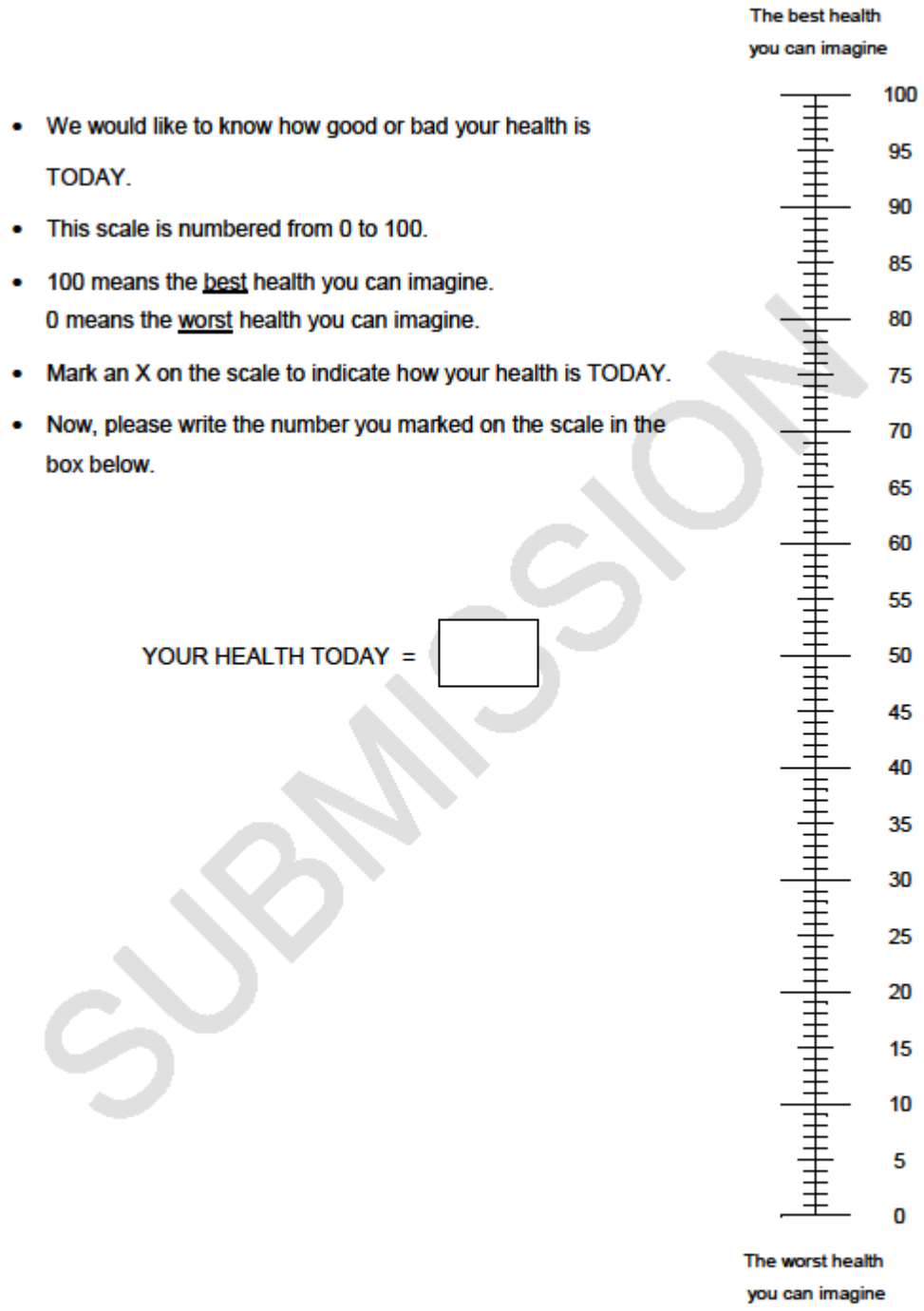
I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

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 Appendix 8: Patients' 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 Appendix 9: Work Productivity and Activity Impairment Questionnaire: Anaemic Symptoms V2.0 (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 anaemic symptoms 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

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5): 353-65.

Appendix 3: Protocol Instructions Subjects Moving from Protocol v1.0 to Protocol v2.0

Visit Schedule

Subjects who have entered the study under protocol v1.0 should, upon signing the updated informed consent, adapt their visit frequency according to Table 1, Schedule of Assessments.

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

Study drug will be dosed TIW throughout the Treatment Period, unless otherwise specified.

Subjects who have entered the study under protocol version 1.0 should, upon signing the updated informed consent, adapt their dose frequency and dose amount. At this visit it is first determined if the subject would need a dose titration according to the dose adjustment rules. Once that is established, patients 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, the dose assigned must not exceed 3.0 mg/kg (based on dry weight in HD subjects and weight minus abdominal fluid based on last filling in peritoneal dialysis subjects) or 400 mg per administration, whichever is lower.

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

a) Subjects in the maintenance period on BIW dosing will change to TIW dosing immediately, per conversion table below, at the visit when the updated informed consent 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

b) 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 adjustment has been met;

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

ESA Rescue Therapy

Protocol v2.0 allows subjects to receive ESA rescue treatment twice. If a third ESA treatment is required subject will be discontinued from the study treatment.

If, upon implementation of protocol v2.0, a subject has already received 3 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.

13 ATTACHMENT 1: NON-SUBSTANTIAL AMENDMENT 1

I. The purpose of this amendment is:

Non-Substantial Changes
1. Update contact details of key sponsor personnel
DESCRIPTION OF CHANGE:
Update the sponsor personnel to be contacted for SAE to the Product Safety & Pharmacovigilance group and the affiliation of the medical monitor and clinical research contact.
RATIONALE:
To provide the most up-to-date information for the key sponsor personnel.
2. Update abbreviation list
DESCRIPTION OF CHANGE:
Add ANOVA, DD-CKD, IUD, IUS, MRI, NDD-CKD, PPD, PPK/PD and SmPC to the abbreviation list. Delete ANCOVA, APEBV, APGD, BIW, CHOIR, CIOMS, CL/F, Composite Safety Endpoint, DSP, (e)CTD, EDTA, ELISA, EU, EWB, FDA, FWB, GGT, GMP, hCG, Hct, IB, IMPD, IND, INN, k_a, kg, Ki, LLN, LSO, MedDRA, mg, min, mL, MTD, NASH, NONMEM, PCS, PD, PHI, PK, pmp, QW, SOC, SQ, TESAE, t_{max}, V/F, VHL, WHODRL and Wk from the abbreviation list.
RATIONALE:
Complete abbreviation list.
3. Update post study follow-up
DESCRIPTION OF CHANGE:
Update wording to include follow-up of SAEs, cardiovascular and thromboembolic AEs during the post study follow-up and to remove the word ‘hospitalizations’.
RATIONALE:
The additional wording is to provide clarification on events that are required for collection during the post study follow-up period. Information about hospitalizations is already stated in Section ‘5.3.3.2 Hospitalizations’ and is therefore removed from the description of the post study follow-up.
4. Update planned study period
DESCRIPTION OF CHANGE:
Update the planned study period.

RATIONALE:
To reflect current recruitment and completion timelines of the study.
5. Clarify study population description
DESCRIPTION OF CHANGE:
Update the study population description.
RATIONALE:
To reflect inclusion criterion 3.
6. Clarify follow-up of discontinued subjects with ongoing adverse event or unresolved laboratory result
DESCRIPTION OF CHANGE:
Add wording relating to follow-up of subjects who have discontinued from the study.
RATIONALE:
To provide additional clarity to investigators to ensure that discontinued subjects who have ongoing adverse events or unresolved laboratory results are followed up until condition stabilizes or is no longer clinically significant.
7. Update dose adjustment rules
DESCRIPTION OF CHANGE:
Remove the wording attached to criteria for moving subjects from correction period to maintenance period.
RATIONALE:
Primary efficacy text is incorrectly placed under the dose adjustment rules.
8. Clarify description of EOT visits
DESCRIPTION OF CHANGE:
Add description of EOT visit to include EOT visit and EOT + 2 weeks visit.
RATIONALE:
To provide clarity that EOT visits relate to 2 visits, 2 weeks apart.
9. Update to the order of the secondary efficacy endpoints
DESCRIPTION OF CHANGE:
Update of the order of the secondary endpoints for the fixed sequence testing procedure. Change from BL in MAP and occurrence and time to occurrence of hypertension are moved down, and change from BL in SF-36 PF and VT are moved up.

RATIONALE:
To adapt the order of statistical testing of key secondary endpoints on QoL related to the secondary objective of the study which are considered more important than the blood pressure endpoints.
10. Modify unscheduled visits
DESCRIPTION OF CHANGE:
Change the mandatory collection of Hb assessment and vital signs at unscheduled visits to optional.
RATIONALE:
To update the protocol so that the collection of Hb and vital signs is optional at unscheduled visits leaving the decision as to which assessments are relevant with the investigator. When testing Hb, both the HemoCue assessment (used for dose decisions) and central lab Hb (used for statistical analysis) should be tested. However, unscheduled visits can be planned for other purposes without there being a need for Hb and vital signs assessment.
11. Update the schedule of assessments
DESCRIPTION OF CHANGE:
Updates to the Schedule of Assessments to reflect changes made in this Amendment and to add clarifications to the footnotes.
RATIONALE:
To provide up to date and accurate information.
12. Update pharmacokinetic and pharmacodynamics information on roxadustat and clarify concomitant medication (drug and therapies)
DESCRIPTION OF CHANGE:
Update the pharmacokinetic and pharmacodynamic information based on the results of the drug-drug interaction studies performed with statins and phosphate binders and add additional clarifications and advice regarding potential drug-drug interaction with roxadustat including drugs that are substrates of OATP 1B1 and multivalent cation-containing drugs and mineral supplements.
RATIONALE:
To replace the interim results with the final results of the completed drug-drug interaction studies and update advice provided based on final results.

13. Clarify liver enzyme and pancreatitis event monitoring in roxadustat clinical program
DESCRIPTION OF CHANGE:
Add the development phase during which liver enzymes and number of pancreatitis events are closely monitored during the roxadustat clinical development program.
RATIONALE:
To add clarity to the summary of key information.
14. Remove additional secondary evaluation of efficacy
DESCRIPTION OF CHANGE:
Remove an additional secondary efficacy evaluation endpoint relating to Hb correction and maintenance.
RATIONALE:
To remove an endpoint that is not well defined as it is confounding the treatment effect with the endpoint by subgroup defined as the patients who reach 11 or higher Hb values.
15. Clarify discontinuation criteria
DESCRIPTION OF CHANGE:
Add wording stating investigator responsibility if a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result.
RATIONALE:
To add clarity to the discontinuation procedure.
16. Update information related to roxadustat study drug handling
DESCRIPTION OF CHANGE:
Remove bullet point relating to storage of tablets.
RATIONALE:
Storage information for roxadustat is included in the Pharmacy Manual.
17. Update information on dosing instructions
DESCRIPTION OF CHANGE:
Add dosing instructions for patients moving from protocol v1.0 or v2.0 to protocol v 2.1.
RATIONALE:
To confirm that no adaptation to dose of study medication is required under this amendment.

18. Update the rescue therapy guidelines of ESAs
DESCRIPTION OF CHANGE:
Add a procedure for subjects meeting ESA rescue therapy while on dialysis.
RATIONALE:
To add the same procedure from Appendix 12.4 to Section 5.1.5 for the administration of ESAs while on dialysis.
19. Update the Modification of Diet in Renal Disease equation
DESCRIPTION OF CHANGE:
Update the Modification of Diet in Renal Disease equation for calculating eGFR.
RATIONALE:
To align with central laboratory equation. There is no impact on entry criteria of the subjects or impact on the safety of subjects.
20. Update blood pressure and heart rate measurements
DESCRIPTION OF CHANGE:
Remove wording related to calculation of blood pressure and heart rate within the eCRF.
RATIONALE:
Blood pressure and heart rate are calculated as an average of all 3 readings taken at each timepoint and not calculated from the 2nd and 3rd readings as currently stated. As blood pressure and heart rate are calculated within RAVE (eCRF) and not by the investigator, they are not required to be stated in the protocol and the calculation wording is being removed.
21. Update adverse event reporting for cardiovascular adjudication
DESCRIPTION OF CHANGE:
Provide a more detailed description of the process of collecting adverse events and submission of documentation for events requiring adjudication is added.
RATIONALE:
To align with other roxadustat phase 3 studies.
22. Update definition of serious adverse events
DESCRIPTION OF CHANGE:
Remove wording ‘always serious’ events reporting may be expedited within the timelines as for SAEs.
RATIONALE:
Expedited reporting by investigators is not required for Adverse Events. Investigators are not provided with an ‘always serious’ list and therefore cannot know if they are classified as SAEs and therefore require expedited reporting.

23. Update contact details for reporting of serious adverse events (SAEs)
DESCRIPTION OF CHANGE:
Add additional contact details for a delegated CRO.
RATIONALE:
A second CRO, in addition to [redacted], is supporting the SAE reporting in countries within South America, Belarus, Estonia and Greece. Contact details of the second CRO, [redacted] is added.
24. Clarify the procedure for supplying new information affecting the conduct of the study
DESCRIPTION OF CHANGE:
Clarify procedure for supplying new information that affects the conduct of the study.
RATIONALE:
To clarify that the regulatory authorities can be informed of new information relating to the proper conduct of the clinical study, which many not necessarily be included in Dear Doctor Letters or that will lead to a protocol amendment.
25. Update primary analysis of secondary efficacy endpoints
DESCRIPTION OF CHANGE:
Removal of the non-inferiority test for time to use of rescue therapy (only the superiority test is to be performed). Removal of the superiority test for both 'time to occurrence of hypertension' and 'MAP change from BL'. Alignment of wording with regards to the definition of noninferiority margin, where applicable.
RATIONALE:
To align with the assumption that roxadustat is expected to show superiority versus placebo for the time to use of rescue therapy. For time to hypertension and MAP change from BL, the assumption is that roxadustat is not worse than placebo.
26. Update the secondary analysis of secondary efficacy endpoints
DESCRIPTION OF CHANGE:
Delete the analysis for the key secondary efficacy endpoints on the PPS.
RATIONALE:
To align with Section 7.4.2.1 which states that the PPS is used for the noninferiority tests and the FAS for the superiority tests.

27. Removal of the sensitivity analysis
DESCRIPTION OF CHANGE:
Delete the sensitivity analysis using ANCOVA with the LOCF method.
RATIONALE:
The LOCF method is potentially a biased method in favor of roxadustat.
28. Publication of clinical study
DESCRIPTION OF CHANGE:
Delete the information describing process of publication or data disclosure.
RATIONALE:
Publication is included in individual site contracts.
29. Minor administrative-type changes
DESCRIPTION OF CHANGE:
Minor administrative-type changes, e.g., typos, format, numbering, consistency and clarity throughout the protocol, are included.
RATIONALE:
Update the protocol to correct formatting and to provide clarifications to ensure complete understanding of study procedures.

II. Amendment Summary of Changes: Nonsubstantial Changes

II Contact Details of Key Sponsor's Personnel	
WAS:	
SAE Fax number	See SAE form
24h-Contact for Serious Adverse Events (SAEs) See Section 5.5.5	[redacted]
EU Medical Monitor:	[redacted] Astellas Pharma Europe B.V. [redacted]
Clinical Research Contact:	[redacted] Astellas Pharma Europe B.V. [redacted]
IS AMENDED TO:	
SAE Fax number	See SAE form
~~24h~~ Contact for Serious Adverse Events (SAEs) See Section 5.5.5	**Astellas Pharma Europe B.V.** [redacted]
~~EU~~ Medical Monitor:	[redacted] Astellas Pharma Europe B.V. [redacted]
Clinical Research Contact:	[redacted]

	[redacted] - Astellas Pharma Europe B.V. [redacted]

III List of Abbreviations and Key Terms

List of Abbreviations

ADDED:

ANOVA	**Analysis of variance**
DD-CKD	**Dialysis-dependent chronic kidney disease**
IUD	**Intrauterine device**
IUS	**Intrauterine system**
MRI	**Magnetic resonance imaging**
NDD-CKD	**Non dialysis-dependent chronic kidney disease**
PPD	**Population pharmacodynamic**
PPK/PD	**Population pharmacokinetic/pharmacodynamic**
SmPC	**Summary of Product Characteristics**

DELETED:

~~ANCOVA~~	~~Analysis of Covariance~~
~~APEBV~~	~~Astellas Pharma Europe BV Netherlands~~
~~APGD~~	~~Astellas Pharma Global Development~~
~~AUC~~	~~Area under the plasma concentration – time curve~~
~~BIW~~	~~Twice Weekly~~
~~CHOIR~~	~~Correction of Hemoglobin and Outcomes in Renal Insufficiency~~
~~CIOMS~~	~~Council for International Organizations of Medical Sciences~~
~~CL/F~~	~~Apparent total body clearance~~
	~~Composite Safety Endpoint~~
~~DSP~~	~~Drug Safety and Pharmacovigilance (department at Astellas Pharma Europe BV)~~
~~(e)CTD~~	~~Electronic Common Technical Document~~
~~EDTA~~	~~Ethylenediaminetetraacetic acid (anticoagulant)~~
~~ELISA~~	~~Enzyme linked Immunosorbent Assay~~
~~EU~~	~~European Union~~
~~EWB~~	~~Emotional Wellbeing~~
~~FDA~~	~~Food and Drug Administration~~
~~FWB~~	~~Functional Wellbeing~~
~~GGT~~	~~Gamma Glutamyl Transferase~~
~~GMP~~	~~Good Manufacturing Practice~~
~~hCG~~	~~Human Chorionic Gonadotropin~~

~~Hct~~	~~Hematocrit~~
~~IB~~	~~Investigator's Brochure~~
~~IMPD~~	~~Investigational Medicinal Product Dossier~~
~~IND~~	~~Investigational New Drug (Application)~~
~~INN~~	~~International Nonproprietary Name~~
~~k_a~~	~~First order absorption rate constant~~
~~kg~~	~~Kilogram~~
~~Ki~~	~~Inhibition Constant~~
~~LLN~~	~~Lower Limit of Normal~~
~~LSO~~	~~Last Subject Out~~
~~MedDRA~~	~~Medical Dictionary for Regulatory Activities~~
~~mg~~	~~Milligram~~
~~min~~	~~Minute~~
~~mL~~	~~Milliliter~~
~~MTD~~	~~Maximum Tolerated Dose~~
~~NASH~~	~~Non-Alcoholic SteatoHepatitis~~
~~NONMEM~~	~~Non-linear Mixed Effects Modeling~~
~~PCS~~	~~Physical Component Scores~~
~~PD~~	~~Pharmacodynamic~~
~~PHI~~	~~Protected health information~~
~~PK~~	~~Pharmacokinetic~~
~~pmp~~	~~Per million population~~
~~QW~~	~~Once Weekly~~
~~SOC~~	~~System Organ Class~~
~~SQ~~	~~subcutaneous~~
~~TESAE~~	~~Treatment-Emergent Serious Adverse Event~~
~~t_{max}~~	~~Time to Attain C_{max}~~
~~V/F~~	~~Apparent volume of distribution~~
~~VHL~~	~~Von Hippel-Lindau~~
~~WHODRL~~	~~World Health Organization Drug Reference list~~
~~Wk~~	~~Week~~

III List of Abbreviations and Key Terms, IV Synopsis, 2 Study Objective(s), Design, and Endpoints, 3 Study Population, 5 Treatments and Evaluation

List of Key Study Terms, Design and Methodology, Discontinuation Criteria, 2.2.1.3 Description of Study, 2.2.1.3.4 Post-study Follow-up Period (Only for Subjects Prematurely Discontinued from Treatment), 3.3 Discontinuation Criteria for Individual Subjects, 5.1.5 Rescue Therapy Guidelines

WAS:

Subjects that have discontinued treatment prior to their projected week 104 will continue to be followed for vital status and hospitalizations in post study follow up.

IS AMENDED TO:

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

IV Synopsis, Planned Study Period
WAS:
From 1Q2013 to 3Q2017
IS AMENDED TO:
From 1Q2013 to ~~3~~**4**Q2017

IV Synopsis, 2 Study Objective(s), Design, and Endpoints and 3 Study Population *Design and Methodology, 2.2.1.2 Study Population*
WAS:
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.
IS AMENDED TO:
The study population consists of subjects with CKD ~~as defined by CKD~~ stages 3, 4, and 5 (**estimated glomerular filtration rate [**eGFR**]** < 60 mL/min/1.73 m^2) who are anemic and not ~~in need of~~ **receiving** dialysis.

IV Synopsis and 5 Treatments and Evaluation *Design and Methodology, 5.1.2 Changes in Study Drug Dose*
DELETED:
• ~~However, the decision to move from the correction period rules to the maintenance period rules is based upon 2 central laboratory Hb values taken at least 5 days apart with Hb ≥ 11.0 g/dL and a Hb increase from BL by ≥ 1.0 g/dL if BL Hb > 8.0 g/dL, or an increase from BL by ≥ 2.0 g/dL if BL Hb ≤ 8.0 g/dL.~~

IV Synopsis, 2 Study Objective(s), Design, and Endpoints, 3 Study Population and 5 Treatments and Evaluation *Design and Methodology, Discontinuation Criteria,2.2.1.3.4 Post-study Follow-up Period (Only for Subjects Prematurely Discontinued from Treatment),3.3 Discontinuation Criteria for Individual Subjects, and 5.1.5 Rescue Therapy Guidelines*
WAS:
Subjects that have stopped treatment prior to their projected week 104 will complete the EOT visit and EOS visit.
IS AMENDED TO:
Subjects that have stopped treatment prior to their projected week 104 will complete the EOT visit**s (EOT** visit **and EOT + 2 weeks visit)** and **the** EOS visit.

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

Efficacy, Statistical Methods (Secondary), 2.3.2 Secondary Endpoints

WAS:

The secondary efficacy endpoints in this study are:

- Change from BL in Hb to the average Hb in weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period
- Change from BL in LDL cholesterol to the average value of LDL cholesterol in weeks 12-28
- Blood pressure effect
  - Change from BL in Mean Arterial Pressure (MAP) to the average MAP in weeks 20-28.
  - Occurrence and time to occurrence of hypertension (defined as either SBP > 170 mmHg AND an increase from BL ≥ 20 mmHg or as DBP > 110 mmHg, AND an increase from BL of ≥ 15 mmHg on 2 consecutive visits)
- Use and time to use of rescue therapy (composite of RBC transfusions, ESA use, and IV iron) in the first 24 weeks of treatment.
- Change from BL in SF-36 Physical Functioning (PF) subscore to the average SF-36 PF subscore in weeks 12-28
- Change from BL in SF-36 Vitality (VT) subscore to the average SF-36 VT subscore in weeks 12-28

IS AMENDED TO:

The **key** secondary efficacy endpoints in this study are:

- **Hb maintenance: Hb** ~~C~~**c**hange from BL ~~in Hb~~ to the average Hb ~~in~~**of** weeks 28-36, 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 value of LDL cholesterol in weeks 12-28
- **Use and time to use of rescue therapy (composite of RBC transfusions, ESA use, and IV iron) in the first 24 weeks of treatment.**
- **Change from BL in Short Form (SF)-36 Physical Functioning (PF) subscore to the average SF-36 PF subscore in weeks 12-28**
- **Change from BL in SF-36 Vitality (VT) subscore to the average SF-36 VT subscore in weeks 12-28**
- Blood pressure effect
  - Change from BL in Mean Arterial Pressure (MAP) to the average MAP in weeks 20-28
  - Occurrence and time to occurrence of hypertension (defined as either **systolic blood pressure [**SBP**]** > 170 mmHg AND an increase from BL ≥ 20 mmHg or as DBP > 110 mmHg, AND an increase from BL of ≥ 15 mmHg ~~on 2 consecutive visits~~)
- ~~Use and time to use of rescue therapy (composite of RBC transfusions, ESA use, and~~

~~IV iron) in the first 24 weeks of treatment.~~

- ~~Change from BL in SF-36 Physical Functioning (PF) subscore to the average SF-36 PF subscore in weeks 12-28~~
- ~~Change from BL in SF-36 Vitality (VT) subscore to the average SF-36 VT subscore in weeks 12-28~~

Flow Chart and Schedule of Assessments

Table 1: Schedule of Assessments

WAS:

Study Period:	**Screening**			**Treatment**[a]				**Follow-up**				**Post study Follow- up**
	Up to 6 Weeks											
Visit / Week:	**S1**	**S2**	**S3**	**Day 1**[b]	**Weekly** (wks 1 to 2) ± 2 days	**Every 2 Weeks** (wks 4 to 24) ± 2 days	**Every 4 Weeks** (wks 28 to 100) ± 3 days	**EOT** (wk 104) ± 3 days	**EOT + 2 wks** ± 3 days	**EOS** (EOT **+ 4 wks**) ± 3 days	**Unscheduled Visits**	Every 6 months until projected wk 108
Written informed consent	X											
Randomization				X								
Eligibility criteria	X			X								
Demographics and medical history including tobacco use	X											
Weight	X			X		wks 12, 24	wks 36, 52, 76	X		X	O[d]	
Physical examination	X			X		wks 12[c] 24[c]	wks 36[c], 52[c], 76[c]	X		X[c]	O[c, d]	
Blood pressure[e], heart rate[e], respiratory rate[g]	X	X	X	X	X	X	X	X		X	X	
CBC with WBC differential, red cell indices and platelet count	X			X	X	wks 4, 8, 12, 20	wks	X		X	O[d]	
Reticulocyte count, Hemoglobin content of reticulocytes (CHr)	X			X	X	wks 4, 6, 8, 12, 16, 20	wk 28 and every following 8 wks	X		X	O[d]	
Hemoglobin[h]		X	X			X	X		X		X	
HemoCue® assessment [i]				X	X	X	X				X	
Serum chemistry (incl LFT)	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X	X	X	O[d]	
LFTs [j]					wk 2	wks 6, 16					O[d]	
Serum Lipid panel (fasting whenever possible)	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O[d]	
Serum iron, ferritin, TIBC, TSAT	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X		X	O[d]	
HbA1c	X			X		wk 12	wks 28, 36, 44, 60, 84	X		X	O[d]	
Vitamin B_{12}, folate	X											

Study Period:	**Screening**			**Treatment**[a]				**Follow-up**			**Unscheduled Visits**	**Post study Follow- up**
Visit / Week:	**Up to 6 Weeks**			**Day 1**[b]	**Weekly** (wks 1 to 2) ± 2 days	**Every 2 Weeks** (wks 4 to 24) ± 2 days	**Every 4 Weeks** (wks 28 to 100) ± 3 days	**EOT** (wk 104) ± 3 days	**EOT + 2 wks** ± 3 days	**EOS** (EOT + **4 wks**) ± 3 days		Every 6 months until projected wk 108
	S1	**S2**	**S3**									
HIV Immunoassay, HBsAg, anti-HCV antibody	X											
Serum Pregnancy test[k]	X					wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O[d]	
eGFR (Cr Clear Modified Diet Abbreviated)[l]	X			X		wk 20	wks 36, 52, 68, 84	X		X	O[d]	
Special laboratory analytes (hepcidin, sTfR, hs-CRP)				X		wks 4, 12, 20	wks 36, 52	X		X		
Archival serum/plasma samples for biomarkers				X		wks 4, 12, 20	wks 52, 76	X		X		
Blood sample for population PK					wks 2 to 8[m]							
Genotyping[n]					X							
Urinary testing[o]				X		wks 12, 24	wks 36, 52, 64, 76, 88	X			O[d]	
Quality of Life Questionnaires[p]				X		wks 8, 12, 28	wks 36, 52, 76	X			O[d]	
12-lead ECG	X			X		wks 12, 24	wks 36, 52, 76	X			O[d]	
Renal ultrasound[q]	X										O[d]	
Dose adjustment review[r]						X	X				O[d]	
Hospitalization recording[s]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	
Procedure and non-drug therapy recording	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensing[t]				X[u]	X	X	X				O[d]	
Vital Status												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; see below for footnotes)

Note: see Appendix 3: Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0

Note: see Appendix 4: Instructions for Subjects Requiring Dialysis

[a] In case of premature discontinuation or withdrawal during the treatment period, the subject should complete the EOT and EOS visits. Thereafter, this subject will continue to be followed up at a 6-monthly frequency for vital status and hospitalizations until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent withdrawn.

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

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

[d] The study drug dosing is to be reviewed and if needed new or additional study drug is to be dispensed.

[e] Blood pressure (BP) measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period, blood pressure measurement 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 will be recorded prior to, and after dialysis (hemodialysis [HD]/hemodiafiltration [HDF] subjects only).

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

[g] Respiratory rate measured singly during all visit. It is recommended during the treatment period, respiratory rate 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] Hemoglobin (Hb) should be collected at all the visits where complete Blood Count (CBC) is not collected

[i] Hb will be assessed by HemoCue on the blood sample, collected for Central Laboratory hemoglobin assessment

[j] Liver Function Tests (LFTs) to be collected at visits where full Serum Chemistry is not collected

[k] Collect from female subjects of child bearing potential only.

[l] Calculated by the Central Laboratory.

[m] Sampling roxadustat will be done at 6 time points over 1 to 3 visits. See section 5.6. At each pharmacokinetic visit, an additional sample will be collected for albumin and alpha-acid glycoprotein determination.

[n] 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.

[o] 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. At day 1, weeks 24, 52 and 76 and EOT a urine sample will be archived for potential future biomarker analysis.

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

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

[r] Dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (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.

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

[t] For subjects requiring dialysis, it is recommended for HD/HDF subjects that study drug is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day).

[u] Intake of initial study drug on day of randomization.

IS AMENDED TO:

Study Period:	Screening			Treatment[a]				Follow-up				Post study Follow-up
Visit / Week:	Up to 6 Weeks **S1**	**S2**	**S3**	Day 1[b]	Weekly (wks 1 to 2) ± 2 days	Every 2 Weeks (wks 4 to 24) ± 2 days	Every 4 Weeks (wks 28 to 100) ± 3 days	EOT (wk 104) ± 3 days	EOT + 2 wks ± 3 days	EOS (EOT + 4 wks) ± 3 days	Unscheduled Visits	Every 6 months until projected wk 108
Written informed consent	X											
Randomization				X								
Eligibility criteria	X			X								
Demographics and medical history including tobacco use	X											
Weight	X			X		wks 12, 24	wks 36, 52, 76	X		X	O[dc]	
Physical examination	X			X		wks 12[ed] 24[ed]	wks 36[ed], 52[ed], 76[ed]	X		X[c]	O[c, d]	
Blood pressure[e], heart rate[e], respiratory rate[g]	X	X	X	X	X	X	X	X		X	~~X~~**O**[c]	
CBC with WBC differential, red cell indices and platelet count	X			X	X	wks 4, 8, 12, 20	~~wks~~ **wk 28 and every following 8 wks**	X		X	O[dc]	
Reticulocyte count, Hemoglobin content of reticulocytes (CHr)	X			X	X	wks 4, 6, 8, 12, 16, 20	wk 28 and every following 8 wks	X		X	O[dc]	
Hemoglobin[h]		X	X			X	X		X		~~X~~**O**[c]	
HemoCue® assessment [i]				X	X	X	X				~~X~~**O**[c]	
Serum chemistry (incl LFT)	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X	X	X	O[dc]	
LFTs [j]					wk 2	wks 6, 16					O[dc]	
Serum Lipid panel (fasting whenever possible)	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O[dc]	
Serum iron, ferritin, TIBC, TSAT	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X		X	O[dc]	
HbA1c	X			X		wk 12	wks 28, 36, 44, 60, 84	X		X	O[dc]	
Vitamin B_{12}, folate	X											
HIV Immunoassay, HBsAg, anti-HCV antibody	X											

Study Period:	Screening			Treatment[a]				Follow-up			Unscheduled Visits	Post study Follow-up
	Up to 6 Weeks											
Visit / Week:	**S1**	**S2**	**S3**	Day 1[b]	Weekly (wks 1 to 2) ± 2 days	Every 2 Weeks (wks 4 to 24) ± 2 days	Every 4 Weeks (wks 28 to 100) ± 3 days	EOT (wk 104) ± 3 days	EOT + 2 wks ± 3 days	EOS (EOT + 4 wks) ± 3 days		Every 6 months until projected wk 108
Serum Pregnancy test[k]	X					wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O~~dc~~	
eGFR (Cr Clear Modified Diet Abbreviated)[l]	X			X		wk 20	wks 36, 52, 68, 84	X		X	O~~dc~~	
Special laboratory analytes (hepcidin, sTfR, hs-CRP)				X		wks 4, 12, 20	wks 36, 52	X		X		
Archival serum/plasma samples for biomarkers				X		wks 4, 12, 20	wks 52, 76	X		X		
Blood sample for population ~~PK~~**pharmacokinetics**					wks 2 to 8[m]							
Genotyping[n]					X							
Urinary testing[o]				X		wks 12, 24	wks 36, 52, 64, 76, 88	X			O~~dc~~	
Quality of Life Questionnaires[p]				X		wks 8, 12~~, 28~~	wks **28,** 36, 52, 76	X			O~~dc~~	
12-lead ECG	X			X		wks 12, 24	wks 36, 52, 76	X			O~~dc~~	
Renal ultrasound[q]	X										O~~dc~~	
Dose adjustment review[r]						X	X				O~~dc~~	
Hospitalization recording[s]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	~~X~~
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	
Procedure and non-drug therapy recording	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensing[t]				X[u]	X	X	X				O~~dc~~	
Vital Status**, SAEs, cardiovascular and thromboembolic AEs**												X

AE: adverse events; CBC: complete blood count; CHr: hemoglobin content of reticulocytes; Cr: creatinine; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOT**=:** End of Treatment; EOS**=:** End of Study; **HbA1c: hemoglobin A1c glycated hemoglobin; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: Human Immunodeficiency Virus; hs-CRP: high sensitivity C-reactive protein; LFT: liver function test;** O**=:** optional test/assessment~~;~~ **(**see below for footnotes**);** S1/S2/S3**=:** screening visit 1, 2 and 3; **SAE: serious adverse event; sTfR: soluble transferrin receptor; TIBC: total iron binding capacity; TSAT: Transferrin Saturation (also known as FeSAT, iron saturation); WBC: white blood cell;** wk(s)**=:**week(s); X **=:** mandatory test/assessment.
Note: see Appendix 3: Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0

Note: see Appendix 4: Instructions for Subjects Requiring Dialysis

[a] In case of premature discontinuation or withdrawal during the treatment period, the subject should complete the EOT visit**s (EOT visit and EOT + 2 weeks visit)** and **the** EOS visit~~s~~. Thereafter, this subject will continue to be followed up at a 6-monthly frequency for vital status and ~~hospitalizations~~ **SAEs, cardiovascular and thromboembolic AEs** until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent **is** withdrawn.

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

[c] ~~Targeted physical examination only (e.g., respiratory and cardiovascular).~~ **The study drug dosing is to be reviewed and if needed new or additional study drug is to be dispensed.**

[d] ~~The study drug dosing is to be reviewed and if needed new or additional study drug is to be dispensed.~~ **Targeted physical examination only (e.g., respiratory and cardiovascular).**

[e] Blood pressure (BP) measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period, ~~blood pressure~~**BP** measurement 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~~**pharmacokinetic** sampling purpose. For subjects requiring dialysis, BP will be recorded prior to, and after dialysis (hemodialysis [HD]/hemodiafiltration [HDF] subjects only).

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

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

[h] Hemoglobin (Hb) should be collected at all the visits where ~~complete Blood Count (~~CBC~~)~~ is not collected**.**

[i] **If during an unscheduled visit** Hb ~~will~~ **needs to** be assessed ~~by~~**, this should always be done with the** HemoCue ~~on the blood sample, collected for~~ **AND** ~~C~~**c**entral ~~L~~**l**aboratory ~~hemoglobin~~**Hb** assessment**. Hb will be assessed by HemoCue on the blood sample collected for central laboratory Hb assessment.**

[j] Liver Function Tests (LFTs) to be collected at visits where full Serum Chemistry is not collected

[k] Collect from female subjects of child bearing potential only.

[l] Calculated by the Central Laboratory~~.~~

[m] Sampling roxadustat will be done at 6 time points over 1 to 3 visits~~. See~~ **(see ~~s~~S**ection 5.6**)**. At each pharmacokinetic visit, an additional sample will be collected for albumin and alpha-acid glycoprotein determination.

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

[o] 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~~**Cr** for calculation of albumin/~~creatinine~~**Cr** ratio. At day 1, weeks 24, 52 and 76 and EOT a urine sample will be archived for potential future biomarker analysis.

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

[q] Renal ultrasound examination within 12 weeks of randomization. Not required if result of a previous renal ultrasound (or other imaging modality such as CT scan or **magnetic**

resonance imaging [MRI**]**) within 12 weeks prior to randomization is available and rules out renal cell carcinoma. If other imaging modality, a conclusive report on the kidney should be available.

[r] Dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (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.

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

[t] For subjects requiring dialysis, it is recommended for HD/HDF subjects that study drug is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day).

[u] Intake of initial study drug on day of randomization.

1 Introduction
1.2.2.1 Pharmacokinetics and Pharmacodynamics
WAS:
Based on interim study results, roxadustat increases the C_{max} and AUC_{inf} of simvastatin 1.9-fold; of rosuvastatin 4.5-fold and 2.9-fold, respectively; and of atorvastatin 1.3-fold and 2.0-fold, respectively. Based on interim study results, the C_{max} and AUC_{inf} of roxadustat are decreased by the phosphate-binders (sevelamer carbonate or calcium acetate).
IS AMENDED TO:
Additional drug-drug interaction studies were performed with statins and phosphate binders. ~~Based on interim study results, r~~**R**oxadustat increases the ~~C_{max} and~~ AUC_{inf} of simvastatin 1.9 fold~~;~~**,** of rosuvastatin ~~4.5 fold and~~ 2.9-fold~~, respectively;~~ and of atorvastatin ~~1.3 fold and~~ 2.0 fold~~, respectively~~. ~~Based on interim study results, the C_{max} and~~ **The** AUC_{inf} of roxadustat ~~are~~ **is** decreased **2.9-fold and 1.8-fold respectively** by **simultaneous administration with** the phosphate binders **(**sevelamer carbonate ~~or~~ **and** calcium acetate**)**. **Administration of roxadustat at least 1 hour before or 1 hour after the phosphate binder minimized the interactions.**

1 Introduction
1.3 Summary of Key Safety Information for Study Drugs
WAS:
Liver enzymes were monitored closely throughout the roxadustat clinical development program. AND A number of pancreatitis events were noted during the roxadustat clinical development program,
IS AMENDED TO:
Liver enzymes were monitored closely throughout the **phase 2** roxadustat clinical development program. AND A number of pancreatitis events were noted during the **phase 2** roxadustat clinical development program,

2 Study Objective(s), Design and Endpoints
2.3.3.1 Additional Secondary Evaluation of Efficacy
DELETED:
• ~~Hb change from BL to the average Hb value of weeks 28-36 and weeks 44-52, without use of rescue therapy within 6 weeks prior to and during this evaluation period in a subject who has reached Hb ≥ 11.0 g/dL prior to week 28~~

3 Study Population

3.3 Discontinuation Criteria for Individual Subjects

ADDED:

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.

4 Study Drugs

4.3 Study Drug Handling

DELETED:

- ~~Tablets should be protected from light, and stored at 15ºC to 30ºC (59ºF to 86ºF).~~

5 Treatments and Evaluation

5.1.1 Dose/Dose Regimen and Administration Period

ADDED:

There were no adaptations to dose frequency or dose amount for subjects moving from Protocol v2.0 to Protocol v2.1.

5 Treatments and Evaluation

5.1.3.2 Concomitant Medication (Drugs and Therapies)

WAS:

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)

There is a risk that roxadustat will increase the plasma levels of statins 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 4].

Table 4: 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

Phosphate Binders

Interim results from a drug-drug interaction study demonstrated a clinically significant reduction in roxadustat plasma exposure when a single dose of roxadustat was administered simultaneously with the phosphate binders sevelamer carbonate or calcium acetate. To reduce the effect of phosphate binders on roxadustat exposure, subjects should be advised that roxadustat be taken at least one hour before or one hour after their phosphate binder.

AND

Supplemental Vitamin B12, Folate and Iron

Vitamin B12, folate and oral iron can be taken without restriction at any time during the study.

Supplemental Iron and ESA Use

Oral iron is recommended as the first-line treatment for iron supplementation and can be taken without any restriction. However, IV iron and ESA use is restricted to use as rescue therapy, see rescue therapy guidelines, [Section 5.1.5].

IS AMENDED TO:

~~Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)~~**Statins and Other Substrates for OATP 1B1**

There is a risk that roxadustat will increase the plasma levels of statins **and other drugs that are substrates of OATP 1B1,** 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 4].

The investigator is also advised to consider this potential interaction between roxadustat and other drugs that are substrates for OATP 1B1 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 Summary of Product Characteristics (SmPC) of these drugs for further details and guidance.

Table 4: 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

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

~~Interim~~ ~~r~~**R**esults from a drug-drug interaction study demonstrated a ~~clinically~~ 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 intakes, 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 be advised that roxadustat be taken at least ~~one~~**1** hour before or ~~one~~**1** hour after their phosphate binder.

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

AND

Supplemental Vitamin B12, Folate~~ and Iron~~

Vitamin B12~~,~~ **and** folate~~ and oral iron~~ can be taken without restriction at any time during the study.

Supplemental Iron and ESA Use

Oral iron is recommended as the first-line treatment for iron supplementation and can be taken without any restriction. However, IV iron and ESA use is restricted to use as rescue therapy, see rescue therapy guidelines, [Section 5.1.5]. **Administration of roxadustat between -1 and +1 hour of intake of oral iron is not recommended.**

5 Treatments and Evaluation *5.1.5 Rescue Therapy Guidelines*
ADDED:
If subjects meet the criteria for ESA rescue therapy whilst on dialysis, ESAs will be administered IV or SC according to the Package Insert or SmPC of the respective ESA for dialysis patients.

5 Treatments and Evaluation *5.2.4 Diagnosis of the Target Disease, Severity, and Duration of Disease*
WAS:
eGFR will be calculated using the following MDRD equation: eGFR (mL/min per 1.73 m^2) = 186.3 × Serum Cr $^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.21 if black).
IS AMENDED TO:
eGFR will be calculated using the following MDRD equation: eGFR (mL/min per 1.73 m^2) = ~~186.3~~**175** × Serum Cr $^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.21 if black).

5 Treatments and Evaluation *5.4.1.1 Blood Pressure*
WAS:
Blood pressure (systolic and diastolic) will be measured singly on each of the three visits during the screening period, and in triplicate with at least two minute intervals for all other visits. An average 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 each of the ~~three~~**3** visits during the screening period, and in triplicate with at least ~~two~~**2** minute intervals for all other visits. ~~An average 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. **All values will be reported in the eCRF.**

5 Treatments and Evaluation *5.4.1.2 Heart Rate*
WAS:
Heart rate will be measured singly on each of 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:
Heart rate will be measured singly on each of the ~~three~~**3** visits during the screening period, and in triplicate with at least ~~two~~**2** 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 *5.4.2 Adverse Events*
WAS:
See [Section 5.5 Adverse Events and Other Safety Aspects] for information regarding adverse event collection and data handling. Adverse event (AE) collection will begin at the time the informed consent form is signed and continue through to EOS visit and will be recorded in the eCRF. The description of the collection and adjudication of pre-specified cardiovascular and cerebrovascular events will be detailed in a separate adjudication charter.
IS AMENDED TO:
~~See [~~**Adverse Events (AEs) will be collected at all study visits (see** Section 5.5 ~~Adverse Events and Other Safety Aspects]~~ for **detailed** information regarding ~~adverse event~~**AE** collection and data handling~~. Adverse event (AE)~~**). AE** collection ~~will begin at the time the~~ **starts after obtaining signed** informed consent ~~form is signed~~ and ~~continue through to~~**continues until the** EOS visit**. For subjects who continue in the post study follow-up period, SAEs and cardiovascular** and **thromboembolic AEs** will be ~~recorded in the eCRF~~**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 ~~pre-specified~~**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 1 back-up person) will be required to review the manual prior to getting access to the system.**

5 Treatments and Evaluation *5.5.1 Definition of Adverse Events (AEs)*
ADDED:
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) or until the last subject randomized reaches EOS, whichever comes first.

5 Treatments and Evaluation
5.5.2 Definition of Serious Adverse Events (SAEs)
WAS:
The sponsor has a list of events that they classify as "always serious" events. If an adverse event 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.
IS AMENDED TO:
The sponsor has a list of events that they classify as "always serious" events. If an adverse event 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.~~

5 Treatments and Evaluation
5.5.5 Reporting of Serious Adverse Events (SAEs)
WAS:
The investigator should complete and submit a SAE report form containing all information that is required by the Regulatory Authorities to delegated CRO by fax immediately (within 24 hours of awareness). Toll free fax number for each country is provided on the fax coversheet of the SAE worksheet. In case of fax failure the SAE worksheet should be emailed to the delegated CRO. If the faxing of a SAE report form is not possible or is not possible within 24 hours, the drug safety contact should be informed by phone. The contact details of the delegated CRO are: [redacted] If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or his/her designee on the 24-hours Astellas Pharmacovigilance contact details, see Section II Contact Details of Key Sponsor's Personnel. 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. Follow-up information for the event should be sent promptly (within 7 days) as necessary. Full details of the SAE should also be recorded on the medical records and in the eCRF. The investigator must ensure that the information on the SAE worksheet matches the information on the AE pages within the eCRF.

IS AMENDED TO:

The investigator should complete and submit a SAE ~~report form~~ **Worksheet** containing all information that is required by the Regulatory Authorities to delegated CRO by fax immediately (within 24 hours of awareness). Toll free fax number for each country is provided on the fax coversheet of the SAE ~~w~~**W**orksheet. In case of fax failure the SAE ~~w~~**W**orksheet should be emailed to the delegated CRO.

If the faxing of a SAE **Worksheet** ~~report form~~ is not possible or is not possible within 24 hours, the drug safety contact should be informed by phone.

The contact details of the delegated CRO**s** are:

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or his/her designee ~~on the 24 hours Astellas Pharmacovigilance contact details,~~ **(**see Section II Contact Details of Key Sponsor's Personnel**)**.
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.

Follow-up information for the event should be sent promptly (**preferable** within 7 days ~~as necessary~~ **of the initial notification**).

Full details of the SAE should also be recorded on the medical records and in the eCRF. The investigator must ensure that the information on the SAE ~~w~~**W**orksheet matches the information on the AE pages within the eCRF.

5 Treatments and Evaluation
5.5.6 Follow-up to Adverse Events
WAS:
All adverse events occurring during 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.
IS AMENDED TO:
All adverse events 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.

5 Treatments and Evaluation
5.5.9 Supply of New Information Affecting the Conduct of the Study
WAS:
When new information becomes available, including "Dear Doctor Letters" but not limited to that, necessary for conducting the clinical study properly will lead to a protocol amendment. The sponsor should inform regulatory authorities, as well as all investigators involved in the clinical study, and the head of the study site, who will then inform the IRB/IEC of such information, and when needed, should amend the subject information.
IS AMENDED TO:
When new information becomes available, ~~including "Dear Doctor Letters" but not limited to that,~~ necessary for conducting the clinical study properly**,** ~~will lead to a protocol amendment. T~~**t**he sponsor ~~should~~**will** inform ~~regulatory authorities, as well as~~ all investigators involved in the clinical study~~,~~ **as well as the regulatory authorities, as applicable/needed. Investigators should** ~~and the head of the study site, who will then~~ inform the IRB/IEC of such information~~, and~~ when needed~~, should amend the subject information~~.

7 Statistical Methodology
7.4.2.1 Primary Analysis
WAS:
Once the primary hypothesis has been rejected for the EU (EMA) primary efficacy endpoint [see Section 7.4.1.1], the key secondary endpoints below will be tested using a fixed sequence testing procedure, as depicted in [Table 9], in order to maintain the overall two-sided type I error rate at 0.05. If P value from a test is < 0.05, the claim of superiority (or non-inferiority for tests 7 and 8) will be considered successful and the test will progress to the next comparison in sequence. The analysis set for the analysis of the secondary endpoints will be the PPS for the non-inferiority tests and the FAS for the superiority tests. Table 9: Secondary Endpoints Fixed Sequence Testing Procedure

Test	Endpoint	Test (superiority unless otherwise specified)
1	Hb change from BL	*Pooled roxadustat versus pooled placebo
2	LDL change from BL	*Pooled roxadustat versus pooled placebo
3	MAP change from BL	*Pooled roxadustat versus pooled placebo
4	Occurrence and time to occurrence of hypertension	Non-inferiority of pooled roxadustat versus pooled placebo
5	Use and time to use of rescue therapy	Non-inferiority of pooled roxadustat versus pooled placebo
6	Occurrence and time to occurrence of hypertension	*Pooled roxadustat versus pooled placebo
7	use and time to use of rescue therapy	*Pooled roxadustat versus pooled placebo
8	SF-36 PF subscore change from BL	*Pooled roxadustat versus pooled placebo
9	SF-36 vitality subscore change from BL	*Pooled roxadustat versus pooled placebo

*Subjects randomized to roxadustat QW, BIW and TIW prior to implementation of protocol v2.0 will be pooled together. Subjects randomized to placebo will also be pooled together.

- Change from BL in the average Hb of weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period (superiority of pooled roxadustat versus pooled placebo) will be analyzed using a 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.
- Change from BL in LDL cholesterol to the average value of LDL cholesterol of weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) using a MMRM model with unstructured covariance containing terms for treatment arm, baseline measurement, visit, visit x treatment arm, and other stratification factors.
- Change from BL in MAP to the average MAP in weeks 20–28 will be compared (superiority of pooled roxadustat versus pooled placebo) using a MMRM model with unstructured covariance containing terms for treatment arm, baseline measurement, visit, visit x treatment arm, and other stratification factors.
- Occurrence and time to occurrence of hypertension will be reported and compared (non-inferiority of pooled roxadustat versus pooled placebo) using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and its 95% will be calculated for the frequency of pooled roxadustat as relative to pooled placebo. Non-inferiority will be declared if the upper bound of the 2-sided 95% CI does not exceed 1.3. Once this hypothesis is rejected, superiority will be checked.
- Use and time to use of rescue therapy (composite of RBC transfusion, ESA use and IV iron) in the first 24 weeks of treatment will be reported and compared (non-inferiority of pooled roxadustat versus pooled placebo) using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and its 95% will be calculated for the frequency of pooled roxadustat as relative to pooled placebo. Non-inferiority will be declared if the upper bound of the 2-sided 95% CI does not exceed 1.3. Once this hypothesis is rejected, superiority will be checked.

- Change from BL in SF-36 PF subscore to the average in weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subset of subjects with BL PF subscore below 35, using a MMRM model with unstructured covariance containing terms for treatment arm, baseline measurement, visit, visit x treatment arm, and other stratification factors.
- Change from BL in SF-36 vitality subscore to the average SF-36 vitality subscore in weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subset of subjects with BL vitality subscore below 50, using a MMRM model with unstructured covariance containing terms for treatment arm, baseline measurement, visit, visit x treatment arm, and other stratification factors.

The secondary efficacy endpoints will be analyzed using the FAS population as the primary analysis population.

IS AMENDED TO:

Once the primary hypothesis has been rejected for the EU (EMA) primary efficacy endpoint [see Section 7.4.1.1], the key secondary endpoints below will be tested using a fixed sequence testing procedure, as depicted in [Table 9], in order to maintain the overall ~~two~~**2**-sided type I error rate at 0.05. If P value from a test is < 0.05, the claim of superiority (or non-inferiority for tests ~~7~~ **6** and ~~8~~ **7**) will be considered successful and the test will progress to the next comparison in sequence. The analysis set for the analysis of the secondary endpoints will be the PPS for the non-inferiority tests and the FAS for the superiority tests.

Table 9: Secondary Endpoints Fixed Sequence Testing Procedure

Test	Endpoint	Test (superiority unless otherwise specified)
1	Hb change from BL	*Pooled roxadustat versus pooled placebo
2	LDL change from BL	*Pooled roxadustat versus pooled placebo
3	**Use and time to use of rescue therapy**	***Pooled roxadustat versus pooled placebo**
~~3~~**4**	~~MAP~~**SF-36 PF subscore** change from BL	*Pooled roxadustat versus pooled placebo
~~4~~**5**	~~Occurrence and time to occurrence of hypertension~~**SF-36 vitality subscore change from BL**	~~Non-inferiority of pooled~~***Pooled** roxadustat versus pooled placebo
~~5~~**6**	~~Use and time to use of rescue therapy~~**MAP change from BL**	Non-inferiority of pooled roxadustat versus pooled placebo
~~6~~**7**	Occurrence and time to occurrence of hypertension	~~*Pooled~~**Non-inferiority of pooled** roxadustat versus pooled placebo
~~7~~	~~use and time to use of rescue therapy~~	~~*Pooled roxadustat versus pooled placebo~~
~~8~~	~~SF-36 PF subscore change from BL~~	~~*Pooled roxadustat versus pooled placebo~~
~~9~~	~~SF-36 vitality subscore change from BL~~	~~*Pooled roxadustat versus pooled placebo~~

*Subjects randomized to roxadustat QW, BIW and TIW prior to implementation of protocol v2.0 will be pooled together. Subjects randomized to placebo will also be pooled together.

- Change from BL in the average Hb of weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period (superiority of pooled roxadustat versus pooled placebo) will be analyzed using a MMRM with unstructured covariance matrix model. The model will contain terms for treatment arm, ~~baseline~~**BL** measurement, visit, visit x treatment arm and other stratification factors.
- Change from BL in LDL cholesterol to the average value of LDL cholesterol of weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) using a MMRM model with unstructured covariance containing terms for treatment arm, ~~baseline~~**BL** measurement, visit, visit x treatment arm, and other stratification factors.
- ~~Change from BL in MAP to the average MAP in weeks 20–28 will be compared (superiority of pooled roxadustat versus pooled placebo) using a MMRM model with unstructured covariance containing terms for treatment arm, baseline measurement, visit, visit x treatment arm, and other stratification factors.~~
- ~~Occurrence and time to occurrence of hypertension will be reported and compared (non-inferiority of pooled roxadustat versus pooled placebo) using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and its 95% will be calculated for the frequency of pooled roxadustat as relative to pooled placebo. Non-inferiority will be declared if the upper bound of the 2-sided 95% CI does not exceed 1.3. Once this hypothesis is rejected, superiority will be checked~~.
- Use and time to use of rescue therapy (composite of RBC transfusion, ESA use and IV iron) in the first 24 weeks of treatment will be reported and compared ~~(non-inferiority of pooled roxadustat versus pooled placebo)~~ using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and its 95% will be calculated for the frequency of pooled roxadustat as relative to pooled placebo. ~~Non-inferiority~~**Superiority** will be declared if the ~~upper~~**lower** bound of the 2-sided 95% CI ~~does not exceed~~ **is higher than** 1.~~3~~**0**. ~~Once this hypothesis is rejected, superiority will be checked.~~
- Change from BL in SF-36 PF subscore to the average in weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subset of subjects with BL PF subscore below 35, using a MMRM model with unstructured covariance containing terms for treatment arm, ~~baseline~~**BL** measurement, visit, visit x treatment arm, and other stratification factors.
- Change from BL in SF-36 vitality subscore to the average SF-36 vitality subscore in weeks 12-28 will be compared (superiority of pooled roxadustat versus pooled placebo) for all subjects and in the subset of subjects with BL vitality subscore below 50, using a MMRM model with unstructured covariance containing terms for treatment arm, ~~baseline~~**BL** measurement, visit, visit x treatment arm, and other stratification factors.
- **Change from BL in MAP to the average MAP in weeks 20–28 will be compared (noninferiority of pooled roxadustat versus pooled placebo) using a MMRM model with unstructured covariance containing terms for treatment arm,BL measurement, visit, visit x treatment arm, and other stratification factors. Non-inferiority will be declared if the upper bound of the 2-sided 95% CI of the difference between roxadustat and placebo is below 2 mmHg.**
- **Occurrence and time to occurrence of hypertension will be reported and compared**

(noninferiority of pooled roxadustat versus pooled placebo) using stratified Cox Proportional Hazards regression adjusting for stratification factors. Hazard ratio and its 95% will be calculated for the frequency of pooled roxadustat as relative to pooled placebo. Noninferiority will be declared if the upper bound of the 2-sided 95% CI does not exceed 1.3. Once this hypothesis is rejected, superiority will be checked but as part of the sequence testing procedure.

~~The secondary efficacy endpoints will be analyzed using the FAS population as the primary analysis population.~~

7 Statistical Methodology

7.4.2.2 Secondary Analysis

WAS:

The key secondary efficacy endpoints will be analyzed using the PPS population as supportive analysis population.

For the first key secondary endpoints analyzed using MMRM, an additional sensitivity analysis will be performed to handle missing data using an ANCOVA model with LOCF method using BL value and the stratification factors as covariates.

Each of the key secondary endpoints will be repeated separately by gender, age group, region, BL Hb categories, iron repletion at BL, diabetes and eGFR categories. Subgroup analyses will be detailed in the SAP

IS AMENDED TO:

~~The key secondary efficacy endpoints will be analyzed using the PPS population as supportive analysis population.~~

~~For the first key secondary endpoints analyzed using MMRM, an additional sensitivity analysis will be performed to handle missing data using an ANCOVA model with LOCF method using BL value and the stratification factors as covariates.~~

Each of the key secondary endpoints will be repeated separately by gender, age group, region, BL Hb categories, iron repletion at BL, diabetes and eGFR categories. Subgroup analyses will be detailed in the SAP**.**

8 Operational and Administrative Considerations

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

DELETED:

~~The study will be considered for publication or presentation at (scientific) symposia and congresses. The investigator will be entitled to publish or disclose the data generated at their respective study site only after submission to the sponsor all transcripts, texts of presentations, and abstracts related to the study at least 90 days prior to the intended submission for publication or any other disclosure for APEB sponsored studies. This is necessary to confirm whether any inventive knowledge should be protected by a patent or not~~

~~and to prepare and file a patent application accordingly. In addition this is in no way intended to restrict publication of facts or opinions formulated by the investigator. The sponsor will inform the investigator in writing of any objection or question arising within 30 days of receipt of the proposed publication material~~.

12 Appendices

12.3: Appendix 3: Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0

ADDED:

Note: There are no adaptations to dose frequency or dose amount for subjects moving from Protocol v2.0 to Protocol v2.1.

III. Non-Substantial Amendment Rationale:

Rationale for Non-Substantial Designation

The revisions made to the protocol are considered non-substantial as they do not have a significant impact on the safety or the scientific value of the trial.

Changes for clarification have been made to reflect the latest available information regarding roxadustat (item 11, 12, 15), the sponsor and CRO personnel (1, 22), most accurate description of study procedures (5, 6, 7, 9, 10, 14, 16, 17, 18, 19, 20, 21, 23), and to reflect updates to Astellas' protocol template and for minor administrative reasons (2, 27, 28).

Post study follow-up (3)

Clarification of the safety information that is of specific interest during the post study follow-up period.

Update to the planned study period (4)

Minor extension of the complete study duration to reflect the current projection when the study will be completed without any change to the study period for individual subjects.

Update of analysis methods (8, 13, 24, 25, 26)

Adjustments and changes made for the analysis methods have no impact on the study objectives, primary endpoints or primary analyses.

The change in order of the key secondary endpoints used for the fixed sequence procedure has been made to reflect the importance of the Quality of Life endpoints (SF-26 Vitality and Physical Functioning subscores), which is line with the secondary objective of the study.

The change in hypothesis testing for some of the key secondary endpoints has been made to align with the assumption that roxadustat is expected to be superior to placebo for the use of rescue therapy and not worse for the blood pressure endpoints (hypertension and MAP).

Additional changes were made in order to clarify some methodology aspects that were not well defined (removal of the LOCF method in favor of other methods, removal of additional Hb endpoints).

14 SPONSOR'S SIGNATURES

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