

# 1 TITLE PAGE

NCT # NCT02273726

## CLINICAL STUDY PROTOCOL

**STUDY TITLE:** A Phase 3, Open-Label, Randomized, Active-Controlled Study of the Efficacy and Safety of Roxadustat (FG-4592) in the Maintenance Treatment of Anemia in Subjects with End Stage Renal Disease (ESRD) on Stable Dialysis

**PROTOCOL NUMBER:** FGCL-4592-064

**SPONSOR:** FibroGen, Inc.  
409 Illinois Street  
San Francisco, California 94158 USA

**IND NUMBER:** 074454

**STUDY DRUG:** Roxadustat (FG-4592)

**INDICATION:** Anemia associated with ESRD

**FIBROGEN MEDICAL MONITOR:** Name: [REDACTED]  
Title: [REDACTED]  
Telephone: [REDACTED]  
Mobile: [REDACTED]  
Fax: [REDACTED]  
E-mail: [REDACTED]

**PROTOCOL VERSION & DATE:** Original  
25 September 2014  
Amendment 1: 13 December 2016  
Amendment 2: 18 August 2017

## CONFIDENTIALITY STATEMENT

The information contained in this document is confidential and proprietary to FibroGen, Inc. No part of this document or any of the information contained herein may be transmitted, disclosed, shared, reproduced, published or utilized by any persons without prior written authorization by FibroGen, Inc.

**INVESTIGATOR SIGNATURE PAGE****STUDY ACKNOWLEDGEMENT****A Phase 3, Open-Label, Randomized, Active-Controlled Study of the Efficacy and Safety of Roxadustat (FG-4592) in the Maintenance Treatment of Anemia in Subjects with End Stage Renal Disease (ESRD) on Stable Dialysis****FGCL-4592-064**

Amendment 1: 13 December 2016

Amendment 2: 18 August 2017

**INVESTIGATOR STATEMENT**

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

---

Investigator Name (Printed)

---

Institution

---

Signature

---

Date

**Please retain the original for your study files.**

## SUMMARY OF MAJOR PROTOCOL AMENDMENT CHANGES

### Amendment 2

The primary purpose of this amendment is to improve current enrollment. Incident dialysis subjects, target patient population for this study, are difficult to find; furthermore, they are less willing to participate in a clinical study due to start of routine dialysis, a life changing event. Among those who are interested to participate, the vast majority are not qualifying per current protocol eligibility criteria. Upon analyzing reasons for screen-fail and feedback from various investigators, it appears that some of the eligibility criteria and conduct of the study are overly restrictive and/or not per current standard of care. As a result, a large number of incident dialysis subjects who are otherwise good candidates and would benefit from this study are not being able to participate under existing eligibility criteria and protocol design. In order to be able to enroll and retain a representative sample of real-life incident dialysis subjects, we modified the following eligibility criteria and study conducts to reflect current standard of care in this patient population. None of these proposed modifications are expected to compromise safety and wellbeing of the subjects who may now qualify under revised criteria.

In addition to the major changes listed below, minor editorial changes will be made throughout the document to correct typographical errors and to improve consistency and clarity.

Description of Change	Rationale for Change	Section(s) Affected <sup>a</sup>
<p><b>Inclusion Criteria:</b></p> <p>Inclusion criteria # 3.1 has been modified by removing “native kidney” – the revised verbiage reads as follows:</p> <p style="padding-left: 40px;">3.1 Amendment 2 : Incident dialysis subjects receiving dialysis for ESRD for <math>\geq 2</math> weeks but <math>\leq 4</math> months at the time of randomization</p> <p>Inclusion criteria # 6.1 has been streamlined by reducing hemoglobin (Hb) testing frequency (from three to two) and interval between Hb tests (from <math>\geq 4</math> days to <math>\geq 2</math> days) to confirm eligibility - the revised verbiage reads as follows (revised text is italicized and bolded):</p> <p style="padding-left: 40px;">6.1 Amendment 2: For Incident dialysis subjects (as defined in 3.1), mean of the subject’s <i>two</i> most recent central lab Hb values during the Screening Period must be <math>\geq 8.5</math> g/dL and <math>\leq 12.0</math> g/dL; with an absolute difference of <math>\leq 1.3</math> g/dL between the highest and the lowest value. Samples are obtained at least <b>2</b> days apart and the last Hb value must be within 10 days prior to the randomization visit</p> <p>Inclusion criteria # 7, 8, 9, 10 additional text has been added to allow for subjects that may qualify</p>	<p>To allow subjects who restarted dialysis recently due to transplanted kidney end-stage renal disease (see revised Exclusion # 20 below)</p> <p>Reducing Hb testing frequency and interval between tests will shorten the minimum screening time requirement and is expected to improve overall screening success. Also, to align with the Hb eligibility criteria in the FGCL-4592-063 incident-dialysis study - currently being conducted at the same centers in the US.</p> <p>Revised TSAT/ferritin/B12/folate criteria (subjects with lower values are allowed to</p>	<p>SYNOPSIS; Section 5.1</p>

Description of Change	Rationale for Change	Section(s) Affected <sup>a</sup>
<p>upon receiving supplementation. It now reads as follows (added text is italicized):</p> <p>7. Subject has a ferritin level <math>\geq</math> 100 ng/mL at screening <i>Amendment 2: Subjects with a ferritin level &lt; 100 ng/mL at screening may qualify upon receiving iron supplement (per local standard of care)</i></p> <p>8. Subject has a transferrin saturation (TSAT) level <math>\geq</math> 20% at screening <i>Amendment 2: Subjects with a TSAT level &lt; 20% at screening may qualify upon receiving iron supplement (per local standard of care)</i></p> <p>9. Subject has a serum folate level <math>\geq</math> lower limit of normal (LLN) at screening <i>Amendment 2: Subjects with a serum folate level &lt; LLN at screening may qualify upon receiving folate supplement (per local standard of care)</i></p> <p>10. Subject has a serum vitamin B<sub>12</sub> level <math>\geq</math> LLN at screening <i>Amendment 2: Subjects with a Vitamin B<sub>12</sub> level &lt; LLN at screening may qualify upon receiving B<sub>12</sub> supplement (per local standard of care)</i></p>	<p>participate upon receiving supplement) will improve screening success rate. Also, this would help to shorten screening period by minimizing “unscheduled visit” to retest these parameters via central lab.</p>	
<p><b>Exclusion Criteria:</b> Exclusion criteria 1, 11, 15, 16, 18, 19, 20 and 24 have been modified to read as follows (revised text is bolded and italicized):</p> <p>1. Subject has received a red blood cell (RBC) transfusion within 8 weeks prior to randomization <i>Amendment 2: Subject has received a red blood cell (RBC) transfusion within 4 weeks prior to randomization</i></p> <p>11. Subject <i>with</i> New York Heart Association (NYHA) Class III or IV congestive heart failure</p> <p>15. Subject has a diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category II or higher) of renal cell carcinoma as shown on</p>	<p>These exclusion criteria have been modified to allow more incident subjects to participate who are otherwise good candidate for this study</p> <p>RBC transfusion within 4 weeks prior to randomization is not expected to impact baseline Hb. No additional safety concerns.</p> <p>Changing “has known” to “with” to align with other incident dialysis protocol</p> <p>Changing from renal ultrasound to renal imaging will allow all acceptable imaging options e.g. ultrasound, CT scans, MRI etc.</p>	<p>SYNOPSIS; Section 5.2</p>

Description of Change	Rationale for Change	Section(s) Affected <sup>a</sup>
<p>renal <b>imaging</b> performed within 12 weeks prior to randomization</p> <p>16. Amendment 2 Subject has a history of malignancy, except for the following: cancers determined to be cured or in remission for <math>\geq 2</math> years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps</p> <p>18. Subject has an active, clinically significant (CS) infection or evidence of an underlying infection, as manifested by white blood cell count (WBC) &gt; ULN, and/or fever, in conjunction with clinical signs or symptoms of infection <b>at the time of randomization</b></p> <p>19. Subject has any of the following known untreated conditions: proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion (<b>subjects who are already blind may qualify to participate</b>)</p> <p>20. <b>Prior organ transplant: subjects who have one of the following conditions or states</b></p> <p><b>a) experienced rejection of transplanted organ within 6 months of transplantation</b></p> <p><b>b) currently on high doses of immunosuppressive therapy (per discretion of the PI)</b></p> <p>c) are scheduled for organ transplantation (on the waiting list for kidney transplant is not exclusionary)</p> <p>24. Amendment 2: Subject has a history of alcohol or drug abuse within <b>6 months</b> prior to screening</p>	<p>Changing (cancer cured) from <math>\geq 5</math> years to <math>\geq 2</math> years will allow more incident subjects to qualify. No apparent safety concerns.</p> <p>“at the time of randomization” has been added to clarify the timing of exclusion due to this criterion.</p> <p>Text is added to clarify that subjects who are already blind due to the complications of one or more of these conditions are OK to participate as there is no possibility of further worsening.</p> <p>Revised to allow otherwise eligible incident subjects with prior organ transplant to participate except who experienced transplant rejection within 6 months of transplantation or on high doses of immunosuppressive therapy (due to potential confounding effects on safety and efficacy assessments)</p> <p>Potential subjects with no history of alcohol or drug abuse within 6 months are OK to participate – changing from 2 years to 6 months does not pose any additional safety risk</p>	
<p><b>Investigational Product</b></p> <p>Dose Adjustments text regarding &lt;20 mg dosing has been to modified to read as follows (revised text is bolded and italicized):</p> <p>If a subject requires &lt; 20 mg TIW (i.e., &lt; 60 mg per week) to maintain a Hb level of approximately 11 g/dL, <b>the dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc.</b></p>	<p>To provide guidance on IP dosing if a subject requires further dose reduction from 20 mg TIW given 20 mg is the lowest tablet strength available.</p>	<p>SYNOPSIS; Sections 2.6, 4.5.3.1, 6.4.1, Appendix 2</p>

Description of Change	Rationale for Change	Section(s) Affected <sup>a</sup>
<p>Added text to clarify subject weight used for dose adjustments as follows (revised text is bolded and italicized):</p> <p><i>For dose adjustment purposes, post-dialysis weight (dry-weight) should be used. If the post-dialysis weight of the current visit is not available at the time of dose adjustment, post-dialysis weight of the prior dialysis session or last recorded post-dialysis weight may be used</i></p>	<p>Text added to clarify the options for post dialysis weight that may be used during dose adjustment to ensure that maximum allowable dose (3.0 mg/kg/dose) has not been exceeded.</p>	<p>SYNOPSIS; Sections 2.6, 4.5.3.1, 7.1</p>
<p><b>Rescue Therapy and Emergency Procedures:</b></p> <p>Inadvertent ESA use or ESA received at the hospital with regards to ESA rescue has been revised</p> <p>From:</p> <p>Roxadustat subject who receives an ESA inadvertently and does not meet the criteria above may be allowed to continue taking study medication, if considered safe by the Investigator or Medical Monitor.</p> <p>To:</p> <p>Inadvertent ESA administration or ESA administration by the hospital staff in Roxadustat subjects should not be counted as rescue unless above criteria are met; these subjects may be allowed to continue taking study medication, if considered safe by the Investigator or Medical Monitor.</p>	<p>ESA therapy is the only standard of care to treat anemia in ESRD patients. It is a common practice to administer ESA as a routine therapy during dialysis session. Text has been added to clarify that inadvertent ESA administration or ESA administration by the hospital staff as part of the standard of care in Roxadustat subjects should not be counted as ESA rescue unless protocol specified rescue criteria are met.</p>	<p>SYNOPSIS; Section 4.6.3.2</p>
<p><b>Supplemental Iron Use:</b></p> <p>Text has been modified to change oral iron supplementation from 1<sup>st</sup> line of therapy to preferred 1<sup>st</sup> line of therapy to read as follows (revised text is bolded) :</p> <p><i>In this study, oral iron <b>should</b> be allowed as the <b>preferred</b> first-line of iron supplementation for both treatment arms without restriction.</i></p> <p><i>All subjects <b>should</b> be encouraged to take oral iron <b>if they can tolerate</b> as the <b>preferred</b> first-line iron supplementation during the Treatment Period.</i></p> <p>Supplemental iron use language has been modified to lessen restrictions on IV iron use. IV iron administration criteria/rules have been replaced by local standard of care. Revised text reads as follows (deleted IV iron guidelines is not shown here)</p>	<p>Many ESRD patients cannot tolerate oral iron therapy due to GI adverse effects including GI bleeding. Channing to “preferred 1<sup>st</sup> line” would allow flexibility.</p> <p>IV iron has been the standard of care for iron supplementation in ESRD anemia subjects and it is routinely administered in subjects who are on ESA therapy. Current protocol IV iron administration guidelines are seen as overly restrictive and not in line with the current standard of care. Text has been revised to</p>	<p>SYNOPSIS; Sections 4.6.2, 4.6.2.2, Appendix 6</p>

<b>Description of Change</b>	<b>Rationale for Change</b>	<b>Section(s) Affected<sup>a</sup></b>
<p><i>Intravenous iron supplementation is permitted if in the opinion of the Investigator the subject has not responded adequately and is considered iron deficient. <b>IV iron may be administered per local standard of care as deemed necessary by the investigator.</b></i></p>	<p>allow IV iron per discretion of the PI based on the local standard of care.</p>	
<p><b>Screening Period:</b></p> <p>Text added regarding subjects who are on ESA dose-hold due to high hemoglobin during screening reads as follows:</p> <p><i>Subjects on dose-hold due to high haemoglobin may qualify for screening however, they cannot be randomized if in investigator's opinion they are not ready to resume epoetin-alfa or roxadustat upon randomization.</i></p>	<p>Text has been added to guide how subjects on ESA dose hold are to be handled during screening and randomization</p>	<p>SYNOPSIS; Section 4.1.1</p>
<p><b>Screening 3 Visit</b></p> <p>Screening 3 Visit has been deleted. Unique tests and procedures from Screening Visit 3 have been moved to Screening 2 Visit.</p> <p><b>Additional Screening Assessments</b></p> <p>Following verbiage has been deleted from this section</p> <p>“Iron, Vitamin B12, and folate laboratory tests may be repeated during the screening period upon completing a course of therapy, if necessary.”</p>	<p>Screening 3 visit has been deleted to align with the revised Inclusion criteria # 3.1</p> <p>Per revised Inclusion Criteria #7, 8, 9, and 10 – Iron, Vitamin B12, and folate laboratory tests need not to be repeated to confirm eligibility</p>	<p>Sections 7.1.1.2, 7.1.1.3, Appendix 3</p>
<p><b>Randomization/Treatment Period:</b></p> <p>Added text regarding 1<sup>st</sup> dose of study medication in subjects who were on long-acting ESAs during screening to read as follows:</p> <p><i>Subjects on long-acting ESAs (Aranesp or Mircera) may not receive the 1<sup>st</sup> dose of study medication on the day of randomization due to ESA dosing schedule (e.g. once weekly or once bi-weekly); in these subjects, the 1<sup>st</sup> dose of study medication (roxadustat or epoetin-alfa) should be administered on the day when the next dose of current ESA would have been due. For all practical purposes, the date of 1<sup>st</sup> dose of study drug administration should be considered as Day 1.</i></p>	<p>To clarify the process of randomization and Day 1 dosing in subjects who are on long-acting ESAs during screening. Typically, randomization and Day 1 dosing happen on the same day (when ESA dose is due) however, due to long ESA dosing interval (e.g. once every two weeks), randomization and Day 1 dosing may take place on separate days.</p>	<p>Sections 4.1.1, 7.1.2</p>

Description of Change	Rationale for Change	Section(s) Affected <sup>a</sup>
<p><b>Adverse Event Eliciting/Reporting</b></p> <p>Added clarification regarding action taken with study drug (added text is bolded and italicized):</p> <p><i>Action taken regarding study drug (<b>decision taken by the PI in response to an AE</b>)</i></p>	<p>To clarify that “Action taken regarding the study drug” refers to PI’s decision in response to an AE (e.g. PI temporarily stopped the study drug) as opposed to subject’s own decision (subject did not take study drug as s/he was not feeling well or did not have with him/her)</p>	<p>Section 8.3.2</p>
<p><b>Pregnancies: Reporting and Follow-up of Subjects</b></p> <p>Added clarification regarding confirmation of pregnancy</p> <p>A pregnancy in a female subject must be confirmed by positive serum <math>\beta</math>-hCG test. <i>If <math>\beta</math>-hCG test is found positive in a female subject of child bearing potential, study drug should be placed on hold temporarily until pregnancy is ruled out via a repeat test <math>\geq 3</math> days.</i></p>	<p>Text is added to reflect the current clinical practice to confirm pregnancy in this patient population (known to have high false positive pregnancy results – requires repeat testing to confirm). Also, to minimize exposure to the fetus as a precaution (in case pregnancy is confirmed).</p>	<p>Section 8.3.6</p>
<p><b>Blood Pressure and Heart Rate Measurement Guidelines</b></p> <p>Revised BP and HR measurement guidelines (added text is bolded and italicized):</p> <p>Blood pressure <i>should</i> be measured in triplicate (<i>preferred</i>) with at least one minute interval between the measurements.</p> <p>Heart rate (HR) <i>should</i> be measured in triplicate (preferred) with at least one minute interval between the measurements.</p>	<p>Measuring BP and HR three times (at least one minute interval) before dialysis is not per standard clinical practice and is difficult to implement as it requires additional time and manpower. Added verbiage “preferred” will provide flexibility to the sites. Also, will help to avoid protocol deviations.</p>	<p>Appendix 5</p>
<p><b>Protocol Deviations:</b></p> <p>Texts have been added to pre-specify issues that are not to be considered as protocol deviations. Added texts read as follows:</p> <p><i>Due to the unique nature of this study, following issues are not to be considered as protocol deviations:</i></p> <p><i>Given the complexity in EPO dose adjustments and the need to take into account the various clinical parameters in EPO dose titration, one would not consider it a protocol deviation when patients are dosed according to local standard of care whether or not it is concordant with package insert/SmPC</i></p> <p><i>Given the complexity in Roxadustat dose adjustments and the need to take into account the various clinical parameters in Roxadustat dose titration, one would</i></p>	<p>To allow flexibility with EPO dosing where investigators/sites are not able to follow epoetin-alfa package insert guidelines due to various factors including clinical status of the subjects.</p> <p>Per study design, various factors such as, HemoCue Hb value, Central lab Hb value, PI’s decision etc. can influence dose titration decisions at the time of the visit or after the visit. As a result, dose prescribed may not match exactly with the dose that would have been prescribed per dose adjustment algorithm.</p> <p>However, as the stable dose would be achieved through titration, dosing discrepancy when subjects are dosed based on their clinical status</p>	<p>Section 9.7</p> <p>Section 9.7</p>



Description of Change	Rationale for Change	Section(s) Affected <sup>a</sup>
<p><i>not consider it a protocol deviation when subjects are dosed based on their clinical circumstances whether or not it is concordant with the Roxadustat dose adjustment guidelines unless it was related to “excessive hematopoiesis” (Hb <math>\geq</math>13 g/dL, requires a dose-hold) or “Overdose” (prescribed &gt;3.0 mg/kg per dose or 400 mg per dose, whichever is lower)</i></p> <p><i>ESA administrations in Roxadustat subjects during hospitalization are not be reported as protocol deviation, if the roxadustat dosing were not allowed or available during that hospitalized period</i></p> <p>IV Iron administrations in study subjects during hospitalization are not be reported as protocol deviation</p>	<p>is not considered as a protocol deviation unless it is related to excessive hematopoiesis (<math>\geq</math>13.0 g/dL, requires a dose-hold) or overdose (&gt;3.0 mg/kg/dose or 400 mg per dose, whichever is lower).</p> <p>Roxadustat subjects often receive ESA when they are hospitalized either because the hospital doesn’t allow subjects to take any experimental therapy such as Roxadustat at the hospital or subjects do not have access to their study drug while they are at the hospital. Given that ESA is administered to treat anemia as part of the hospital standard care, ESA administration in any of these circumstances should not be considered as protocol deviation.</p> <p>IV iron is the standard of care for iron supplementation in this patient population. IV iron is administered routinely in all hospitalized patients who are on dialysis including study subjects as part of the hospital standard of practice. IV iron administered in study subjects while they are hospitalized are not to be reported as protocol deviation in this study.</p>	<p>Section 9.7</p>
<p><b>Baseline Hb value calculation</b></p> <p>Added text regarding baseline Hb value calculation for subjects enrolled under Amendment 2. Revised texts read as follows -</p> <p><i>Subjects enrolled under Amendment 2, baseline Hb value for efficacy analysis is defined as the mean of <b>three</b> central laboratory Hb values, <b>two</b> of the latest screening Hb values plus the pre-dose Hb value collected on Day 1.</i></p> <p><i>In subjects with missing Day 1 Hb value, the mean of three (<b>two, for Amendment 2</b>) latest screening laboratory Hb values will be considered as BL Hb value.</i></p>	<p>To align with the revised Inclusion Criteria # 6.1</p>	<p>Section 9.4.3</p>
<p><b>Analyses stratification</b></p> <p>The analyses stratified by original protocol and amendment 1 were updated to original protocol and amendments.</p>	<p>To align with this 2nd amendment.</p>	<p>Section 9.4.3</p>

<b>Description of Change</b>	<b>Rationale for Change</b>	<b>Section(s) Affected<sup>a</sup></b>
<p><b>Analysis Model Description</b></p> <ul style="list-style-type: none"> <li>a. Other stratification factors changed to randomization stratification factors in the model terms.</li> <li>b. Factors were updated to fixed effects in the model terms.</li> <li>c. LOCF was removed from MMRM models.</li> <li>d. Visit and interaction of visit and treatment arm were removed from MI-ANCOVA models and added to MMRM models</li> </ul>	<p>Changes a and b are making the wording more precise.</p> <p>Change c and d are corrections.</p>	<p>SYNOPSIS; Section 9.4.3</p>
<p><b>Potential EMA Interim Analysis</b></p> <p>Potential EMA interim analysis description part was removed.</p>	<p>Minimum 52-week treatment was not a requirement anymore per FDA response. It would be applicable to 064.</p>	<p>Section 9.5</p>

## TABLE OF CONTENTS

1	Title Page .....	1
2	Background .....	40
2.1	Introduction .....	40
2.1.1	Epidemiology of Chronic Kidney Disease and End-Stage Renal Disease .....	40
2.1.2	Anemia Associated with Chronic Kidney Disease .....	41
2.2	Current standard of care for CKD or DD-CKD Anemia .....	42
2.3	Mechanism of Action of Roxadustat .....	43
2.4	Clinical Experience with Roxadustat .....	45
2.4.1	Pharmacokinetics and Pharmacodynamics .....	46
2.4.2	Efficacy .....	47
2.4.3	Safety (for detailed current safety information please refer to the Investigator’s Brochure) .....	49
2.5	Summary .....	50
2.6	Roxadustat Dose Rationale .....	50
2.7	Risks/Benefits of Roxadustat Treatment .....	52
3	Objectives and Endpoints .....	54
3.1	Objectives .....	54
3.1.1	Primary Objectives .....	54
3.1.2	Secondary Objectives .....	54
3.2	Efficacy Endpoints .....	54
3.2.1	Primary Efficacy Endpoint: .....	54
3.2.2	Secondary Efficacy Endpoints .....	54
3.2.3	Additional Evaluation of Efficacy .....	55
3.3	Safety Endpoints .....	57
4	Study Design .....	59
4.1	Description of the Study .....	59
4.1.1	Screening Period .....	59
4.1.2	Treatment Period .....	60
4.1.3	Post-Treatment Follow-Up Period .....	61
4.1.4	Long-term Follow-Up for Premature Treatment Discontinued Subjects .....	61
4.2	Randomization, Treatment Assignment, and Rationale for Open-label Design .....	61
4.3	Procedures for Handling Incorrectly Enrolled or Randomized subjects .....	62

4.4	Replacement of Subjects.....	62
4.5	Study Treatment.....	62
4.5.1	Dose and Schedule.....	62
4.5.2	Starting Dose of Study Drug.....	62
4.5.3	Dose Adjustment.....	64
4.6	Concomitant Medications, Procedures and Nondrug Therapies.....	65
4.6.1	Concomitant Medications.....	65
4.6.2	Supplemental Iron Use.....	66
4.6.3	Rescue Therapy Guidelines.....	67
4.6.4	Emergency Procedure (Therapeutic Phlebotomy).....	68
4.6.5	Prohibited Medications/Therapies/Substances.....	68
4.6.6	Contraception.....	68
4.7	Safety Monitoring Plan.....	69
4.8	Data Safety and Monitoring Board.....	69
5	Study Enrollment and Withdrawal.....	70
5.1	Inclusion Criteria.....	70
5.2	Exclusion Criteria.....	71
5.3	Subject Discontinuation and Withdrawal.....	73
5.4	Replacement of Subjects.....	74
5.5	Study Termination.....	74
6	Investigational Product.....	75
6.1	Formulation.....	75
6.2	Storage.....	75
6.3	Study Drug Handling and Disposal.....	75
6.4	Route of Administration and Dose.....	75
6.4.1	Roxadustat.....	75
6.4.2	Epoetin Alfa.....	76
6.5	Overdose, Emergency Procedures and Management of Overdose.....	76
7	Assessment of Efficacy.....	77
7.1	Study Procedures by Visit.....	77
7.1.1	Screening Period.....	77
7.1.2	Treatment Period.....	79
7.2	Post-Treatment Follow-Up Period.....	83

7.2.1	End of Study (EOS): 4 weeks after EOT or ET ( $\pm 7$ days).....	83
7.2.2	Long-Term Follow-Up of Subjects who Discontinued Study Medication Prematurely.....	83
7.3	Missed Visits.....	84
7.4	Unscheduled Visits.....	84
7.5	Laboratory Assessments.....	84
7.6	Central Laboratory.....	84
7.6.1	Archival Serum and Plasma Samples (Optional).....	86
7.7	Electrocardiogram.....	86
7.8	Renal Ultrasound.....	86
7.9	Health Related Quality of Life Questionnaires.....	86
7.9.1	36-Item Short Form Health Survey.....	86
7.9.2	FACT-An.....	87
7.9.3	European Quality of Life Questionnaire in 5 Dimensions.....	87
8	Safety.....	88
8.1	Background.....	88
8.2	Definitions.....	88
8.2.1	Definition of an Adverse Event.....	88
8.2.2	Definition of a Serious Adverse Event.....	88
8.2.3	Definition of a Suspected Adverse Reaction.....	89
8.2.4	Definition of an Adverse Reaction.....	89
8.3	Procedures for Eliciting, Recording, and Reporting Adverse Events.....	89
8.3.1	Adverse Event Reporting Period.....	89
8.3.2	Adverse Event Eliciting/Reporting.....	90
8.3.3	Assessing Adverse Event Severity.....	90
8.3.4	Assessing Relationship to Study Drug.....	91
8.3.5	Reporting Serious Adverse Events on the SAE Report Form.....	92
8.3.6	Pregnancies: Reporting and Follow-up of Subjects.....	93
8.3.7	Abnormal Laboratory Findings.....	94
8.3.8	Disease Progression.....	94
9	Statistical Considerations.....	95
9.1	Sample Size Determination.....	95
9.2	Randomization.....	95

9.3	Analysis Populations.....	95
9.3.1	Intent to Treat Population (ITT) .....	95
9.3.2	Full Analysis Set (FAS).....	96
9.3.3	Per-Protocol Set (PPS).....	96
9.3.4	Safety Analysis Set (SAF) .....	96
9.4	Statistical Analysis.....	96
9.4.1	Subject Enrollment and Disposition .....	96
9.4.2	Demographics and Baseline Characteristics .....	96
9.4.3	Efficacy Analyses .....	96
9.4.4	Safety Analyses.....	99
9.5	Interim Data Cut .....	101
9.6	Statistical Analysis Plan.....	101
9.7	Protocol Deviations.....	101
10	Direct Access to Source Documents.....	103
11	Quality Control and Quality Assurance .....	104
11.1	Data Quality Assurance .....	104
11.2	Audit and Inspection.....	104
11.3	Database Audit.....	104
12	Ethics.....	105
12.1	Ethical Considerations .....	105
12.2	Communication with the Institutional Review Board or Independent Ethics Committee .....	105
12.3	Informed Consent Form .....	105
12.4	Subject Confidentiality .....	106
13	Data Handling and Record Keeping .....	107
13.1	Source Documents .....	107
13.2	Data Collection, Handling, and Verification .....	107
14	Financing and Insurance .....	108
15	Publication Policy .....	109
16	Investigator Requirements .....	110
16.1	Study Drug Accountability .....	110
16.2	Disclosure of Data.....	110
16.3	Retention of Records.....	110

17	References.....	111
18	Appendices.....	115

### LIST OF TABLES

Table 1.	Baseline Epoetin to Starting Roxadustat Dose Conversion.....	51
Table 2.	Initial Dosing of Roxadustat: Conversion Table from ESAs to Roxadustat .....	63
Table 3.	Initial Dosing of Epoetin Alfa: Conversion table from Non-Epoetin ESAs to Epoetin Alfa .....	64
Table 4.	Laboratory Tests .....	85

### LIST OF FIGURES

Figure 1.	Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI) Mechanism of Action.....	44
-----------	--	----

### LIST OF APPENDICES

Appendix 1	Study Schema (Original Protocol) .....	116
Appendix 2	Roxadustat Dose Adjustment Rules.....	117
Appendix 3	Schedule of Assessments .....	119
Appendix 4	Liver Safety Monitoring Assessment.....	122
Appendix 5	Blood Pressure and Heart Rate Measurement Guidelines .....	124
Appendix 6	Recommended Intravenous Iron Therapy .....	125

**LIST OF ABBREVIATIONS**

~	Approximately
Ab	Antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance model
AST	aspartate aminotransferase
AUC	area under the concentration curve
AV	Arteriovenous
BIW	twice weekly
BL	Baseline
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CHr	reticulocyte hemoglobin content
CI	confidence interval
CKD	chronic kidney disease
C <sub>max</sub>	maximum concentration
CMH	Cochran-Mantel-Haenszel
CS	clinically significant
CYP	cytochrome P450
dBp	diastolic blood pressure
DD-CKD	dialysis-dependent chronic kidney disease
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
eEPO	endogenous erythropoietin
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study
EOT	End of Treatment



EPO	Erythropoietin
EQ-5D	European Quality Of Life questionnaire in 5 dimensions
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
ET	Early Termination (visit)
FACT-An	Functional Assessment of Cancer Therapy – Anemia
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hb	Hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HD	Hemodialysis
HDL	high-density lipoprotein
HHD	home-hemodialysis
HIF	hypoxia-inducible factor
HIF-PH	HIF prolyl hydroxylase
HIF-PHI	HIF prolyl hydroxylase inhibitor
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator’s brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IERC	Independent Event Review Committee

IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat Population
IV	Intravenous
IXRS	interactive voice and web response system
KDOQI	kidney disease outcomes quality initiative
LDL	low-density lipoprotein
LLN	lower limit of normal
LFT	liver function test
LOCF	last observation carried forward
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
N (or n)	sample size
NCS	not clinically significant
NDD-CKD	nondialysis dependent chronic kidney disease
NYHA	New York Heart Association
PD	peritoneal dialysis
PEY	patient-exposure-year
PH	prolyl hydroxylase
PK	Pharmacokinetics
PPS	per protocol set
QW	once weekly
RBC	red blood cell
RR	respiratory rate
RRT	renal replacement therapy
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
sBP	systolic blood pressure
SF-36	The 36-Item Short Form Health Survey

---

SC	Subcutaneous
SmPC	Summary of Product Characteristics
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIBC	total iron binding capacity
TIW	three times weekly
TSAT	transferrin saturation
UIBC	unsaturated iron binding capacity
ULN	Upper limit of normal
USRDS	United States Renal Data System
VEGF	vascular endothelial growth factor
WBC	white blood cell
Wt	Weight

**PROTOCOL SYNOPSIS**

<b>Study Title:</b>	A Phase 3, Open-Label, Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat (FG-4592) in the Maintenance Treatment of Anemia in subjects with End Stage Renal Disease (ESRD) on Stable Dialysis
<b>Protocol Number:</b>	FGCL-4592-064
<b>Investigational Product:</b>	Roxadustat (FG-4592)
<b>Target Population:</b>	<p>The study population consists of subjects with ESRD who are on stable hemodialysis (HD) or peritoneal dialysis (PD) and treated with an erythropoiesis-stimulating agent (ESA) for anemia.</p> <p><b>Amendment 1 &amp; 2: Incident dialysis subjects with ESRD who are on dialysis for at least 2 weeks but no more than 4 months (at the time of randomization) and treated with an erythrocyte stimulating agent (ESA) for anemia for at least 4 weeks (prior to screening).</b></p>
<b>IND Number:</b>	074454
<b>Study Phase:</b>	Phase 3
<b>Study Centers Planned:</b>	Up to approximately 200 study centers worldwide.
<b>Number of Subjects Planned:</b>	<p>A total of up to approximately 1200 subjects are planned to be randomized in an open-label, 1:1 ratio to receive either of the following two treatments:</p> <ul style="list-style-type: none"> <li>• Roxadustat (up to approximately 600 subjects)</li> <li>• Active Control: epoetin alfa (up to approximately 600 subjects)</li> </ul> <p>Under Amendment 1 &amp; 2, approximately 150 incident dialysis subjects (as defined above) will be randomized to either roxadustat or epoetin alfa (active control) in a 1:1 ratio</p>
<b>Primary Objectives:</b>	Evaluate the efficacy and safety of roxadustat compared with active control (epoetin alfa) for the maintenance treatment of anemia in subjects with ESRD on stable dialysis.
<b>Secondary Objectives:</b>	<ul style="list-style-type: none"> <li>• Evaluate the utilization of intravenous (IV) iron with roxadustat compared with active control (epoetin alfa)</li> <li>• Evaluate the effect of roxadustat on serum lipid parameters compared with active control (epoetin alfa)</li> </ul>

<p><b>Study Design Overview:</b></p>	<p>This open-label, randomized, active controlled study is designed to evaluate the efficacy and safety of roxadustat compared to epoetin alfa for the maintenance of hemoglobin (Hb) levels in subjects on HD or PD originally on ESA for treatment of anemia.</p> <p>Home-hemodialysis (HHD) subjects may be allowed to participate if all eligibility criteria are met.</p> <p><b>The study periods are as follows:</b></p> <ul style="list-style-type: none"> <li>• <b>Screening Period:</b> Up to 6 weeks. For subjects currently taking Mircer<sup>®</sup>, the Screening Period can be extended up to 8 weeks</li> <li>• <b>Treatment Period:</b> Treatment duration is variable for individual subjects, with a minimum treatment duration of 52 weeks and a maximum duration of up to approximately 3 years after the last subject is randomized</li> </ul> <p><b>Amendment 1 &amp; 2:</b> In order to complete the Phase 3 program in a timely manner, minimum treatment duration of subjects enrolled under Amendment 1 &amp; 2 may be shortened. Subjects will be informed at least 4 weeks in advance if such decision is made. All active subjects will end the study at the same time.</p> <ul style="list-style-type: none"> <li>• <b>Post-Treatment Follow-Up Period:</b> 4 weeks</li> </ul> <p>During the course of the study, visits and assessments will be performed as defined in the schedule of assessments.</p> <p><b>Screening Period</b></p> <p>After signing the informed consent, subjects enter the Screening Period. During the Screening Period eligibility assessments will be performed. Subjects in screening will continue their existing ESA therapy (eg, epoetin alfa, beta, theta, or zeta, darbepoetin alfa, Mircer<sup>®</sup>) for the treatment of anemia associated with ESRD.</p> <p>Subjects on dose-hold due to high haemoglobin may qualify for screening however, they cannot be randomized if in investigator's opinion they are not ready to resume epoetin-alfa or roxadustat upon randomization. Upon successful completion of screening, a total of up to 1200 eligible subjects will be randomized to receive either roxadustat or epoetin alfa (active control) in a 1:1 ratio. Both roxadustat and epoetin alfa will be administered in an open label manner.</p> <p>Randomization must be completed prior to administration of study medication.</p>
--------------------------------------	--

	<p>Randomization to treatment arms will be provided by an interactive web and voice response system (IWRS) based on stratification factors.</p> <p>If Day 1 lab values (collected prior to administration of study medication) suggests potential of pretreatment condition confounding safety assessment or poses safety risks to study subject, in the opinion of the Investigator or Medical Monitor, the subject may be discontinued from the study (example: At Screening 1 visit, LFT values were within the protocol range but at Day1, AST or ALT &gt; 3x ULN and Total bilirubin &gt; 2x ULT, or AST or ALT &gt; 5x ULN).</p> <p><b>Treatment Period</b></p> <p>Administration of the first dose of study treatment (roxadustat or epoetin alfa) will occur on Day 1 (Week 0) which should correspond to the administration of the subject's next dose of their current ESA treatment. At the Day 1, subjects randomized to Roxadustat Arm will discontinue prior ESA therapy and initiate roxadustat therapy; subjects randomized to Epoetin-Alfa Arm will receive epoetin-alfa irrespective of their prior ESA use.</p> <p>The initial dose of study medication will be determined based on the average prescribed ESA dose in the last 4 weeks prior to randomization if on epoetin or darbepoetin (8 weeks if on Mircera<sup>®</sup>) as outlined in <a href="#">Table S1</a> or <a href="#">Table S2</a> for subjects randomized to receive roxadustat or epoetin alfa, respectively. The initial dose of roxadustat will remain constant during the first 4 weeks of the Treatment Period, except if a dose reduction is required for excessive hematopoiesis.</p> <p>Subsequent dose adjustments for roxadustat subjects will follow the dose adjustments guidelines as outlined in Appendix 2 in order to maintain a Hb level of approximately 11 g/dL during the Treatment Period. Dose adjustments for epoetin alfa subjects should follow the dosing recommendations as per the approved country-specific epoetin alfa Package Insert or Summary of Product Characteristics (SmPC). In PD and HHD subjects, if receiving epoetin alfa subcutaneously, the dose and frequency may be determined by the Investigator per local standard of care.</p> <p>Day 1 study procedures including laboratory blood draws are to be completed prior to administration of the first dose of study treatment. In HD subjects, Day 1 procedures with the exception of health-related quality of life (HRQoL) assessments should be completed prior to the subject receiving dialysis that day. Weight</p>
--	--

	<p>measurement will be taken after completion of dialysis (ie, dry weight).</p> <p>Total treatment duration is variable for individual subjects. Subjects will receive study treatment (roxadustat or epoetin alfa) for a minimum of 52 weeks. The maximum treatment duration may be up to approximately 3 years from the date the last subject is randomized.</p> <p>In order to complete the Phase 3 program in a timely manner, minimum treatment duration of subjects enrolled under Amendment 1 &amp; 2 may be shortened. Subjects will be informed at least 4 weeks in advance if such decision is made. All active subjects will end the study at the same time.</p> <p>During the Treatment Period, subjects will attend weekly study visits from Day 1 to Week 2, followed by every 2 weeks study visits from Weeks 4 to 24 (eg, Weeks 4, 6). Following Week 24, study visits will occur every 4 weeks (eg, Weeks 28, 32) until End of Treatment (EOT). A common closeout will occur when a predetermined number of adjudicated cardiovascular (CV) events have been accrued across multiple studies in the overall Phase 3 dialysis program.</p> <p>At each study visit during the Treatment Period, Hb will be measured (prior to dialysis in HD subjects) locally to determine the need for a dose adjustment or to assess for excessive hematopoiesis. In the event that the Hb value from the central laboratory is significantly different from the value that measured locally, and per Investigator that warrants a reversal of the dose adjustment decision made earlier based on locally measured Hb value, the Medical Monitor should be informed, if possible.</p> <p><b>Post-Treatment Follow-Up Period</b></p> <p>After completing the Treatment Period, subjects proceed to the post-treatment Follow-up Period and will return for the End of Study (EOS) visit. The choice of anemia treatment during the Follow-up Period is up to the discretion of the Investigator. If the Investigator decides to resume ESA treatment in roxadustat treated subjects, the first dose of ESA should be administered at least three days after the last dose of roxadustat.</p> <p><b>Long-term Follow-Up for Premature Treatment Discontinued Subjects</b></p> <p>Subjects who discontinue study medication prematurely will be followed up for vital status, CV events, and hospitalization until study closure, unless consent to participate is withdrawn. Upon completion of EOT and EOS visits, these subjects will be followed up every 3-6 month interval (depending on the availability of</p>
--	---

	<p>subjects) until study closure. These visits may occur either in-person or via telephone.</p> <p><b>Data Safety Monitoring Board</b></p> <p>A Data Safety Monitoring Board (DSMB) will review safety data at least every 6 months or twice per calendar year while the trial is ongoing to ensure subject safety during the study. Details will be specified in a DSMB charter.</p> <p><b>Independent Event Review Committee</b></p> <p>An Independent Event Review Committee (IERC), blinded to treatment group, will adjudicate prespecified CV, cerebrovascular, and thromboembolic safety events of interest. These events include all cause death, myocardial infarction (MI), stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, deep venous thrombosis (DVT), pulmonary embolism, vascular access thrombosis, and hypertensive emergency. A separate event adjudication charter will describe the process in detail, and training materials will be provided to study sites.</p>
<p><b>Inclusion Criteria:</b></p>	<p>A subject is eligible for the study if all of the following criteria are met:</p> <ol style="list-style-type: none"> <li>1. Subject has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines</li> <li>2. Subject age is <math>\geq 18</math> years</li> <li>3. Subject receiving adequate dialysis using the same modality of dialysis for native kidney ESRD for <math>\geq 3</math> months prior to screening and during screening <ul style="list-style-type: none"> <li><b>3.1 Amendment 2: Incident dialysis subjects receiving dialysis for ESRD for <math>\geq 2</math> weeks but <math>\leq 4</math> months at the time of randomization</b></li> </ul> </li> <li>4. For subjects receiving HD, the vascular access must be via native arteriovenous fistula or graft, or permanent, tunneled catheter. For subjects receiving PD, a PD catheter must be in use</li> <li>5. Subject is on IV or subcutaneous ESA for <math>\geq 8</math> weeks prior to screening. The prescribed ESA dose must remain stable (<math>\leq 30\%</math> change) during the 4 weeks prior to randomization if on epoetin or darbepoetin and 8 weeks if on Mircera<sup>®</sup> <ul style="list-style-type: none"> <li><b>5.1 Amendment 2: Incident dialysis subjects (as defined in 3.1) must be on ESA for <math>\geq 4</math> weeks prior to screening.</b></li> </ul> </li> <li>6. Mean of the subject's three most recent central lab Hb values during the Screening Period must be <math>\geq 9.0</math> g/dL and <math>\leq 12.0</math> g/dL;</li> </ol>



	<p>with an absolute difference of <math>\leq 1.3</math> g/dL between the highest and the lowest value. Samples are obtained at least 4 days apart and the last Hb value must be within 10 days prior to the randomization visit</p> <p><b>6.1 Amendment 2: For Incident dialysis subjects (as defined in 3.1), mean of the subject's two most recent central lab Hb values during the Screening Period must be <math>\geq 8.5</math> g/dL and <math>\leq 12.0</math> g/dL; with an absolute difference of <math>\leq 1.3</math> g/dL between the highest and the lowest value. Samples are obtained at least 2 days apart and the last Hb value must be within 10 days prior to the randomization visit</b></p> <p>7. Subject has a ferritin level <math>\geq 100</math> ng/mL at screening  <b>Amendment 2:</b> Subjects with a ferritin level <math>&lt; 100</math> ng/mL at screening may qualify upon receiving iron supplement (per local standard of care)</p> <p>8. Subject has a transferrin saturation (TSAT) level <math>\geq 20\%</math> at screening  <b>Amendment 2:</b> Subjects with a TSAT level <math>&lt; 20\%</math> at screening may qualify upon receiving iron supplement (per local standard of care)</p> <p>9. Subject has a serum folate level <math>\geq</math> lower limit of normal (LLN) at screening  <b>Amendment 2:</b> Subjects with a serum folate level <math>&lt; LLN</math> at screening may qualify upon receiving folate supplement (per local standard of care)</p> <p>10. Subject has a serum vitamin B<sub>12</sub> level <math>\geq LLN</math> at screening  <b>Amendment 2:</b> Subjects with a Vitamin B<sub>12</sub> level <math>&lt; LLN</math> at screening may qualify upon receiving B<sub>12</sub> supplement (per local standard of care)</p> <p>11. Subject's alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are <math>\leq 3</math> x upper limit of normal (ULN), and total bilirubin (TBL) is <math>\leq 1.5</math> x ULN at screening</p> <p>12. Subject's body weight (dry weight in HD subjects) is 45.0 to 160.0 kg</p> <p><b>Only incident dialysis subjects who meet criteria 3.1, 5.1, and 6.1 (instead of criteria 3, 5, and 6) are allowed to participate under Protocol Amendment 2</b></p>
<b>Exclusion Criteria:</b>	Subjects will be excluded if any of the following criteria are met:

	<ol style="list-style-type: none"><li>1. Subject has received a red blood cell (RBC) transfusion within 8 weeks prior to randomization <b>Amendment 2:</b> Subject has received a red blood cell (RBC) transfusion within 4 weeks prior to randomization</li><li>2. Subject has a known history of myelodysplastic syndrome or multiple myeloma</li><li>3. Subject has a known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia or other known causes for anemia other than chronic kidney disease (CKD)</li><li>4. Subject has known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition</li><li>5. Subject has a known chronic inflammatory disease that could in the opinion of the Investigator impact erythropoiesis (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission</li><li>6. Subject is anticipated to undergo elective surgery that is expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization.</li><li>7. Subject has active or chronic gastrointestinal bleeding</li><li>8. Subject has received any prior treatment with roxadustat or another hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)</li><li>9. Subject has been treated with iron-chelating agents within 4 weeks prior to randomization</li><li>10. Subject has a history of chronic liver disease (eg, chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver)</li><li>11. Subject with New York Heart Association (NYHA) Class III or IV congestive heart failure</li><li>12. Subject has had an MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within a major vessel (excluding vascular dialysis access) (eg, DVT or pulmonary embolism) within 12 weeks prior to randomization</li><li>13. Subject has uncontrolled hypertension, in the opinion of the Investigator, (eg, that requires change in anti-hypertensive medication) within 2 weeks prior to randomization</li><li>14. Subject has one or more contraindications for treatment with epoetin alfa or other ESA including known hypersensitivity</li></ol>
--	---

	<p>15. Subject has a diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category II or higher) of renal cell carcinoma as shown on renal imaging performed within 12 weeks prior to randomization</p> <p>16. Subject has a history of malignancy, except for the following: cancers determined to be cured or in remission for <math>\geq 5</math> years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps</p> <p><b>Amendment 2</b> Subject has a history of malignancy, except for the following: cancers determined to be cured or in remission for <math>\geq 2</math> years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps</p> <p>17. Subject is positive for any of the following:</p> <ul style="list-style-type: none"> <li>• Human immunodeficiency virus (HIV)</li> <li>• Hepatitis B surface antigen (HBsAg)</li> <li>• Anti-hepatitis C virus antibody (anti-HCV Ab)</li> </ul> <p>18. Subject has an active, clinically significant (CS) infection or evidence of an underlying infection, as manifested by white blood cell count (WBC) <math>&gt;</math> ULN, and/or fever, in conjunction with clinical signs or symptoms of infection at the time of randomization</p> <p>19. Subject has any of the following known untreated conditions: proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion (subjects who are already blind may qualify to participate)</p> <p>20. Subject has had any prior organ transplant (that has not been explanted), or subject is scheduled for organ transplantation (on the waiting list for kidney transplant is not exclusionary)</p> <p><b>Amendment 2:</b> Prior organ transplant: subjects who have one of the following conditions or states</p> <ul style="list-style-type: none"> <li>a) Experienced rejection of transplanted organ within 6 months of transplantation</li> <li>b) Currently on high doses of immunosuppressive therapy (per discretion of the PI)</li> <li>c) Are scheduled for organ transplantation (on the waiting list for kidney transplant is not exclusionary)</li> </ul> <p>21. Subject has participated in an interventional clinical study or has been treated with an investigational drug within 4 weeks prior to screening</p>
--	--

	<p>22. Subject has drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that may lead to reduced absorption of study drug</p> <p>23. Subject has an anticipated use of dapsone or androgen in any dose amount or anticipated chronic use of acetaminophen or paracetamol &gt; 2.0 g/day during the study</p> <p>24. Subject has a history of alcohol or drug abuse within 2 years prior to screening</p> <p><b>Amendment 2:</b> Subject has a history of alcohol or drug abuse within 6 months prior to screening</p> <p>25. Females of childbearing potential, if not practicing complete sexual abstinence or using contraception as detailed in the protocol; male subjects (if not surgically sterile; ie, no vasectomy) with sexual partners of childbearing potential, if not practicing complete sexual abstinence or using contraception</p> <p>26. Pregnant or breastfeeding females</p> <p>27. Subject has any medical condition that in the opinion of the Investigator may pose a safety risk to the subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation</p>
<b>Study Procedures:</b>	See Schedule of Assessments (Appendix 3)
<b>Investigational Product</b>	<p><b>Roxadustat</b></p> <ul style="list-style-type: none"> <li>• Tablets</li> <li>• Strengths of 20 mg, 50 mg and 100 mg</li> </ul> <p><b>Route of Administration:</b></p> <p>Oral (all tablets must be administered whole)</p> <p><b>Doses:</b></p> <p>In subjects on HD or PD or HHD randomized to roxadustat, the initial roxadustat dose will be determined using a conversion table based on the subject's previous average weekly prescribed ESA dose in the last 4 weeks prior to randomization if the subject is on epoetin or darbepoetin, and average monthly (4 weeks) prescribed ESA dose in 8 weeks prior to randomization if the subject is on Mircera<sup>®</sup> (Table S1). If the mean qualifying screening Hb value at randomization is &lt; 10 g/dL, the starting roxadustat dose will be increased by one dose step. For example, a subject on epoetin (ie, epoetin alfa, beta, theta, zeta, delta, or omega) 6,000 IU/week with</p>

mean screening Hb of 9.4 g/dL at randomization will start roxadustat at a dose of 150 mg three times weekly (TIW).

If the converted initial dose exceeds the maximum dose of 3.0 mg/kg/dose then the lower dose step should be chosen as the initial dose.

The dose of roxadustat will remain constant during the first 4 weeks of the Treatment Period unless a dose reduction is required for excessive hematopoiesis.

**Table S1 Initial Dosing of Roxadustat: Conversion Table from ESAs to Roxadustat**

Epoetin (ie, alfa, beta, theta, zeta, delta, or omega) <sup>a</sup> (IU/week)	Darbepoetin alfa <sup>a, b</sup> (µg/week)	Mircera <sup>®c</sup> (µg/ monthly)	Roxadustat Dose <sup>d</sup> (mg/dose) TIW
< 5,000	< 25	< 80	70
5,000 to 8,000	25-40	80-120	100
> 8,000 to 16,000	> 40-80	> 120-200	150
> 16,000	> 80	> 200	200

Abbreviations: ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; IU = international units; TIW = three times a week.

- a Average weekly prescribed dose in last 4 weeks prior to randomization
- b If darbepoetin is used biweekly, use half the dose to get per week dose
- c Average prescribed monthly (4-wks) dose in last 8 weeks prior to randomization
- d Starting dose will be one step higher if the mean Hb at randomization is < 10.0 g/dL, however, not to exceed 3.0 mg/kg/dose.

Notes: The roxadustat dose steps are 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.

### Dose Adjustments:

During the Treatment Period, roxadustat dose adjustment will be made according to the dose adjustment algorithm in Appendix 2, in order to maintain a Hb level of approximately 11 g/dL.

Roxadustat dose adjustments are permitted from Week 4 onwards, and every 4 weeks thereafter (eg, Week 4, Week 8, Week 12); however, dose may be adjusted between two prespecified windows (eg, anytime between Week 4 and Week 8 visits, Week 8 and Week 12 visits) if the following two criteria are met:

- No dose adjustment has been made in last 4 weeks,
- Hemoglobin (Hb) < 9.0 g/dL.

Subjects on HD or PD or HHD randomized to roxadustat will take doses TIW for the entire duration of the Treatment Period. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain a

	<p>Hb level of approximately 11 g/dL, the dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc.</p> <p>In this study, a rate of rise of Hb &gt; 2 g/dL within 4 weeks or a Hb level of <math>\geq 13</math> g/dl at any time would be considered as excessive haematopoiesis. For a rate of rise of Hb &gt; 2 g/dL within 4 weeks, dose should be reduced by one dose step and for a Hb value <math>\geq 13.0</math> g/dL, the dose should be on hold until Hb drops &lt; 12.0 g/dL per guidelines provided in the protocol (Appendix 2). When roxadustat will be resumed, the dose should be reduced by one dose step.</p> <p>Dose adjustments or temporary dose holds for excessive hematopoiesis can occur at any time during the Treatment Period. Any dose adjustment will reset the dose-adjustment window to every 4 weeks thereafter (eg, dose adjustment for a qualified reason at Week 6 leads to next dose adjustment at Week 10).</p> <p>Prescribed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower. For dose adjustment purposes, post-dialysis weight (dry-weight) should be used. If the post-dialysis weight of the current visit is not available at the time of dose adjustment, post-dialysis weight of the prior dialysis session or last recorded post-dialysis weight may be used.</p>
<p><b>Reference Therapy:</b></p>	<p><b>Epoetin Alfa</b> (active control)</p> <p><b>Route of Administration:</b></p> <p>Hemodialysis (HD): Intravenous</p> <p>Peritoneal dialysis (PD) or home hemo-dialysis (HHD): Intravenous or subcutaneous</p> <p>Subjects randomized to the epoetin alfa arm who are currently taking nonepoetin alfa treatment will be switched to epoetin alfa treatment on Day 1. All subjects on HD will receive IV epoetin alfa TIW starting from Day 1, irrespective of their baseline route of administration or frequency of ESA use. Subjects requiring ultra-low dose of EPO (eg, <math>\leq 1000</math> IU/per week), frequency of administration may be adjusted per local standard of care.</p> <p>Subjects on PD or HHD may continue using the same route of administration as baseline; however, if the Investigator decides to change the route of administration in a PD subject from subcutaneous to IV after randomization it should be done during the early part of the treatment phase (preferably prior to Week 16).</p> <p>All epoetin alfa administrations should be performed by the Investigator or an authorized member of the site staff or other trained personnel. In subjects on PD or HHD, epoetin alfa may be self-</p>

administered subcutaneously by the subject or a caregiver after adequate training or, if in the opinion of the Investigator, the subject or a caregiver is already adequately trained in self-administering ESA prior to the study.

**Doses:**

In subjects who have been randomized to the epoetin alfa treatment arm, the initial epoetin alfa dose that the subject will receive on Day 1 will be determined using a conversion table based on the subject's average weekly prescribed ESA dose in 4 weeks prior to randomization if on epoetin or darbepoetin, and average monthly (4-week) prescribed ESA dose in 8 weeks prior to randomization if on Mircera<sup>®</sup> (Table S2).

In case of a change in route of administration from subcutaneous to IV (TIW), the initial dose of IV epoetin alfa will be determined by the Investigator per local standard of care.

In subjects on PD or HHD, if receiving epoetin alfa subcutaneously, the dose and frequency may be determined by the Investigator per local standard of care.

**Table S2 Initial Dosing of Epoetin Alfa: Conversion Table from ESAs to Epoetin Alfa**

Baseline ESA	Conversion Ratio	Examples of Converted Initial Epoetin Alfa dose (approximate) IU/week <sup>c</sup>
Epoetin (ie, alfa, beta, theta, zeta, delta, or omega) (IU/week) <sup>a</sup>	x 1	6,000 IU/week x 1 = 6,000 IU/week
Darbepoetin alfa (µg/week) <sup>a</sup>	x 200	40 µg/week x 200 = 8,000 IU/week
Mircera <sup>®</sup> (µg/once monthly) (ie, 4-wks) <sup>b</sup>	x 70 – 80 (for lower Mircera <sup>®</sup> dose lower conversion ratio may be used) <sup>d</sup>	100 µg/month x 70 = 7,000 IU/week 200 µg/month x 80 = 16,000 IU/week

Abbreviations: ESA = erythropoiesis-stimulating agent; IU = international units.

- a Mean weekly ESA in 4 weeks prior to randomization
- b Mean monthly (4-week) ESA in 8 weeks prior to randomization
- c May be rounded as deemed necessary by the Investigator
- d Per discretion of the Investigator

	<p>Subsequent epoetin alfa dosing and dose adjustment during the study, if indicated, should be based on the country specific package insert or SmPC.</p> <p>For countries using prefilled epoetin alfa syringes, the initial dose and subsequent dosages following dose adjustments during the Treatment Period should be approximated to the closest total weekly dose.</p>
<p><b>Rescue Therapy and Emergency Procedures:</b></p>	<p><b>Rescue Therapy Guidelines:</b></p> <p>Rescue therapy guidelines are provided to optimize the standardization of rescue therapy by Investigators and to ensure the safety of individual study subjects. Use of rescue therapy and reason for rescue therapy should be recorded in the electronic case report form (eCRF).</p> <p><b>Red Blood Cell Transfusion (for all subjects)</b></p> <p>For subjects in both treatment arms, RBC transfusion is allowed if rapid correction of anemia is required to stabilize the subject's condition (eg, acute hemorrhage) or the Investigator is of the opinion that the blood transfusion is a medical necessity. If the situation permits, the Medical Monitor should be informed prior to any scheduled RBC transfusion. Study treatment may continue during or after the RBC transfusion.</p> <p><b>Erythropoiesis Stimulating Agent (ESA) Use</b></p> <p>For subjects randomized to roxadustat the use of ESAs is generally prohibited. Erythropoiesis stimulating agent rescue is restricted to no more than one cycle of use during the Treatment Period; the Investigator may initiate use of an approved erythropoietin (EPO) analogue if all of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• A subject's Hb level has not sufficiently responded to two or more dose increases or the maximum dose limit of the study drug has been reached, and</li> <li>• The subject's Hb is &lt; 8.5 g/dL on two consecutive measurements (central lab) drawn at least five days apart; and</li> <li>• Clinical judgment does not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in Hb, and</li> <li>• Reducing the risk of alloimmunization in transplant eligible patients and/or reduction of other RBC transfusion-related risks is a goal</li> </ul>



	<p>The subject is not allowed to be administered both EPO analogue and study drug at the same time. Treatment with an EPO analogue should be started <math>\geq 3</math> days after the last dose of roxadustat, and should be stopped when Hb <math>&gt; 9</math> g/dL or after 4-weeks, whichever comes first. If a subject requires longer than 4-weeks therapy due to inadequate response, the Medical Monitor should be contacted. Study treatment should be resumed after the following intervals:</p> <ul style="list-style-type: none"> <li>• Two days after stopping epoetin</li> <li>• One week after stopping darbepoetin alfa</li> <li>• Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera<sup>®</sup>)</li> </ul> <p>If more than one cycle of EPO analogue rescue is required, the Investigator should permanently discontinue study drug. Use of EPO analogues will be recorded in the eCRF.</p> <p>Inadvertent ESA administration or ESA administration by the hospital staff in Roxadustat subjects should not be counted as rescue unless above criteria are met; these subjects may be allowed to continue taking study medication, if considered safe by the Investigator or Medical Monitor.</p> <p>For subjects randomized to epoetin alfa, the Investigator may initiate use of a different EPO analogue if clinically indicated. Use of the different EPO analogue will be recorded in the eCRF and will be considered rescue therapy.</p> <p><b>Emergency Procedure (Therapeutic Phlebotomy)</b></p> <p>If there are clinical concerns for a subject’s high Hb levels, the Investigator may decide to perform a therapeutic phlebotomy in addition to temporarily withholding the study drug. This should be documented and discussed with the Medical Monitor.</p>
<p><b>Supplemental Iron Use:</b></p>	<p>In a Phase 2 study, there was no significant difference in Hb levels in roxadustat -treated dialysis patients receiving oral iron supplementation compared to subjects receiving IV iron supplementation, in patients with ferritin <math>&lt; 100</math> ng/mL and in those with TSAT <math>&lt; 20\%</math>. Based on the mechanism of action of roxadustat and the Phase 2 study results, in subjects randomized to roxadustat, oral iron supplementation is considered to be sufficient.</p> <p>In this study, oral iron should be allowed as the preferred first-line of iron supplementation for both treatment arms without restriction.</p> <p>In addition to the scheduled assessments, iron indices may be assessed at any time (via central lab) to evaluate iron storage status of the subjects, if considered necessary by the Investigator.</p>

	<p><b>Oral Iron Supplementation</b></p> <p>All subjects should be encouraged to take oral iron if they can tolerate as the preferred first-line iron supplementation during the Treatment Period. Provision of an oral iron supplement is encouraged; the dose and frequency are at the discretion of the principal Investigator. Oral Iron therapy should be started before the subject becomes iron depleted.</p> <p><b>Intravenous Iron Supplementation</b></p> <p>Intravenous iron supplementation is permitted if in the opinion of the Investigator the subject has not responded adequately and is considered iron deficient. IV iron may be administered per local standard of care as deemed necessary by the investigator.</p> <p>Treatment with study medication (roxadustat or epoetin) will continue during IV iron administration. Discontinuation of IV iron supplementation is recommended once the subject is no longer considered iron deficient (eg, ferritin <math>\geq</math> 100 ng/mL and TSAT <math>\geq</math> 20%)</p> <p>Subjects may receive IV iron during the post-treatment Follow-up Period per discretion of the Investigator. If IV iron is to be administered at the EOT visit, all visit procedures including lab draws should be completed prior to administering IV iron.</p>
<p><b>Prohibited Medication:</b></p>	<p>The following medications/therapies are prohibited during the period identified:</p> <ul style="list-style-type: none"> <li>• Any investigational drug from 4 weeks prior to screening until EOS</li> <li>• Androgens from screening until EOS</li> <li>• Iron-chelating agents (eg, deferoxamine/deferrioxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to randomization until EOS</li> <li>• Dapsone (at any dose) from screening until EOS</li> <li>• Chronic doses acetaminophen/paracetamol <math>&gt;</math> 2.0 g/day from randomization until 1 week after EOT</li> </ul>
<p><b>Efficacy Endpoints and Assessments:</b></p>	<p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>• US (FDA) submission: Hemoglobin (Hb) change from baseline to the average Hb level during the evaluation period defined as Week 28 until Week 52</li> <li>• EU regulatory submission : Hemoglobin (Hb) change from baseline to the average level Hb of Weeks 28 to 36, without having received rescue therapy (ie, RBC transfusion or rescue</li> </ul>

	<p>ESA therapy) within 6 weeks prior to and during this 8-week evaluation period.</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• US (FDA) submission: proportion of subjects with mean Hb level during the evaluation period defined as Week 28 until Week 52 <math>\geq 10.0</math> g/dL.</li> <li>• EU regulatory submission: Hemoglobin (Hb) response, defined as mean Hb during Weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.</li> <li>• Average monthly IV iron use per subject during Weeks 1 to 36 (monthly defined as a period of 4 weeks).</li> <li>• Change from BL in low-density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28</li> <li>• Change from BL in SF-36 Physical Functioning (PF) subscore to the average PF subscore of Weeks 12 to 28</li> <li>• Change from BL in SF-36 Vitality (VT) subscore to the average VT subscore of Weeks 12 to 28</li> <li>• Effect on predialysis blood pressure (BP): <ul style="list-style-type: none"> <li>○ Time to an exacerbation of hypertension from BL during Weeks 1 to 36 <ul style="list-style-type: none"> <li>▪ An increase from BL of <math>\geq 20</math> mm Hg systolic blood pressure (sBP) and sBP <math>&gt; 170</math> mmHg</li> </ul> </li> <li>OR</li> <li>▪ An increase from BL of <math>\geq 15</math> mm Hg diastolic blood pressure (dBP) and dBP <math>&gt; 100</math> mmHg</li> </ul> </li> <li>○ Change from BL in mean arterial pressure (MAP) to the MAP value averaged over Weeks 20 to 28</li> </ul> <p><b>Additional Efficacy Endpoints:</b></p> <p>Additional efficacy endpoints are described in the body of the protocol.</p>
<p><b>Safety Assessments and Endpoints:</b></p>	<p><b>Study-specific safety will be assessed by evaluating the following:</b></p> <ul style="list-style-type: none"> <li>• Occurrence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs)</li> </ul>

	<ul style="list-style-type: none"> <li>• Adverse events (AEs), serious adverse events (SAEs), and clinically significant changes in laboratory values from baseline</li> <li>• Vital signs, electrocardiogram (ECG) parameters, and clinical laboratory values.</li> </ul> <p>Safety interpretation will also be made based on analyses of composite endpoints derived from adjudicated events pooled across multiple studies in the roxadustat Phase 3 program. The members of an independent adjudication committee blinded to treatment assignment will adjudicate the following events in multiple Phase 3 studies:</p> <p>All cause death, MI, stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, hypertensive emergency, DVT, pulmonary embolism, and vascular access thrombosis.</p> <p>Various region-specific pooled analyses of composites of these adjudicated events, pooled across multiple studies will be conducted. The analyses of the adjudicated events will be detailed in the region-specific PSAPs.</p> <p>For US (FDA) Submission Only:          The primary safety endpoint in this study is the MACE (Major Adverse Cardiac Event) composite endpoint, defined as time to first occurrence of death from all causes, MI, or stroke, for the purpose of being pooled across multiple similar studies in the Phase 3 program. None of the individual studies are powered to meet the MACE primary safety endpoint individually. The pooled MACE analysis is only for purposes of supporting a US FDA regulatory filing of roxadustat.</p> <p>The above adjudicated safety events may also be used to support the pooled analyses of additional composite safety endpoints across multiple studies in the Phase 3 program, such as MACE+ (death, MI, stroke, congestive heart failure requiring hospitalization, and unstable angina requiring hospitalization), or a composite which consists of all of the adjudicated events.</p>
<p><b>Statistical Methods:</b></p>	<p><b>Stratification:</b></p> <p>Up to 1200 subjects will be randomized via IWRS to receive roxadustat or epoetin alfa in an open-label manner in a 1:1 ratio.</p> <p>Randomization will be stratified by the following four factors:</p>

	<ul style="list-style-type: none"> <li>• Mean qualifying screening hemoglobin (<math>\leq 10.5</math> vs. <math>&gt;10.5</math> g/dL)</li> <li>• History of CV, cerebrovascular, or thromboembolic diseases (yes vs. no)</li> <li>• Mean prescribed weekly epoetin alfa dose (or, equivalent epoetin dose for non-epoetin subjects) in the 4 weeks prior to randomization (<math>\leq 150</math> vs. <math>&gt; 150</math> IU/kg/week)</li> <li>• Geographical region (US vs. Ex-US regions)</li> </ul> <p><b>Sample size determination:</b></p> <p>At least 600 subjects will be enrolled in this study. During the course of this study, which is being conducted in parallel with other Phase 3 studies, up to 1200 subjects may be enrolled for safety evaluation of roxadustat in comparison to epoetin alfa including adjudicated and prespecified safety events of interest (ie, all-cause death, MI, stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, DVT, pulmonary embolism, vascular access thrombosis, and hypertensive emergency). The final number of patients to be enrolled will be based on the enrollment rate of other studies within the same indication, in order to optimize stopping these studies at comparable time frame</p> <p>With at least 600 subjects, the study will provide at least 99% power to demonstrate statistical noninferiority of roxadustat versus ESA in the primary endpoint for US (FDA) submission (ie, specifically, Hb change from baseline to the average level during the evaluation period defined as Week 28 until Week 52).</p> <p>The study will provide at least 99% power to demonstrate statistical noninferiority of roxadustat versus ESA in the primary endpoint outside of the United States (ie, specifically, Hb change from BL in the averaged Hb over Weeks 28 to 36).</p> <p>This assumes a difference (roxadustat minus ESA) of <math>-0.30</math> g/dL, a noninferiority margin for this difference of <math>0.75</math> g/dL and a standard deviation of <math>1.25</math> g/dL.</p> <p><b>Analysis Sets</b></p> <p>For US regulatory submission, efficacy and safety analyses will be based on all subjects stratified by the protocol amendment, on subjects enrolled during the original protocol but before the amendment, and on subjects enrolled after the amendment separately.</p> <p>For EU regulatory submission, efficacy and safety analyses will be based on subjects enrolled during the original protocol before the</p>
--	---

	<p>amendments, as the subjects enrolled after the amendments may be considered as a sub-study for EU regulatory purpose.</p> <p>The following analysis sets are defined and will be used for the statistical analysis:</p> <p><b>Intent to Treat (ITT) Population:</b> The ITT population consists of all randomized subjects.</p> <p><b>Full Analysis Set (FAS):</b> The FAS consists of all randomized subjects who receive at least one dose of study drug and have at least one postdose Hb assessment. If treatment received differs from the randomized treatment, the randomized treatment arm will be used.</p> <p><b>Per-Protocol Set (PPS):</b> The PPS consists of all randomized subjects who received at least 8 weeks of study treatment, have at least one postdose Hb assessment and are without major protocol violations.</p> <p><b>Safety Analysis Set (SAF):</b> The SAF will consist of all randomized subjects who received at least one dose of study medication. If treatment received for the duration of the study differs from the randomized treatment, the actual treatment arm will be used.</p> <p><b>Efficacy:</b></p> <p><b>Primary Hypothesis</b></p> <p>The primary efficacy endpoint for US (FDA) submission is defined as each subject's Hb change from baseline to the average level during the evaluation period, defined as Weeks 28 to 52. The analysis will be based on the ITT Population.</p> <p>A Multiple Imputation Analysis of Covariance (MI-ANCOVA) model will be used. The model will contain terms for treatment arm, baseline Hb measurement, and randomization stratification factors except Screening Hb values (<math>\leq 10.5</math> g/dL vs. <math>&gt; 10.5</math> g/dL).</p> <p>The primary efficacy analysis will be based on the estimated difference between the two treatments throughout the evaluation period based on the MI-ANCOVA model.</p> <p>The primary efficacy endpoint for EU regulatory submission is defined as the Hb change from BL to the average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period and will be based on the PPS population. The primary efficacy analysis will be based on the</p>
--	---

	<p>estimated difference between the two treatments overall mean effects throughout the evaluation period based on the MMRM model.</p> <p><i>Secondary efficacy analyses are described in the body of the protocol</i></p> <p><b>Safety</b></p> <p>The Safety analyses will be performed using the Safety Analysis Set (SAF). Safety parameters include adverse events, SAEs, laboratory parameters, vital signs, ECG parameters, and PE</p> <p>The number and percentage of subjects reporting TEAEs and TESAEs in each treatment group will be tabulated. Descriptive statistics will be presented for laboratory, vital signs values and ECG parameters by visit and for the changes from BL to each visit.</p> <p>The CV safety assessment of roxadustat will also be based on pooled analysis of composites of adjudicated CV events pooled across multiple global Phase 3 clinical studies which includes this study, according to the regional pooled SAPs for meeting regional regulatory requirements.</p> <p>For the US (FDA) submission only: The primary safety endpoint in this study is the MACE (Major Adverse Cardiac Event) composite endpoint, defined as time to first occurrence of death from all causes, MI, or stroke, only for the purpose of being pooled across multiple similar studies in the Phase 3 program. None of the individual studies are powered to meet the MACE primary safety endpoint individually. The pooled MACE analysis is only for purposes of supporting a US FDA regulatory filing of roxadustat.</p> <p>Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be conducted by an independent DSMB.</p> <p>For each safety parameter, the last assessment made prior to the first dose of study medication will be used as the BL for all analyses of that safety parameter.</p>
--	---

This study will be conducted in accordance with the guidelines of Good Clinical Practice and the applicable regulatory requirement(s), including the archiving of essential documents.

## 2 BACKGROUND

Hypoxia-inducible factor (HIF) is a key transcription factor that coordinates the body's physiological response to changes in oxygen levels in the cellular environment (Semenza, 2000). It induces the expression of erythropoietin (EPO) and the EPO receptor, as well as the expression of other proteins that promote iron absorption and recycling (Peyssonnaud et al, 2008). The activity of HIF is regulated by hypoxia-inducible factor prolyl hydroxylase (HIF-PH) enzymes (HIF-PHD1 to D3). These enzymes target HIF for degradation.

Roxadustat (FG-4592/ ASP1517/ AZD9941) is an orally active novel small-molecule that inhibits these HIF-PH enzymes. By inhibiting HIF-PH, roxadustat stimulates erythropoiesis via the HIF pathway in a manner consistent with the body's normal response to hypoxia. Its ability to stimulate erythropoiesis makes it a candidate for the treatment of anemia associated with chronic kidney disease (CKD) in patients with nondialysis-dependent (NDD-CKD) and dialysis-dependent (DD-CKD).

### 2.1 Introduction

#### 2.1.1 Epidemiology of Chronic Kidney Disease and End-Stage Renal Disease

Chronic kidney disease is a growing worldwide public health problem. It is associated with significant morbidity and mortality, yet is underdiagnosed and undertreated. It is characterized by progressive loss of kidney function, resulting in premature death or renal replacement therapy (RRT) (kidney transplant or dialysis).

The average prevalence of CKD, regardless of age, ranges between 5% to 11% in Europe and the all-cause mortality risk increases exponentially as CKD stages advance (Tonelli et al., 2006). The prevalence of DD-CKD is 887 per million people in China (2011 Shanghai Dialysis Registry Report) and in the US, CKD affected 13% of the US adult population (~ 29 million adults) in 2007, and the prevalence is rapidly growing (Coresh et al., 2007). In Europe, the average prevalence of CKD regardless of age lies between 5 and 11% (Zoccali et al., 2010).

The number of patients suffering from end-stage renal disease (ESRD) also continues to increase worldwide. The US has one of the highest prevalence rates of ESRD in the world: in 2010, the US had over 1700 patients with ESRD per million population, a 23% increase compared to 10 years before (USRDS, 2011). In 2009 (point prevalence as of December 31st), there were approximately 570,000 patients with ESRD in the US, of whom 370,000 were receiving hemodialysis (HD), 27,000 were receiving peritoneal dialysis (PD), and 173,000 had a functioning kidney transplant (USRDS, 2011). In recent years, those older than 75 years have been observed to have the highest incidence of treated ESRD (1735 per million populations in 2007, US by age and race/ethnicity). The adjusted ESRD incidence rates were 998 per million populations for African Americans, 396 per million population for Asians/Pacific Islanders, and 273 per million populations for whites in 2007 (USRDS, 2009). In Europe, over the period 1992–2005, the overall crude prevalence of RRT for patients with ESRD increased from 480 to 807 patients per million populations (Zoccali et al., 2010).

The average expected life expectancy of a dialysis patient 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 patients on RRT 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).

### 2.1.2 Anemia Associated with Chronic Kidney Disease

Anemia is a common complication in patients with CKD, and although its pathogenesis is multifactorial, the decreased production of 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 a second etiologic factor.

Anemia may present in the early stages of CKD and its prevalence increases as CKD progresses. Anemia is present in 17% of patients with late Stage 3 disease; this increases to 25% in patients with Stage 4 disease, and to 49% in patients with Stage 5 disease 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 all patients new to dialysis (50.1%) have hemoglobin (Hb) levels below 10 g/dL and approximately 28% have Hb levels 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 predialysis patients and found that 60% of patients with a creatinine clearance of < 20 ml/min/1.73 m<sup>2</sup> were anemic (Hb < 11 g/dL) (Jungers et al., 2002). Between 2003 and 2005, Thilly studied predialysis anemia care in 6271 incident dialysis patients. The average level of predialysis 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 is associated with excess morbidity and mortality in patients with CKD and ESRD. In patients with CKD, the severity of anemia correlates directly with the risk of hospitalization, cardiovascular (CV) disease, and death (Collins et al., 1998). Anemia contributes to eccentric left ventricular hypertrophy and maladaptive remodeling of the left ventricle. 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 Hb and Outcomes in Renal Insufficiency (CHOIR) study in the Food and Drug Administration (FDA) briefing document for the October 2007 Cardiovascular and Renal Advisory Committee (Unger, 2007). Similar observations are found in the United States Renal Data System (USRDS) mortality data stratified by Hb. All-cause mortality stratified by Hb (between the years of 1993 to 1996) indicated significantly higher first-year death rates in patients with Hb levels < 9 g/dL, compared to 11 to 12 g/dL. This trend continued to worsen, as reflected in USRDS data collected between 1998 1999 where the death rate rose by ~75% compared to the 1993 to 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 ratio of CV hospitalization increases 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 suggested that treatment of anemia reduces the need for blood transfusions and improves health-related quality of life (HRQoL) (NKF K/DOQI, 2007).

## 2.2 Current standard of care for CKD or DD-CKD Anemia

Today, therapy with erythropoiesis-stimulating agents (ESAs) is a major alternative to transfusion in managing anemia associated with CKD. For those 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 the treatment of anemia in patients with CKD (Winearls et al., 1986; Eschbach et al., 1987; Eschbach et al., 1989a, Eschbach et al. 1989b), despite the documented safety risks. These safety risks include hypertension, thrombosis, and cerebrovascular events which may be associated with supraphysiologic plasma EPO levels frequently observed with ESA therapy. Anemic patients with CKD or ESRD will require life-long treatment with these agents.

Although the treatment of anemia in CKD and ESRD is thought to contribute positively to a patient's quality of life, several studies in subjects with ESRD and NDD-CKD have shown higher mortality or trends in that direction in the higher-dosed ESA-treated cohorts when the protocol objective was to treat one of the cohorts to high, almost normal 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, particularly in those more anemic (ie, Hb < 11 g/dL). The FDA has recognized these excess morbidity and mortality risks (FDA, 2007). Updated product labeling for the approved ESAs in 2007 include a boxed warning of greater risk of death and CV events when ESAs are administered to target high Hb concentrations ( $\geq 13.5$  g/dL) compared with lower Hb targets. The FDA also acknowledged the potential off-target effect of ESAs contributing to excess mortality due to CV events and thrombosis (Unger, 2010). The currently approved ESA labeling directs prescribers to target Hb levels of 10 to 11 g/dL in the US and 10 to 12 g/dL outside the US. The literature on this topic, including meta-analyses, supports the view that the AEs associated with ESAs are typically observed when high doses are administered (Zhang et al., 2004; Unger, 2007; Szczech, 2008; Fishbane and Besarab, 2007; Besarab et al., 2009). Posthoc analyses of three major RCTs, (Kilpatrick et al., 2008; Szczech, 2008; Solomon et al., 2010) NHCT, CHOIR, and TREAT, indicates that outcomes correlate with "achieved" and not "target" Hb levels.

Additionally, some patients are hyporesponsive to ESA therapy. A significant proportion (~17%) of DD-CKD patients require stable ESA dosing at 2 to 6 times the median seen in the entire CKD population (150 to 450 U/kg of IV epoetin TIW). This "hyporesponder" patient population accounts for approximately 50% of epoetin alfa consumption in the US (Besarab et al., 2009). This is a significant economic burden, and as noted above, higher doses of ESAs have been associated with higher rates of morbidity and mortality (Zhang et al., 2004; Unger, 2007; Szczech, 2008). Thus, this patient population has the greatest need for an effective and safe therapy for anemia. In turn, the increasing perception that high ESA dosing is associated with significant risk, especially in patients not achieving target, is expected to lead to lower ESA dosing and an associated higher prevalence of patients with low Hb levels. In December of 2007, 2.1% of patients had Hb levels < 9 g/dL, 7% had Hb levels < 10 g/dL, and 21.6% did not reach 11 g/dL, while 34.8% were 11 to 12 g/dL (USRDS, 2009). Hb levels < 11 g/dL in this population are associated with increased mortality and hospitalization rates, and failure to achieve a Hb level > 11 g/dL is a prognostic indicator of poor outcomes (Ma, 1999; Regidor, 2006). In patients with persistently low Hb levels, mortality risk is strongly associated with the patient's ability to achieve a hematopoietic response (Bradbury, 2009).

Additionally, ESA therapy for anemia in patients with ESRD on HD usually requires concomitant IV iron supplementation to avoid functional iron deficiency and epoetin dose escalation; however, IV iron use is not without risk. However, as reported by the USRDS ([USRDS, 2013](#)), administration of IV iron is at an all-time high. Among patients on HD, the transfusion rate, at 2.7% to 2.9% at the beginning of 2010, reached 3.3–3.8 percent in the first six months of 2012. Among patients on PD, the rate has increased from 2.3–2.9 to 3.0–3.9.

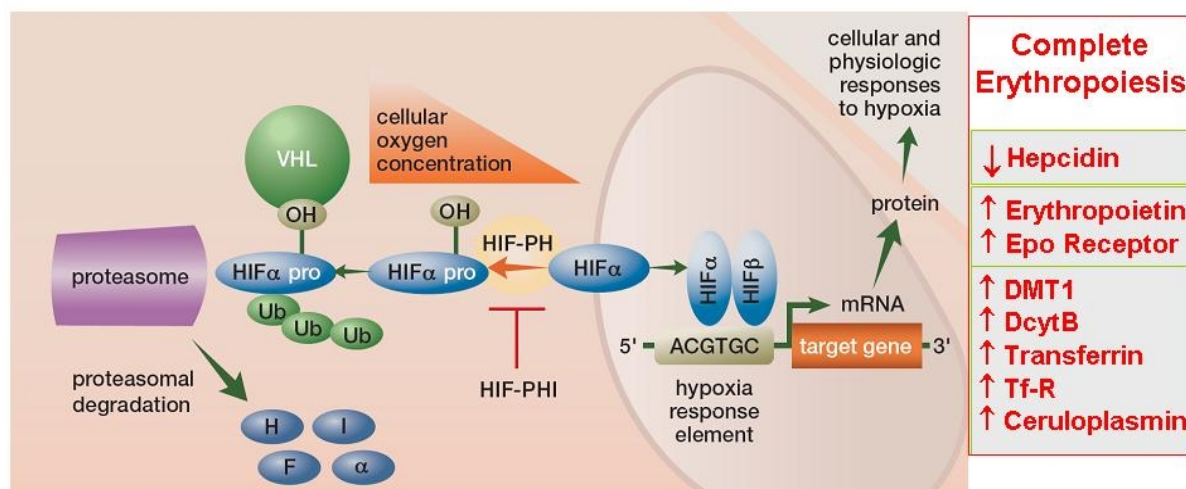
There is currently an unmet medical need for an oral treatment that can correct anemia in patients with NDD-CKD and DD-CKD while avoiding supraphysiologic levels of circulating plasma EPO levels.

Roxadustat is an oral medication that could potentially deliver effective treatment for CKD-related anemia with less need for IV iron supplementation and without producing supraphysiologic levels of circulating EPO, which may translate into an improved safety profile. Roxadustat is being evaluated as a potential alternative treatment for anemia in subjects with NDD-CKD and DD-CKD.

### **2.3 Mechanism of Action of Roxadustat**

Virtually all tissues depend on a sufficient supply of oxygen for survival. Lack of oxygen associated with hypoxic, ischemic, and anemic conditions triggers a series of homeostatic responses (Figure 1). Hypoxia-inducible factor is a transcription factor that is believed to be the key element in the body's oxygen sensing mechanism ([Semenza, 2000](#)). Hypoxia-inducible factor 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](#)). Hypoxia-inducible factor is a heterodimeric transcription factor family comprising three oxygen-sensitive isoforms (HIF-1 $\alpha$ , HIF-2 $\alpha$  and HIF-3 $\alpha$ ), and a constitutively expressed HIF-1 $\beta$  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-1 $\alpha$  has been shown to regulate vascular endothelial growth factor (VEGF) expression ([Gray et al., 2005](#); [Buchler et al., 2003](#)), while HIF-2 $\alpha$  is critical for the induction of the EPO gene and erythropoiesis ([Warnecke et al., 2004](#); [Scortegagna et al., 2005](#)).

**Figure 1. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI) Mechanism of Action**



Abbreviations: DcytB = Duodenal cytochrome B; DMT1 = divalent metal transporter one; EPO = erythropoietin; HIF = hypoxia-inducible factor; HIF-PH = hypoxia-inducible factor prolyl hydroxylase; HIF PHI = hypoxia-inducible factor prolyl hydroxylase inhibitor; mRNA = messenger ribonucleic acid; Tf-R = Transferrin receptor; Ub = ubiquitin; VHL = Von Hippel-Lindau protein.

Source: [Epstein, et al, 2001](#)

Hypoxia-inducible factor target genes are expressed when the active heterodimer binds to a conserved 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- $\alpha$  isoforms are constitutively produced, their accumulation under normoxic conditions is prevented by recruitment and binding by the von Hippel-Lindau (VHL) protein, which targets HIF- $\alpha$  isoforms for degradation through the ubiquitin-proteasome pathway. The molecular mechanism for oxygen-dependent degradation of HIF- $\alpha$  is based on the hydroxylation of specific proline residues, as catalyzed by a family of HIF-PHs that utilize molecular oxygen as the substrate for hydroxylation. Thus, HIF-PH constitutes the body's main oxygen sensor by regulating the prevalence and activity of nuclear HIF protein. Under hypoxic conditions, HIF PHs are inactive and lead to initiation of the HIF-responsive transcriptional cascade ([Wang et al., 1995](#); [Semenza, 1998](#)).

Roxadustat is a potent and reversible hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that transiently induces HIF stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure of humans to intermittent hypoxia. HIF induces expression of not only EPO, but also the EPO receptor and proteins that promote iron absorption and recycling from the macrophage iron storage system ([Peyssonaux 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. In contrast to the classical paradigm, suggesting that anemia in CKD patients is caused by the inability of these patients to produce EPO, results of a study of

roxadustat treatment of CKD subjects not requiring dialysis (Study FGCL-SM4592-017) suggest that the kidneys and other sites of EPO production in this patient population retain the ability to produce sufficient EPO for robust erythropoiesis.

Roxadustat also has the potential to effectively treat anemia caused by inflammation-induced functional iron deficiency, which are typically hyporesponsive to ESAs. In these conditions, iron availability for erythropoiesis is reduced due to a number of inflammatory mediators. Because HIF-PHIs such as roxadustat alter expression not only of the EPO gene but also of genes regulating iron metabolism, it is postulated that roxadustat may be effective in treating these anemias as well (Langsetmo et al., 2005).

Chronic hypoxia and intermittent hypoxia induce different sets of genes associated with HIF transcriptional activity, presumably because intermittent stimulation allows the restoration of HIF degradation, turnover, and inactivation. Transient activation of HIF thereby precludes sustained gene expression and the induction of genes that are expressed late after HIF activation, as well as expression of additional genes that are secondary to activation of HIF-dependent genes. Both nonclinical and clinical studies of roxadustat have successfully used the intermittent dosing paradigm to induce selective erythropoiesis and to optimize the Hb dose response. Furthermore, roxadustat was selected for development over other HIF-PHI 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, transferrin production, and down-regulation of hepcidin production); roxadustat distributes preferentially to these organs.

The physiologic mechanisms underlying the effects of roxadustat on erythropoiesis are distinct from that of ESAs, and these differences result in several potential advantages over ESAs beyond the convenience of oral therapy. These potential advantages include:

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

## 2.4 Clinical Experience with Roxadustat

Roxadustat is currently being studied in DD-CKD and NDD-CKD subjects with anemia. As of 7 September 2013, a total of 1190 subjects with CKD and healthy subjects have been enrolled in 18 completed (12 Phase 1 and 6 Phase 2) and 6 ongoing studies in the United States, Europe, and Asia. Information from these studies is provided below and in the most recent Investigator's Brochure. In these studies, a total of 969 subjects have received roxadustat, comprising 377 healthy subjects, 294 subjects with NDD-CKD, and 298 subjects with DD-CKD.

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 volunteers received single doses of roxadustat up to 4.0 mg/kg and repeat doses up to 3.75 mg/kg three times a week for 4 weeks. In a completed thorough QT study in healthy volunteers, single doses up to 5 mg/kg were administered, without evidence of QT prolongation.

Of the 6 Phase 2 studies completed, 3 were in subjects with ESRD on dialysis treatment. Roxadustat treatment in dialysis patients ranging from 6 weeks to 19 weeks in the Phase 2 studies was well tolerated. Roxadustat has been found to be effective in correcting anemia in incident subjects on HD and PD, as well as in maintaining Hb levels in subjects on HD whose Hb levels were maintained with epoetin alfa, and generally in the absence of IV iron supplementation. Oral iron supplementation was found as effective as IV iron when correcting anemia with roxadustat in incident-dialysis patients.

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

#### **2.4.1 Pharmacokinetics and Pharmacodynamics**

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

A relative bioavailability study was conducted in 24 healthy volunteers comparing capsule formulation, which was used in Phase 1 and Phase 2 studies, with tablet formulation, which was developed for Phase 3. The study demonstrated bioequivalence to bridge the two formulations. With an intermittent dose regimen (once weekly [QW], twice weekly [BIW] or three times a week [TIW]), no or limited accumulation in mean area under the concentration curve (AUC) or maximum concentration ( $C_{max}$ ) was observed. Furthermore, no evidence was found for time-dependent PK (no auto-induction or inhibition). Roxadustat is highly protein bound and the PK of roxadustat is not affected by dialysis. Metabolites found in urine suggested Phase 2 metabolism as the major metabolic pathway. In plasma, parent roxadustat is the main component. The inhibitory potential of roxadustat on cytochrome P450 (CYP) enzymes, based on in-vitro studies is limited, and the lowest inhibition constant ( $K_i$ ) value was observed for CYP 2C8 (16  $\mu$ M). 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.

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

In pharmacodynamic studies conducted with roxadustat in CKD subjects not on dialysis (Study FGCL-4592-017), the mean maximum EPO increase from baseline ranged from 82-443 mIU/mL and 492-554 mIU/mL after a single 1 and 2 mg/kg dose, respectively. Results from PK studies in subjects on HD (Study FGCL-4592-039 in the US and Study CL-1517-203 in Japan) showed similarity in PK and pharmacodynamics of roxadustat in Caucasians and Japanese subjects with ESRD, and the timing of roxadustat dosing relative to dialysis (given before or after dialysis) did not impact the PK profile. Also, comparable dose-dependent increases in EPO levels were observed with both pre and postdialysis dosing. These increases in endogenous EPO (eEPO) were transient, peaked at around 10 hours postdose with eEPO levels returning to BL in 24 to 48 hrs. The magnitude of this transient increase in plasma eEPO levels was modest and the peak plasma eEPO were within physiologic range.

In contrast, EPO levels associated with therapeutic ESA dosing range from 1,500 to over 10,000 mIU/mL (Besarab et al., 2009). In a clinical study with dialysis subjects, the reported mean administered individual ESA dose was 8,000 IU, which would correspond to plasma EPO  $C_{max}$  levels exceeding 3,000 mIU/mL (Fishbane and Besarab, 2007). This is approximately 10-fold higher than the physiologic range.

## 2.4.2 Efficacy

As of 7 September 2013, 700 subjects with NDD-CKD and DD-CKD have participated in the Phase 2 clinical development program. This program includes 6 completed studies. Three of these studies have been in NDD-CKD subjects (2 US, 1 in China), and three have been in subjects with DD-CKD (1 US; 1 US, Asia, Russia; 1 China). For details about dialysis, please see the Investigator's Brochure.

### 2.4.2.1 Studies in NDD-CKD subjects

Data from a 4-week dose ranging study in anemic CKD subjects not on dialysis (Study FGCL-SM4592-017) showed that roxadustat promotes erythropoiesis at lower doses in CKD subjects than in healthy volunteers. With roxadustat 0.7 mg/kg TIW dosing, mean Hb increased by 1.0 g/dL over a 6-week period in anemic CKD subjects who completed 4 weeks of dosing; more robust mean Hb increases of 2.0 to 2.3 g/dL occurred at roxadustat doses of 1.5 and 2.0 mg/kg TIW, respectively. Hemoglobin responder (Hb increase of  $\geq 1.0$  g/dL) rates were 62%, 60%, 91%, and 100% in the roxadustat 0.7, 1.0, 1.5, and 2.0 mg/kg TIW cohorts, respectively. The Hb responses were also robust at 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  $\geq 11$  g/dL as well as increasing by  $\geq 1.0$  g/dL, the Hb responder rate with roxadustat 2.0 mg/kg was 89% and 91% in with 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 16- to 24-week treatment Phase 2b study in CKD subjects not on dialysis (Study FGCL-4592-041) showed that absolute and weight-based doses of roxadustat, administered TIW and BIW, effectively corrected Hb levels to a Hb target of 11 g/dL (range of 11-13 g/dL in 96 subjects and 10.5-12.0 g/dL in 48 subjects). Dose-response trends suggested that starting doses of 1.0 to 1.6 mg/kg roxadustat administered TIW are appropriate to correct Hb levels during 4 weeks of treatment in nondialysis CKD subjects. Roxadustat was also effective in maintaining Hb level following anemia correction.

#### 2.4.2.2 Studies in DD-CKD subjects:

Data from a 12-week study in incident-dialysis (48 HD and 12 PD) subjects (Study FGCL-4592-053), using similarly tiered, weight-based doses as Study FGCL-4592-041 demonstrated increases in mean Hb of approximately 2 g/dL after 6 weeks of treatment. Subjects were randomized to receive either no iron, oral iron or IV iron. The Hb responses were indistinguishable between the oral and IV iron arms; subjects in the no iron arm had a similar Hb response during the first 8 weeks of treatment, with plateauing during the last 4 weeks of treatment, suggesting that with long-term roxadustat treatment, iron supplementation may be necessary, however, oral iron appears to be as effective as IV iron, and is recommended as the first-line treatment in Phase 3. Starting roxadustat doses between 1.0 and 1.6 mg/kg appeared adequate to correct Hb in these subjects. In addition to Hb response, in this study, statistically significant ( $p < 0.001$ ) improvements of 5% to 10% overall average in the SF-36 Physical Functioning, Role physical, and Vitality scores, as well as in the FACT-An anemia and total scores were noted in the roxadustat-treated subjects. Significantly, these improvements were more pronounced (33% on average and up to 100%) in subjects with low BL scores ( $< 35$ ), and improvement was time-dependent. Also, in this study, roxadustat transiently lowered total cholesterol by about 20 mg/dL on average. Importantly, highly significant LDL cholesterol reduction was also observed.

Data from a 6- and 19-week treatment study in US ESRD subjects on dialysis (Study FGCL-4592-040) showed the feasibility of converting subjects from a stable ESA dose to roxadustat. In the 6-week dose range portion of this conversion study in subjects on HD, a dose relationship was observed for Hb response. In subjects dosed with roxadustat at 1 mg/kg, the Hb response was comparable to that in the epoetin alfa control group, which had a small decline from baseline in Hb levels and a lower percentage of Hb responders than did subjects receiving the higher doses of roxadustat. In the 1.5 mg/kg and 2.0 mg/kg dose arms, roxadustat produced an average increase in Hb of 0.9 and 0.7 g/dL from baseline Hb, respectively, and was associated with a 78% to 80% response rate (ie, more than twice that in the epoetin alfa arm [33%]). In the 19-week portion of the study, Hb maintenance was durable and noninferior to epoetin alfa in the roxadustat treatment arms (combined) over a 19-week period. The roxadustat dose requirement for Hb maintenance was mostly between 0.7 mg/kg to 2.0 mg/kg in normoresponder subjects, with occasional subjects requiring doses up to 3.0 mg/kg TIW. Roxadustat treatment also resulted in increased levels of serum iron at the End of Treatment (EOT) compared with baseline in the 6-week treatment arms, whereas serum iron levels decreased from baseline in subjects treated with epoetin alfa. Reticulocyte Hb content (CHr) was better maintained in the pooled roxadustat treatment arm than in the pooled epoetin alfa arm, suggesting that functional iron deficiency does not occur when treating with roxadustat unaccompanied by IV iron. Serum hepcidin was reversibly suppressed during roxadustat treatment. In addition, total cholesterol levels decreased during the course of treatment in subjects treated with roxadustat, but were unchanged in epoetin alfa-treated subjects. Following discontinuation of roxadustat dosing, total cholesterol levels returned to BL at post-treatment follow-up.

Data from a Phase 2 clinical trial in China (FGCL-4592-048), in DD-CKD subjects, roxadustat was found effective for maintaining Hb for 6 weeks. Hemoglobin correction and maintenance was dose-dependent. Roxadustat also transiently lowered total and LDL-cholesterol by about 20 mg/dL on average. Serum iron levels were maintained and total iron binding capacity (TIBC)



increased in roxadustat-treated subjects compared to subjects randomized to continue epoetin alfa. Other serum iron parameters were not significantly different between the treatment arms.

### 2.4.2.3 Ongoing Studies

Data from an ongoing open-label extension study (Study FGCL-4592-059, to which some subjects from Studies FGCL-4592-041 and FGCL-4592-040 rolled over) further shows durability of roxadustat effect in maintaining Hb levels in CKD patients over 52 to 76 week treatment as of 07 September 2013.

### 2.4.3 Safety (for detailed current safety information please refer to the Investigator's Brochure)

The overall frequency and type of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) observed in these clinical studies reflect events that would be expected to occur in CKD subjects with multiple co-morbidities and on a number of concomitant medications. Safety analyses did not reveal any association between the rates of occurrence of CV events with roxadustat, or any effect on adverse event (AE) rates related to either increasing Hb levels or on the rate of change of Hb levels.

As of 7 September 2013, a total of 969 subjects have been exposed to roxadustat in the clinical development program, comprising 377 healthy subjects, 294 NDD-CKD subjects, and 298 DD-CKD subjects. In the healthy subject trials, most subjects were male as enrollment in these trials was generally restricted to men. In the NDD-CKD and DD-CKD studies roughly half of the subjects were male. Most of the healthy subjects were Asian or Caucasian, reflecting the countries where these studies were conducted (Europe, United Kingdom, US, China, and Japan). Most NDD-CKD and DD-CKD subjects were either Caucasian or African-American, as most trials for which demographic data are pooled were conducted in the U.S. or Eastern Europe. In general, the most commonly reported AEs ( $\geq 4\%$  and  $\geq 1\%$  above placebo rate) in healthy volunteers were headache and dizziness. The most commonly reported AEs ( $\geq 5\%$ ) in CKD patients not on dialysis were diarrhea, nausea, urinary tract infection, nasopharyngitis, peripheral edema, hyperkalemia, headache, and hypertension (none were  $\geq 8\%$ ). The most commonly reported AEs ( $\geq 3\%$ ) in CKD patients on dialysis were diarrhea, nausea, hypertension, and upper respiratory tract infection (none were  $\geq 5\%$ ). Adverse event rates of hypertension (1% in Study FGCL-SM4592-017 and 7.6% in Study FGCL-4592-041) and thrombosis (overall incidence  $< 1\%$ ), compare favorably with the rates reported in published ESA studies in similar patient populations (Krapf and Hulter, 2009; Fishbane and Besarab, 2007). No safety risks were associated with rate of rise of Hb levels or with achieving a Hb level above 11 g/dL using roxadustat. Study FGCL-4592-041 subjects achieved Hb  $> 11$  g/dL in  $> 50\%$  of exposure time during study, and there were no CV safety events (death, myocardial infarction [MI], stroke, unstable angina, hospitalization for congestive heart failure, or hospitalization for arrhythmias) reported while Hb  $> 11$  g/dL during treatment of roxadustat.

Supratherapeutic doses of roxadustat in healthy volunteers were associated with an increased frequency of mild to moderate musculoskeletal pain and headaches, tachycardia, and less commonly, low BP. These findings have not been observed at the usual therapeutic dose range in Phase 2 studies in the target populations. In CKD subjects, the observed changes in heart rate (HR) and BP were in general within the normal variations of daily living.

Cumulatively, five TESAEs of pancreatitis have been reported during roxadustat clinical studies. The pancreatitis for three subjects was associated with cholelithiasis or biliary sludge, confirmed by radiological imaging; all three subjects underwent cholecystectomy with complete resolution postoperatively. One subject was found to have a pancreatic duct stricture. One of the five TESAEs of acute pancreatitis was considered by the investigator to be possibly related to roxadustat. However, the causality was assessed as unrelated to study drug by the sponsor after investigations revealed the presence of multiple risk factors for pancreatitis, including a long history of cigarette smoking, diabetes, hyperparathyroidism, and use of vicodin and lisinopril. Of note, approximately 28 months after the last dose of roxadustat, the subject was hospitalized with another episode of acute pancreatitis. Additional information regarding this subject is available in the Investigator's Brochure.

Of note, cholelithiasis is reported to be more common in CKD patients compared to the general population, with a prevalence as high as 20% (Li Vecchi, 2003; Gladziwa, 1993). Furthermore, a higher incidence of pancreatitis in patients with type 2 diabetes mellitus, and hence CKD, has been well described in the literature. No increased cancer risk has been noted with roxadustat treatment; however, the study program was not powered to detect absence of cancer risk.

Liver parameters were monitored closely throughout the roxadustat clinical development program. Increases in liver parameters were infrequently seen, and were generally mild and transient in nature. No cases of Hy's Law were observed throughout the program. An independent data and safety monitoring committee concluded that there was no concern for hepatotoxicity with roxadustat. Based on the safety data collected to date, roxadustat is generally well tolerated and has an acceptable safety profile that supports its further development.

In summary, the cumulative safety data have not identified major risks related to roxadustat. At therapeutic doses, roxadustat is well tolerated by healthy subjects and subjects with CKD. Potential additional benefits of roxadustat compared to ESAs for the treatment of NDD-CKD and DD-CKD anemia include efficacy without the need for IV iron supplementation, and a favorable change in lipid profile.

Taking into account the general measures taken to minimize risk to subjects participating in the Phase 3 clinical trials, the anticipated benefits of treating the anemia associated with CKD in subjects on dialysis and not on dialysis, the data support conduct of Phase 3 trials.

## 2.5 Summary

In summary, roxadustat is an orally active HIF-PHI with potent erythropoietic effects. Intermittent dosing of roxadustat results in transient activation of HIF, intermittent induction of endogenous, physiologic-range EPO, and dose-dependent erythropoiesis, suggests a coordinated mechanism of erythropoiesis that is different from ESA therapy, including beneficial effects on iron handling. The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in healthy adult subjects, and in dialysis and nondialysis CKD subjects who have been enrolled and treated in completed and ongoing clinical studies.

## 2.6 Roxadustat Dose Rationale

Starting doses of roxadustat were studied in three ways in the Phase 2 program: using a strict weight-based dosing approach 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 heavy (> 90 to 140 kg); and using an absolute starting dose regardless of body weight.

In a Phase 2 conversion-maintenance study in dialysis subjects (Study FGCL-4592-040), dose evaluation was performed to determine a suitable conversion method from epoetin to roxadustat. In this study, the dose response to maintain Hb levels was observed to be related to the ratio of the patient's baseline epoetin alfa dose requirement to the roxadustat dose administered, and not related to the roxadustat dose administered per body weight. Two methods of modeling of dose relationship between roxadustat and baseline stable epoetin dose yielded dose ratios for epoetin (U): roxadustat (mg) dose conversion between 17 (for the lowest epoetin dose quartile) and 50 (for the highest quartile).

For this conversion-maintenance study of stable dialysis subjects converting from stable doses of epoetin at baseline to roxadustat, the starting roxadustat dose will be determined using this dose conversion algorithm (Table 1).

**Table 1. Baseline Epoetin to Starting Roxadustat Dose Conversion**

Epoetin alfa <sup>a</sup> (IU/week)	Roxadustat Dose <sup>b</sup> (mg/dose) TIW	Equivalent Range of Epoetin: Roxadustat Ratio <sup>c</sup>
< 5,000	70	< 23
5,000 to 8,000	100	17 to 27
> 8,000 to 16,000	150	18 to 36
> 16,000	200	≥ 27

Abbreviations: ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; IU = international units; TIW = three times a week.

- a Average weekly prescribed dose in last 4 weeks prior to randomization
- b Starting dose will be one step higher if the mean Hb at randomization is < 10 g/dL
- c Ratio of epoetin weekly dose in IU/week to roxadustat dose in mg/week.

Notes: The roxadustat dose steps are 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg

Using these dose tiers, most patients are expected to be in the medium dose tier, requiring an epoetin: roxadustat ratio between 18 and 36, compatible with the dose relationship data derived from the Phase 2 study in a similar patient population (Study FGCL-4592-040).

In this study, the initial dose of roxadustat will be determined by the subject's average prescribed ESA dose in the last 4 weeks prior to randomization if on epoetin or darbepoetin (8 weeks if on Mircera<sup>®</sup>).

Using the conversion table (Table 1), in this study, subjects will receive starting roxadustat doses of 70 mg, 100 mg, 150 mg, or 200 mg. If the mean screening Hb value at randomization is < 10 g/dL, the starting roxadustat dose will be increased by one dose step. If the converted initial dose exceeds the maximum dose of 3.0 mg/kg/dose then the lower dose step should be chosen as the initial dose. Roxadustat doses will be administered at a frequency of TIW.

The completed Phase 2 studies evaluated the need for dose adjustments for both Hb correction and Hb maintenance. Dose adjustments were allowed at regular 4-week intervals to maintain, increase, or decrease the dose according to prespecified rules. Prespecified dosing steps were used to correct and maintain Hb levels within treatment thresholds based on absolute Hb levels

and change of Hb in the previous 4 weeks. Additional rules for dose adjustment were provided to minimize excessive hematopoiesis. These dose adjustment rules were successful in Hb correction and Hb maintenance and will be adopted in this study with minor modifications. Roxadustat subjects will follow the dose adjustments guidelines as outlined in Appendix 2.

Subjects randomized to roxadustat will take doses TIW for the entire duration of the Treatment Period. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain a Hb level of approximately 11 g/dL, the dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc.

### **Maximum Dose for Roxadustat**

The maximum allowed roxadustat dose in this study is set at 400 mg or 3.0 mg/kg/dose (based on dry weight in subjects on HD and normal weight subjects on PD), whichever is lower. The highest dose tested in healthy subjects is 5 mg/kg single dose and 3.75 mg/kg TIW. The doses were safe and well tolerated with transient dose-dependent HR increases observed. No maximum tolerated dose (MTD) was reached in the clinical development of roxadustat based on the observed pharmacodynamic response (plasma EPO levels) and the predicted relation between EPO levels and Hb response; therefore exploration of higher doses was not deemed necessary. Plasma EPO levels increased in a supralinear manner with increasing roxadustat doses. It is expected that the majority of the subjects will show adequate Hb response at substantially lower doses than the maximum allowed dose. This study will provide sufficient data on the efficacy and safety of long term treatment of anemia with roxadustat in ESRD subjects on stable dialysis.

Prescribed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower. For dose adjustment purposes, post-dialysis weight (dry-weight) should be used. If the post-dialysis weight of the current visit is not available at the time of dose adjustment, post-dialysis weight of the prior dialysis session or last recorded post-dialysis weight may be used.

## **2.7 Risks/Benefits of Roxadustat Treatment**

The primary benefit of roxadustat is the correction of anemia, including the relief of associated signs and symptoms and an increased quality of life. Roxadustat is expected to be at least as safe as ESAs, and the current data suggest that CV risk may be lower than with ESAs.

A prespecified dose adjustment algorithm will be used during the Treatment Period to maintain a Hb level of approximately 11 g/dL, while closely monitoring the rate of rise of Hb and Hb levels (Appendix 2). In the event of excessive rate of rise or excessive Hb levels, the dose may be adjusted or held at any time according to the guidelines described in Appendix 2.

If there are clinical concerns for a subject's high Hb levels, the investigator may decide to perform a therapeutic phlebotomy in addition to dose hold. Adverse and serious adverse events, and laboratory parameters including electrolytes, liver enzymes, and iron indices, will be closely monitored to ensure the safety of treatment with roxadustat and epoetin alfa. An independent expert panel will assess and adjudicate prespecified CV, cerebrovascular, and thromboembolic events. In addition, an independent Data and Safety Monitoring Board (DSMB) will perform regular, periodic assessments of safety data (at least every 6 months or twice per calendar year while the trial is ongoing) to detect any potential safety signals that may arise during the study and advise the Sponsor accordingly.

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

### 3 OBJECTIVES AND ENDPOINTS

#### 3.1 Objectives

##### 3.1.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy and safety of roxadustat compared with active control (epoetin alfa) for the maintenance treatment of anemia in subjects with ESRD on stable dialysis.

##### 3.1.2 Secondary Objectives

The secondary objectives in this study are to:

- Evaluate the utilization of intravenous (IV) iron with roxadustat compared with active control (epoetin alfa)
- Evaluate the effect of roxadustat on serum lipid parameters compared with active control (epoetin alfa)

#### 3.2 Efficacy Endpoints

##### 3.2.1 Primary Efficacy Endpoint:

For US (FDA) submission: Hemoglobin (Hb) change from baseline to the average level during the evaluation period defined as Week 28 until Week 52

For EU regulatory submission: Hemoglobin (Hb) change from baseline (BL) to the average Hb of Weeks 28 to 36, without having received rescue therapy (ie, RBC transfusion or rescue ESA therapy) within 6 weeks prior to and during this 8-week evaluation period.

##### 3.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- US (FDA) submission: Proportion of subjects with mean Hb level during the evaluation period defined as Week 28 until Week 52  $\geq 10.0$  g/dL.
- EU regulatory submission: Hemoglobin (Hb) response, defined as mean Hb during Weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
- Average monthly IV iron use per subject during Weeks 1 to 36 (monthly defined as a period of 4 weeks).
- Change from BL in low-density lipoprotein (LDL) cholesterol to the average LDL cholesterol of Weeks 12 to 28
- Change from BL in SF-36 Physical Functioning (PF) subscore to the average PF subscore of Weeks 12 to 28
- Change from BL in SF-36 Vitality (VT) subscore to the average VT subscore of Weeks 12 to 28
- Effect on predialysis BP:
  - Time to an exacerbation of hypertension from BL during Weeks 1 to 36

- An increase from BL of  $\geq 20$  mm Hg systolic blood pressure (sBP) and sBP  $> 170$  mmHg

OR

- An increase from BL of  $\geq 15$  mm Hg diastolic blood pressure (dBP) and dBP  $> 100$  mmHg
- Change from BL in mean arterial pressure (MAP) to the MAP value averaged over Weeks 20 to 28

### 3.2.3 Additional Evaluation of Efficacy

The additional efficacy evaluations in this study are:

- Hb Maintenance:
  - Hemoglobin Long-Term Maintenance: Mean change from BL in Hb averaged over 8 weeks of treatment at Weeks 44 to 52 without rescue therapy within 6 weeks prior to and during this 8-week evaluation period
  - Mean change from BL in Hb averaged over the final 8 weeks of treatment, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period
  - Change from BL in Hb at each of the selected postdosing time points
  - Proportion of subjects with 10-12 g/dL averaged over Weeks 28 to 36, 44 to 52, and the final 8-weeks of treatment without rescue therapy within 6 weeks prior to and during this 8-week evaluation period
  - Hb response during Weeks 28 and 36 regardless of use of rescue therapy
  - Hb change from BL to the average Hb value of Weeks 28 to 36, 44 to 52, and the final 8 weeks of treatment regardless of the use of rescue therapy
- Iron Supplement:
  - Requirement for IV iron supplementation
  - Mean monthly IV iron (mg) per subject during Weeks 37 to 52 and Week 53 to EOS
  - Mean monthly oral iron (mg) use per subject during Weeks 1 to 36, Weeks 37 to 52, and Weeks 53 to EOS
  - Requirement for only oral iron supplementation
- Hospitalizations:
  - Occurrence (number) of hospitalizations
  - Proportion of subjects hospitalized
  - Number of days of hospitalizations per patient-exposure year (PEY)

- Missed Dialysis:
  - Occurrence (number) of missed dialysis sessions
  - Proportion of subjects with missed dialysis sessions
  - Number of days of missed dialysis sessions per patient-exposure year (PEY)
- Rescue Therapy Use:
  - Proportion of subjects who receive RBC transfusions
  - Number of RBC packs per patient-month exposure to study medication
  - Having received rescue therapy [composite of RBC transfusions and rescue ESA]
- Changes in Cholesterol Levels:
  - Change from BL at each of the selected treatment time points in:
    - Total cholesterol
    - Low-density lipoprotein/high-density lipoprotein ratio
    - Non-HDL cholesterol
  - Proportion of subjects achieving LDL target of < 100 mg/dL averaged over Weeks 12 to 28 of treatment
- Blood Pressure Effect:
  - Proportion of subjects achieving BP treatment goal in ESRD subjects (predialysis systolic BP < 140 mmHg and diastolic BP < 90 mmHg) averaged over Weeks 12 to 28
  - Time to a treatment-emergent AE of hypertension
  - Time to intensification from BL of antihypertensive therapy
  - Proportion of subjects with increase in BP, defined as an increase from BL of  $\geq 20$  mm Hg sBP and sBP > 170 mmHg or an increase from BL of  $\geq 15$  mm Hg dBP and dBP > 100 mmHg
  - Proportion of subjects with a treatment-emergent AE of hypertension
  - Proportion of subjects with intensification from BL of antihypertensive therapy
- Vascular Access Thrombosis (HD subjects):
  - Time to a treatment-emergent AE of vascular access thrombosis
  - Proportion of subjects with a treatment-emergent AE of vascular access thrombosis
- HRQoL and EQ-5D-5L Benefits of Anemia Therapy:

Change from BL to the average of Weeks 12 to 28 and 28 to 52 of treatment for those listed below.



- VT Subscale of SF-36: In subjects with BL VT Subscore below 50
- Physical Component Scores of SF-36:
  - In subjects with BL *physical component scores* below 40
  - In all subjects
- Anemia Subscale (“Additional Concerns”) of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scores:
  - In subjects with BL subscale scores below 55 (generally associated with fatigue).
  - In all subjects
- Total FACT-An Scores:
  - In subjects with BL FACT-An scores below 135
  - In all subjects
- *EQ-5D-5L Scores*: In all subjects
- Hepcidin, Iron Indices, and HbA1c:
  - Change from BL in serum hepcidin at each of the selected time points
  - Change from BL in serum ferritin at each of the selected time points, total and subgrouped by BL values of  $\leq 400$  ng/mL, and  $> 400$  ng/mL.
  - Change from BL in TSAT at each of the selected time points, total and subgrouped by BL values of  $\leq 40\%$ , and  $> 40\%$ .
  - Change in HbA1c level at each of the selected time points in all subjects, in subjects with history of diabetes

### 3.3 Safety Endpoints

Study-specific safety will be assessed by evaluating the following:

- Occurrence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs)
- Adverse events (AEs), serious adverse events (SAEs), and clinically significant changes in laboratory values from baseline
- Vital signs, electrocardiogram (ECG) parameters, and clinical laboratory values.

Safety interpretation will also be made based on analyses of composite endpoints derived from adjudicated events pooled across multiple studies in the roxadustat Phase 3 program. The members of an independent adjudication committee blinded to treatment assignment will adjudicate the following events in multiple Phase 3 studies:

All cause death, MI, stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, hypertensive emergency, DVT, pulmonary embolism, and vascular access thrombosis.

Various region-specific pooled analyses of composites of these adjudicated events, pooled across multiple studies will be conducted. The analyses of the adjudicated events will be detailed in the region-specific PSAPs.

For US (FDA) Only: The primary safety endpoint in this study is the MACE (Major Adverse Cardiac Event) composite endpoint, defined as time to first occurrence of death from all causes, MI, or stroke, only for the purpose of being pooled across multiple similar studies in the Phase 3 program. None of the individual studies are powered to meet the MACE primary safety endpoint individually. The pooled MACE analysis is only for purposes of supporting a US FDA regulatory filing of roxadustat

The above adjudicated safety events may also be used to support the pooled analyses of additional composite safety endpoints across multiple studies in the Phase 3 program, such as MACE+ (death, MI, stroke, congestive heart failure requiring hospitalization, and unstable angina requiring hospitalization), or a composite which consists of all of the adjudicated events.

## 4 STUDY DESIGN

### 4.1 Description of the Study

This open-label, randomized, active controlled study is designed to evaluate the efficacy and safety of roxadustat compared to epoetin alfa for the maintenance of hemoglobin (Hb) levels in subjects on HD or PD or HHD originally on ESA for treatment of anemia.

- **Screening Period:** Up to 6 weeks. For subjects currently taking Mircer<sup>®</sup>, the Screening Period can be extended up to 8 weeks
- **Treatment Period:** Treatment duration is variable for individual subjects, with a minimum treatment duration of 52 weeks and a maximum duration of up to approximately 3 years after the last subject is randomized

**Amendment 1& 2:** In order to complete the Phase 3 program in a timely manner, minimum treatment duration of subjects enrolled under Amendment 1 & 2 may be shortened. Subjects will be informed at least 4 weeks in advance if such decision is made. All active subjects will end the study at the same time

- **Post-Treatment Follow-Up Period:** 4 weeks

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

#### 4.1.1 Screening Period

After signing the informed consent, subjects enter the Screening Period. During the Screening Period eligibility assessments will be performed. Subjects in screening will continue their existing ESA therapy (eg, epoetin alfa, beta, theta, or zeta, darbepoetin alfa, Mircer<sup>®</sup>) for the treatment of anemia associated with ESRD.

Subjects on dose-hold due to high haemoglobin may qualify for screening however, they cannot be randomized if in investigator's opinion not ready to resume epoetin-alfa or roxadustat upon randomization.

Upon successful completion of screening, a total of up to 1200 eligible subjects will be randomized to receive either roxadustat or epoetin alfa (active control) in a 1:1 ratio. Both roxadustat and epoetin alfa will be administered in an open label manner. Randomization must be completed prior to administration of study medication. Randomization to treatment arms will be provided by an interactive web and voice response system (IWRS) based on stratification factors.

Subjects on long-acting ESAs (Aranesp or Mircer) may not receive the 1<sup>st</sup> dose of study medication on the day of randomization due to ESA dosing schedule (e.g. once weekly or once bi-weekly); in these subjects, the 1<sup>st</sup> dose of study medication (roxadustat or epoetin-alfa) should be administered on the day when the next dose of current ESA would have been due. For all practical purposes, the date of 1<sup>st</sup> dose of study drug administration should be considered as Day 1.

If Day 1 lab values (collected prior to administration of study medication) suggests the potential of a pretreatment condition confounding safety assessment or poses safety risks to study subject, in the opinion of the Investigator or Medical Monitor, the subject may be discontinued from the

study (example: At Screening 1 visit, LFT values were within the protocol range but at Day1, AST or ALT > 3x ULN and Total bilirubin > 2x ULN, or AST or ALT > 5x ULN).

#### 4.1.2 Treatment Period

Administration of the first dose of study treatment (roxadustat or epoetin alfa) will occur on Day 1 (Week 0) which should correspond to the administration of the subject's next dose of their current ESA treatment.

At the Day 1, subjects randomized to Roxadustat Arm will discontinue prior ESA therapy and initiate roxadustat therapy; subjects randomized to Epoetin-Alfa Arm will receive epoetin-alfa irrespective of their prior ESA use.

The initial dose of study medication will be determined based on the average prescribed ESA dose in the last 4 weeks prior to randomization if on epoetin or darbepoetin (8 weeks if on Mircera<sup>®</sup>) as outlined in Table 1 or Table 2 for subjects randomized to receive roxadustat or epoetin alfa, respectively. The initial dose of roxadustat will remain constant during the first 4 weeks of the Treatment Period, except if a dose reduction is required for excessive hematopoiesis.

Subsequent dose adjustments for roxadustat subjects will follow the dose adjustments guidelines as outlined in Appendix 2 in order to maintain a Hb level of approximately 11 g/dL during the Treatment Period. Dose adjustments for epoetin alfa subjects should follow the dosing recommendations as per the approved country-specific epoetin alfa Package Insert or Summary of Product Characteristics (SmPC). In PD and HHD subjects, if receiving epoetin alfa subcutaneously, the dose and frequency may be determined by the Investigator per local standard of care.

Day 1 study procedures including laboratory blood draws are to be completed prior to administration of the first dose of study treatment. In HD subjects, Day 1 procedures with the exception of health-related quality of life (HRQoL) assessments should be completed prior to the subject receiving dialysis that day. Weight measurement will be taken after completion of dialysis (ie, dry weight).

Total treatment duration is variable for individual subjects. Subjects will receive study treatment (roxadustat or epoetin alfa) for a minimum of 52 weeks. The maximum treatment duration may be up to approximately 3 years from the date the last subject is randomized.

In order to complete the Phase 3 program in a timely manner, minimum treatment duration of subjects enrolled under Amendment 1 & 2 may be shortened. Subjects will be informed at least 4 weeks in advance if such decision is made. All active subjects will end the study at the same time.

During the Treatment Period, subjects will attend weekly study visits from Day 1 to Week 2, followed by every 2 weeks study visits from Weeks 4 to 24 (eg, Weeks 4, 6). Following Week 24, study visits will occur every 4 weeks (eg, Weeks 28, 32) until EOT. A common closeout will occur when a predetermined number of cardiovascular (CV) events have been accrued across multiple studies in the overall Phase 3 dialysis program.

At each study visit during the Treatment Period, Hb will be measured (prior to dialysis in HD subjects) locally to determine the need for a dose adjustment or to assess for excessive hematopoiesis. In the event that the Hb value from the central laboratory is significantly different

from that measured locally, and per Investigator that warrants a reversal of the dose adjustment decision made earlier based on locally measured Hb value, the Medical Monitor should be informed, if possible.

#### **4.1.3 Post-Treatment Follow-Up Period**

After completing the Treatment Period, subjects proceed to the post-treatment Follow-up Period and will return for the End of Study (EOS) visit. The choice of anemia treatment during the Follow-up Period is up to the discretion of the Investigator. If the Investigator decides to resume ESA treatment in roxadustat treated subjects, the first dose of ESA should be administered at least three days after the last dose of roxadustat.

#### **4.1.4 Long-term Follow-Up for Premature Treatment Discontinued Subjects**

Subjects who discontinue study medication prematurely will be followed up for vital status, CV events, and hospitalization until study closure, unless consent to participate is withdrawn. Upon completion of EOT and EOS visits, these subjects will be followed up every 3 to 6 month interval (depending on the availability of subjects) until study closure. These visits may occur either in-person or via telephone.

### **4.2 Randomization, Treatment Assignment, and Rationale for Open-label Design**

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

An open-label design was chosen since double-blinding would require a double-blind, double-dummy design to match the different ESAs made by different manufacturers having different dosing specifications which is considered too challenging without much added benefits to the study. It would expose subjects to multiple additional injections or infusions without additional benefit. Furthermore, the difference in iron supplementation requirements between roxadustat and the ESA will further complicate any efforts to blind, or alternatively end up in inadvertent unblinding. The high probability of these confounding factors rendering the conduct of a double-blind double-dummy study and data becoming invalid is outweighing the advantage of a lower risk for bias. Therefore, in light of the objectivity of primary endpoint measures not influenced by blinding and the lack of operational feasibility without addition of values to subjects, the open label study design is to be considered the most reasonable option.

A total of up to approximately 1200 subjects are planned to be randomized in an open-label, 1:1 ratio to receive either of the following two treatments:

- Roxadustat (up to approximately 600 subjects)
- Active Control: epoetin alfa (up to approximately 600 subjects)

Randomization is stratified by the following four factors:

- Mean qualifying screening Hb ( $\leq 10.5$  vs.  $> 10.5$  g/dL)
- History of CV, cerebrovascular, or thromboembolic diseases (Yes vs. No)
- Mean prescribed weekly baseline epoetin alfa dose (or, equivalent epoetin dose for non-epoetin subjects) in the 4 weeks prior to randomization ( $\leq 150$  vs.  $> 150$  IU/kg/week)

- Geographical region (US vs. Ex-US region)

Randomization of qualified subjects will take place prior to administration of study drug.

### **4.3 Procedures for Handling Incorrectly Enrolled or Randomized subjects**

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Where a subject does not meet all the eligibility criteria but is randomized in error or incorrectly received study medication, the Investigator should inform the Medical Monitor immediately, and a discussion should occur regarding whether to continue or discontinue the patient from treatment. All decisions from such meeting should be appropriately documented.

### **4.4 Replacement of Subjects**

Subjects who drop out prematurely will not be replaced in the study.

### **4.5 Study Treatment**

#### **4.5.1 Dose and Schedule**

Eligible subjects will be randomized via IWRS to receive either roxadustat or epoetin alfa. The first dose of study drug should be administered on Day 1 (Week 0), which should correspond to a day when their next dose of ESA would have been administered. All subjects will attend weekly study visits from Day 1 to Week 2, followed by every two weeks study visits from Weeks 4 to 24. Following Week 24, study visits will occur every four weeks until the EOT. Subjects will receive study medication in an open label manner.

#### **4.5.2 Starting Dose of Study Drug**

##### **4.5.2.1 Roxadustat Arm**

In subjects on HD or PD or HHD randomized to roxadustat, the initial roxadustat dose will be determined using a conversion table based on the subject's previous average weekly prescribed ESA dose in the last 4 weeks prior to randomization if the subject is on epoetin or darbepoetin, and average monthly (4 weeks) prescribed ESA dose in 8 weeks prior to randomization if the subject is on Mircera<sup>®</sup> (Table 2). If the mean qualifying screening Hb value at randomization is < 10 g/dL, the starting roxadustat dose will be increased by one dose step. For example, a subject on epoetin (ie, epoetin alfa, beta, theta, zeta, delta, or omega) 6,000 IU/week with mean screening Hb of 9.4 g/dL at randomization will start roxadustat at a dose of 150 mg three times weekly (TIW).

If the converted initial dose exceeds the maximum dose of 3.0 mg/kg/dose then the lower dose step should be chosen as the initial dose.

The dose of roxadustat will remain constant during the first 4 weeks of the Treatment Period unless a dose reduction is required for excessive hematopoiesis.

**Table 2. Initial Dosing of Roxadustat: Conversion Table from ESAs to Roxadustat**

Epoetin (ie, alfa, beta, theta, zeta, delta, or omega) <sup>a</sup> (IU/wk)	Darbepoetin alfa <sup>a, b</sup> (µg/wk)	Mircera <sup>® c</sup> (µg/monthly)	Roxadustat Dose <sup>d</sup> (mg/dose) TIW
< 5,000	< 25	< 80	70
5,000 to 8,000	25-40	80-120	100
> 8,000 to 16,000	> 40-80	> 120-200	150
> 16,000	> 80	> 200	200

Abbreviations: ESA = erythropoiesis-stimulating agent; Hb = hemoglobin; IU = international units; TIW = three times a week; wk(s) = week(s).

- a Average weekly prescribed dose in last 4 weeks prior to randomization
- b If darbepoetin is used biweekly, use half the dose to get per week dose
- c Average prescribed monthly (4 wks) dose in last 8 weeks prior to randomization
- d Starting dose will be one step higher if the mean Hb at randomization is < 10.0 g/dL, however, not to exceed 3.0 mg/kg/dose.

Notes: The roxadustat dose steps are 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.

#### 4.5.2.2 Epoetin Alfa Arm (Active Control)

Subjects randomized to the epoetin alfa arm who are currently taking non-epoetin alfa treatment will be switched to epoetin alfa treatment on Day 1. All subjects on HD will receive IV epoetin alfa TIW starting from Day 1, irrespective of their baseline route of administration or frequency of ESA use. Subjects requiring ultra-low dose of EPO (eg, ≤1000 IU/per week), frequency of administration may be adjusted per local standard of care.

Subjects on PD or HHD may continue using the same route of administration as baseline; however, if the Investigator decides to change the route of administration in a PD or HHD subject from subcutaneous to IV after randomization it should be done during the early part of the treatment phase (preferably prior to Week 16).

All epoetin alfa administrations should be performed by the Investigator or an authorized member of the site staff or other trained personnel. In subjects on PD or HHD, epoetin alfa may be self-administered subcutaneously by the subject or a caregiver after adequate training or, if in the opinion of the Investigator, the subject or a caregiver is already adequately trained in self-administering ESA prior to the study.

#### Doses:

In subjects who have been randomized to the epoetin alfa treatment arm, the initial epoetin alfa dose that the subject will receive on Day 1 will be determined using a conversion table based on the subject's average weekly prescribed ESA dose in 4 weeks prior to randomization if on epoetin or darbepoetin, and average monthly (4-week) prescribed ESA dose in 8 weeks prior to randomization if on Mircera<sup>®</sup> (Table 3).

In case of a change in route of administration from subcutaneous to IV (TIW), the initial dose of IV epoetin alfa will be determined by the Investigator per local standard of care.

In subjects on PD or HHD, if receiving epoetin alfa subcutaneously, the dose and frequency may be determined by the Investigator per local standard of care.

Subsequent epoetin alfa dosing and dose adjustment during the study, if indicated, should be based on the country specific package insert or SmPC.

For countries using prefilled epoetin alfa syringes, the initial dose and subsequent dosages following dose adjustments during the Treatment Period should be approximated to the closest total weekly dose.

**Table 3. Initial Dosing of Epoetin Alfa: Conversion table from Non-Epoetin ESAs to Epoetin Alfa**

Baseline ESA	Conversion Ratio	Examples of Converted Initial Epoetin Alfa dose (approximate) IU/week <sup>c</sup>
Epoetin (ie, alfa, beta, theta, zeta, delta, or omega) (IU/week) <sup>a</sup>	x 1	6,000 IU/week x 1 = 6,000 IU/week
Darbepoetin alfa (µg/week) <sup>a</sup>	x 200	40 µg/week x 200 = 8,000 IU/week
Mircera <sup>®</sup> (µg/once monthly (ie, 4-wks) <sup>b</sup>	x 70 – 80 (for lower Mircera <sup>®</sup> dose lower conversion ratio may be used) <sup>d</sup>	100 µg/month x 70 = 7,000 IU/week  200 µg/month x 80 = 16,000 IU/week

Abbreviations: ESA = erythropoiesis-stimulating agent; IU = international units.

- a Mean weekly ESA in 4 weeks prior to randomization
- b Mean monthly (4-week) ESA in 8 weeks prior to randomization
- c May be rounded as deemed necessary by the investigator
- d Per discretion of the investigator

### 4.5.3 Dose Adjustment

#### 4.5.3.1 Roxadustat Arm

During the Treatment Period, roxadustat dose adjustment will be made according to the dose adjustment algorithm in Appendix 2, in order to maintain a Hb level of approximately 11 g/dL. Roxadustat dose adjustments are permitted from Week 4 onwards, and every 4 weeks thereafter (eg, Week 4, Week 8, Week 12); however, dose may be adjusted between two prespecified windows (eg, anytime between Week 4 and Week 8 visits, Week 8 and Week 12 visits) if the following two criteria are met:

- No dose adjustment has been made in last 4 weeks,
- Hemoglobin (Hb) < 9.0 g/dL.



Subjects on HD or PD or HHD randomized to roxadustat will take doses TIW for the entire duration of the Treatment Period. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain a Hb level of approximately 11 g/dL, the dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc.

In this study, a rate of rise of Hb > 2 g/dL within 4 weeks or a Hb level of  $\geq$  13 g/dl at any time would be considered as excessive haematopoiesis. For a rate of rise of Hb > 2 g/dL within 4 weeks, dose should be reduced by one dose step and for a Hb value  $\geq$  13.0 g/dL, the dose should be on hold until Hb drops < 12.0 g/dL per guidelines provided in the protocol (Appendix 2). When roxadustat will be resumed, the dose will be reduced by one dose step.

Dose adjustments or temporary dose holds for excessive hematopoiesis can occur at any time during the Treatment Period. Any dose adjustment will reset the dose-adjustment window to every 4 weeks thereafter (eg, dose adjustment for a qualified reason at Week 6 leads to next dose adjustment at Week 10). If a dose adjustment review is scheduled on Week 22, then the next dose adjustment review will be scheduled on Week 28, since there is no scheduled visit on Week 26.

Prescribed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower. For dose adjustment purposes, post-dialysis weight (dry-weight) should be used. If the post-dialysis weight of the current visit is not available at the time of dose adjustment, post-dialysis weight of the prior dialysis session or last recorded post-dialysis weight may be used.

#### **4.5.3.2 Active Control (Epoetin alfa) Arm**

Epoetin dose adjustments during the Treatment Period should be based on country-specific epoetin alfa Package Insert or SmPC.

In subjects on PD or HHD, if receiving epoetin alfa subcutaneously, the dose and frequency may be determined by the Investigator per local standard of care.

## **4.6 Concomitant Medications, Procedures and Nondrug Therapies**

### **4.6.1 Concomitant Medications**

Concomitant medications are any prescription or over-the-counter preparations, including herbal products and “natural remedies”, used by a subject while participating in this clinical study.

For all concomitant medication use, an indication for its use should be provided. If the stated indication is a nonspecific condition (eg, “rash”), documentation of the condition, as specific as possible, should be maintained in the subject’s clinical study records as source documentation.

Use of herbal medicine during the study is not prohibited but strongly discouraged. All herbal and natural remedies should be reviewed by the investigator and if considered safe, may be allowed to continue at the same dose.

To avoid confounding effects on study endpoints, changes to anti-hypertensive medications should be minimized, and made only if deemed medically necessary by the Investigator.

#### **4.6.1.1 Phosphate Binders**

When coadministered with roxadustat, in a clinical pharmacology study, the bioavailability of roxadustat was reduced. Subjects should be advised to discuss with the Investigator when

changing the dose or dosing time of their phosphate binder while taking roxadustat. To optimize the absorption of roxadustat, subjects should be advised that roxadustat be taken at least one hour before or three hours after their phosphate binder if possible.

#### 4.6.1.2 Statins

When coadministered with roxadustat, in clinical pharmacological studies, hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) exposure was increased 2- to 3-fold. For patients randomized to roxadustat, investigators should consider this interaction and local prescribing information when deciding on the appropriate statin dose for individual patients, bearing in mind the impact of ethnicity, other concomitant medications, renal and hepatic function. Goals of lipid lowering treatment should be maintained as clinically indicated. The dose of statins should not exceed the recommended daily dose in the table below for subjects randomized to roxadustat.

#### Recommended Maximum Daily Dose of Statins for Subjects Randomized to Roxadustat

Statins	Recommended maximum dose (mg/day)
Atorvastatin	40
Simvastatin	5
Rosuvastatin	5
Pravastatin	40
Fluvastatin	20
Pitavastatin	1
Lovastatin	20

#### 4.6.2 Supplemental Iron Use

In a Phase 2 study, there was no significant difference in Hb levels in roxadustat-treated subjects on dialysis receiving oral iron supplementation compared to subjects receiving IV iron supplementation, in subjects with ferritin < 100 ng/mL and in those with TSAT < 20%. Based on the mechanism of action of roxadustat and the Phase 2 study results, in subjects randomized to roxadustat, oral iron supplementation is considered to be sufficient.

In this study, oral iron should be allowed as the preferred first-line of iron supplementation for both treatment arms without restriction.

In addition to scheduled assessments (Appendix 3), iron indices may be assessed anytime (via central lab) to evaluate iron storage status of the subjects, if considered necessary by the Investigator.

##### 4.6.2.1 Oral Iron Supplementation

All subjects should be encouraged to take oral iron if they can tolerate as the preferred first-line iron supplementation during the Treatment Period. Provision of an oral iron supplement is encouraged; the dose and frequency are at the discretion of the principal Investigator. Oral Iron therapy should be started before the subject becomes iron depleted.

#### 4.6.2.2 Intravenous (IV) Iron Supplementation

Intravenous iron supplementation is permitted if in the opinion of the Investigator the subject has not responded adequately and is considered iron deficient. IV iron may be administered per local standard of care as deemed necessary by the investigator.

Treatment with study medication (roxadustat or epoetin) will continue during IV iron administration. Discontinuation of IV iron supplementation is recommended once the subject is no longer considered iron deficient (eg, ferritin  $\geq$  100 ng/mL and TSAT  $\geq$  20%)

Subjects may receive IV iron during the post-treatment Follow-up Period per discretion of the Investigator. If IV iron is to be administered at the EOT visit, all visit procedures including lab draws should be completed prior to administering IV iron.

#### 4.6.3 Rescue Therapy Guidelines

Rescue therapy guidelines are provided to optimize the standardization of rescue therapy by Investigators and to ensure the safety of individual study subjects. Use of rescue therapy and reason for rescue therapy should be recorded in the electronic case report form (eCRF).

##### 4.6.3.1 Red Blood Cell Transfusion (all subjects)

For subjects in both treatment arms, RBC transfusion is allowed if rapid correction of anemia is required to stabilize the subject's condition (eg, acute hemorrhage) or the Investigator is of the opinion that the blood transfusion is a medical necessity. If the situation permits, the Medical Monitor should be informed prior to any scheduled RBC transfusion. Study treatment may continue during or after the RBC transfusion.

##### 4.6.3.2 Erythropoiesis Stimulating Agents

For subjects randomized to roxadustat the use of ESAs is generally prohibited. Erythropoiesis stimulating agent rescue is restricted to no more than one cycle of use during the Treatment Period; the Investigator may initiate use of an approved EPO analogue if all of the following criteria are met:

- A subject's Hb level has not sufficiently responded to two or more dose increases or the maximum dose limit of the study drug has been reached; and
- The subject's Hb is  $<$  8.5 g/dL on two consecutive measurements (central lab) drawn at least five days apart; and
- Clinical judgment does not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in Hb; and
- Reducing the risk of alloimmunization in transplant eligible patients and/or reduction of other RBC transfusion-related risks is a goal

The subject is not allowed to be administered both the EPO analogue and roxadustat at the same time. Treatment with an EPO analogue should be started  $\geq$  3 days after the last dose of roxadustat, and should be stopped when Hb  $>$  9 g/dL or after 4-weeks, whichever comes first. If a subject requires longer than 4-weeks therapy due to inadequate response the Medical Monitor should be contacted. Study treatment should be resumed after the following intervals:

- Two days after stopping epoetin
- One week after stopping darbepoetin alfa
- Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera<sup>®</sup>)

If more than one cycle of EPO analogue rescue is required, the Investigator should permanently discontinue roxadustat. Use of EPO analogues will be recorded in the eCRF.

Inadvertent ESA administration or ESA administration by the hospital staff in Roxadustat subjects should not be counted as rescue unless above criteria are met; these subjects may be allowed to continue taking study medication, if considered safe by the Investigator or Medical Monitor.

For subjects randomized to epoetin alfa, the Investigator may initiate use of a different EPO analogue if clinically indicated. Use of the different EPO analogue will be recorded in the eCRF and will be considered rescue therapy.

#### **4.6.4 Emergency Procedure (Therapeutic Phlebotomy)**

If there are clinical concerns for a subject's high Hb levels, the Investigator may decide to perform a therapeutic phlebotomy in addition to temporarily withholding the study drug. This should be documented and discussed with the Medical Monitor.

#### **4.6.5 Prohibited Medications/Therapies/Substances**

The following medications/therapies are prohibited during the period identified:

- Any investigational drug from 4 weeks prior to screening until EOS
- Androgens from screening until EOS
- Iron-chelating agents (eg, deferoxamine/desferrioxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to randomization until EOS
- Dapsone (at any dose) from screening until EOS
- Chronic doses acetaminophen/paracetamol > 2.0 g/day from randomization until 1 week after EOT

#### **4.6.6 Contraception**

Female subjects of childbearing potential, if not practicing complete sexual abstinence, must agree to practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depo progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects (nonsurgically sterile; ie, no vasectomy) with female partners of childbearing potential who are not on birth control must agree to use a barrier method of contraception (eg, condom) or the female partner must agree to use contraception as described above unless practicing complete sexual abstinence.

Subjects must agree to practice above contraceptive methods, as applicable, for the entire duration of the study, from randomization through the EOS visit. It is highly recommended that they continue to practice the contraceptive methods for 12 weeks following the last dose of study treatment. For subjects discontinuing study medication prematurely, it is recommended that they continue to practice contraceptive methods for 12 weeks following the last dose of study treatment.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported (Section 8.3.6)

#### **4.7 Safety Monitoring Plan**

Safety will be assessed throughout the study. A complete baseline profile of each subject will be established through demographics, medical history, clinical laboratory values, vital signs, physical examination (PE), and electrocardiogram (ECG). During the course of the study, vital signs, PE, and laboratory tests will be performed at regular intervals as described in schedule of assessments (Appendix 3).

Blood pressure and HR should be assessed according to the guidelines described in Appendix 5.

A comprehensive PE will be conducted during the Screening visit, Day 1 and at the EOT/ET visit. Targeted PEs (eg, general appearance, CV, respiratory and abdomen,) will be conducted throughout the study as described in the Schedule of Assessments.

Any significant findings prior to administration of study drug will be considered as baseline conditions and if appropriate, will be captured as baseline medical history. Any clinically significant (CS) changes from baseline 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. Liver function abnormalities will be monitored according to drug-induced liver injury (DILI) guidance (Appendix 4).

All adverse events, SAEs, and ongoing concomitant medication usage will be monitored and recorded throughout the study. Serious adverse event reports will be evaluated individually to assess for the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. Serious adverse events and AEs will be followed until resolved, deemed stable, or until the subject's EOS visit. See Section 8 for details on AE and SAE reporting.

An Independent Event Review Committee (IERC), blinded to treatment group, will adjudicate prespecified CV, cerebrovascular, and thromboembolic safety events of interest. These events include all-cause death, MI, stroke, hospitalization for congestive heart failure, hospitalization for unstable angina, deep venous thrombosis, pulmonary embolism, and hypertensive emergency. A separate adjudication charter will describe the process in detail, and training and training materials will be provided to study sites.

#### **4.8 Data Safety and Monitoring Board**

A Data Safety Monitoring Board (DSMB) will review safety data at least every six months or twice per calendar year while the trial is ongoing to ensure subject safety. A separate DSMB charter will establish the rules, meeting frequency, and scope of responsibilities of the DSMB.

## 5 STUDY ENROLLMENT AND WITHDRAWAL

### 5.1 Inclusion Criteria

A subject is eligible for the study if all of the following criteria are met:

1. Subject has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines
2. Subject age is  $\geq 18$  years
3. Subject receiving adequate dialysis using the same modality of dialysis for native kidney ESRD for  $\geq 3$  months prior to screening and during screening
  - 3.1 **Amendment 2: Incident dialysis subjects receiving dialysis for ESRD for  $\geq 2$  weeks but  $\leq 4$  months at the time of randomization**
4. For subjects receiving HD, the vascular access must be via native arteriovenous fistula or graft, or permanent, tunneled catheter. For subjects receiving PD, a PD catheter must be in use
5. Subject is on IV or subcutaneous ESA for  $\geq 8$  weeks prior to screening. The prescribed ESA dose must remain stable ( $\leq 30\%$  change) during the 4 weeks prior to randomization if on epoetin or darbepoetin and 8 weeks if on Mircera<sup>®</sup>
  - 5.1 **Amendment 2: Incident dialysis subjects (as defined in 3.1) must be on ESA for  $\geq 4$  weeks prior to screening**
6. Mean of the subject's three most recent central lab Hb values during the Screening Period must be  $\geq 9.0$  g/dL and  $\leq 12.0$  g/dL; with an absolute difference of  $\leq 1.3$  g/dL between the highest and the lowest value. Samples are obtained at least 4 days apart and the last Hb value must be within 10 days prior to the randomization visit
  - 6.1 **Amendment 2: For Incident dialysis subjects (as defined in 3.1), mean of the subject's two most recent central lab Hb values during the Screening Period must be  $\geq 8.5$  g/dL and  $\leq 12.0$  g/dL; with an absolute difference of  $\leq 1.3$  g/dL between the highest and the lowest value. Samples are obtained at least 2 days apart and the last Hb value must be within 10 days prior to the randomization visit**
7. Subject has a ferritin level  $\geq 100$  ng/mL at screening

**Amendment 2:** Subjects with a ferritin level  $< 100$  ng/mL at screening may qualify upon receiving iron supplement (per local standard of care)
8. Subject has a transferrin saturation (TSAT) level  $\geq 20\%$  at screening

**Amendment 2:** Subjects with a TSAT level  $< 20\%$  at screening may qualify upon receiving iron supplement (per local standard of care)
9. Subject has a serum folate level  $\geq$  lower limit of normal (LLN) at screening

**Amendment 2:** Subjects with a serum folate level  $< LLN$  at screening may qualify upon receiving folate supplement (per local standard of care)

10. Subject has a serum vitamin B<sub>12</sub> level  $\geq$  LLN at screening  
**Amendment 2:** Subjects with a Vitamin B<sub>12</sub> level  $<$  LLN at screening may qualify upon receiving B<sub>12</sub> supplement (per local standard of care)
11. Subject's alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are  $\leq 3$  x upper limit of normal (ULN), and total bilirubin (TBL) is  $\leq 1.5$  x ULN at screening
12. Subject's body weight (dry weight in HD subjects) is 45.0 to 160.0 kg

**Only incident dialysis subjects who meet criteria 3.1, 5.1, and 6.1 (instead of criteria 3, 5, and 6) are allowed to participate under Protocol Amendment 2**

## 5.2 Exclusion Criteria

Subjects will be excluded if any of the following criteria are met:

1. Subject has received a red blood cell (RBC) transfusion within 8 weeks prior to randomization  
Amendment 2: Subject has received a red blood cell (RBC) transfusion within 4 weeks prior to randomization
2. Subject has a known history of myelodysplastic syndrome or multiple myeloma
3. Subject has a known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia or other known causes for anemia other than chronic kidney disease (CKD)
4. Subject has known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition
5. Subject has a known chronic inflammatory disease that could in the opinion of the Investigator impact erythropoiesis (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission
6. Subject is anticipated to undergo elective surgery that is expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization.
7. Subject has active or chronic gastrointestinal bleeding
8. Subject has received any prior treatment with roxadustat or another HIF-PHI
9. Subject has been treated with iron-chelating agents within 4 weeks prior to randomization
10. Subject has a history of chronic liver disease (eg, chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver)
11. Subject with New York Heart Association (NYHA) Class III or IV congestive heart failure
12. Subject has had a MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within a major vessel (excluding vascular dialysis access) (eg, DVT or pulmonary embolism) within 12 weeks prior to randomization

13. Subject has uncontrolled hypertension, in the opinion of the Investigator, (eg, that requires change in anti-hypertensive medication) within 2 weeks prior to randomization
14. Subject has one or more contraindications for treatment with epoetin alfa or other ESA including known hypersensitivity
15. Subject has a diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category II or higher) of renal cell carcinoma as shown on renal imaging performed within 12 weeks prior to randomization
16. Subject has a history of malignancy, except for the following: cancers determined to be cured or in remission for  $\geq 5$  years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps

Amendment 2: Subject has a history of malignancy, except for the following: cancers determined to be cured or in remission for  $\geq 2$  years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps

17. Subject is positive for any of the following:
  - Human immunodeficiency virus (HIV)
  - Hepatitis B surface antigen (HBsAg)
  - Anti-hepatitis C virus antibody (anti-HCV Ab)
18. Subject has an active, clinically significant (CS) infection or evidence of an underlying infection, as manifested by white blood cell count (WBC)  $>$  ULN, and/or fever, in conjunction with clinical signs or symptoms of infection at the time of randomization
19. Subject has any of the following known untreated conditions: proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion (subjects who are already blind may qualify to participate)
20. Subject has had any prior organ transplant (that has not been explanted), or subject is scheduled for organ transplantation (on the waiting list for kidney transplant is not exclusionary)

Amendment 2: Prior organ transplant: subjects who have one of the following conditions or states

  - a) Experienced rejection of transplanted organ within 6 months of transplantation
  - b) Currently on high doses of immunosuppressive therapy (per discretion of the PI)
  - c) Are scheduled for organ transplantation (on the waiting list for kidney transplant is not exclusionary)
21. Subject has participated in an interventional clinical study or has been treated with an investigational drug within 4 weeks prior to screening
22. Subject has drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that may lead to reduced absorption of study drug
23. Subject has an anticipated use of dapsone or androgen in any dose amount or anticipated chronic use of acetaminophen or paracetamol  $>$  2.0 g/day during the study



24. Subject has a history of alcohol or drug abuse within 2 years prior to screening  
Amendment 2: Subject has a history of alcohol or drug abuse within 6 months prior to screening
25. Females of childbearing potential, if not practicing complete sexual abstinence or using contraception as detailed in the protocol; male subjects (if not surgically sterile; ie, no vasectomy) with sexual partners of childbearing potential, if not practicing complete sexual abstinence or using contraception
26. Pregnant or breastfeeding females
27. Subject has any medical condition that in the opinion of the Investigator may pose a safety risk to the subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation

Subjects who fail to meet the above eligibility criteria should not, under any circumstances, be randomized or receive study medication. No exceptions to this rule will be allowed. No prospective waiver with regards to eligibility criteria (inclusion/exclusion) will be issued.

### **5.3 Subject Discontinuation and Withdrawal**

The subject is free to permanently discontinue study medication at any time, without prejudice to further treatment. Discontinuation from study medication is not the same as complete withdrawal from the study (ie, withdrawal of consent).

Subjects may withdraw consent and discontinue from the study at any time by discontinuing study medication and refusing to return for any form of follow-up without any prejudice.

A subject who decides to discontinue study medication will always be asked about the reason(s) to discontinue study medication and the presence of AEs (if any). These data will be ascertained and documented by the investigator and recorded in the eCRF as appropriate. The subject should return all study medications.

Reasons for permanent discontinuation of study medication:

- Subject's decision (subject no longer wants to continue study medication (ie, withdrawal of consent))
- Investigator's decision that it is in the best interest of the subject to be withdrawn from the study
- Adverse events
- Significant noncompliance with study procedures, as determined by Investigator or Sponsor
- Lack of efficacy / Meets ESA withdrawal criteria
- Subject is lost to follow-up
- Subject is no longer requiring dialysis due to kidney transplant
- Site terminated by the sponsor

- Pregnancy
- Death

Upon discontinuation from the study, both female subjects of childbearing potential and male subjects with partners of childbearing potential must continue to use a medically acceptable method of contraception for 12 weeks following the last study drug administration.

#### **5.4 Replacement of Subjects**

Subjects may not be replaced from this study.

#### **5.5 Study Termination**

This trial can be terminated by the sponsor at any time for any reason.

## 6 INVESTIGATIONAL PRODUCT

### 6.1 Formulation

Roxadustat is supplied by FibroGen, Inc. as red coated, oval tablets for oral administration, in strengths of 20 mg, 50 mg, and 100 mg. The excipients include lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, and colorant Red Opadry II. All ingredients used for manufacture of roxadustat comply with US and European Union compendia or regulatory standards. Strengths are different in size and debossing reflects the strength (ie, 20, 50, or 100 mg). Due to the light-sensitive nature of roxadustat and to minimize exposure of the active pharmaceutical ingredient to light, tablets should remain in the original packaging for as long as possible and be administered as intact tablets only.

### 6.2 Storage

Roxadustat tablets should be protected from light, and stored at room temperature between 15°C and 30°C (59°F to 86°F).

Epoetin alfa should be stored according to the package insert.

All study drugs (roxadustat and epoetin alfa) should be stored in a securely locked area to which access is limited to appropriately authorized study personnel.

### 6.3 Study Drug Handling and Disposal

All study drugs provided by the Sponsor or provided at the study site should be retained at the site until otherwise instructed in writing by the Sponsor. Upon completion of the study or termination of the investigational site, all used (vials/syringes or bottles), unused, and partially used study drugs; and all study drugs that were not dispensed will be shipped to a site designated by the Sponsor or may be destroyed according to local/institutional policies by the Pharmacy/authorized staff after drug accountability and reconciliation has been completed by Sponsor. Please refer to the Study Reference Manual or Pharmacy Manual for additional information.

### 6.4 Route of Administration and Dose

#### 6.4.1 Roxadustat

Subjects on HD or PD or HHD randomized to roxadustat will take doses TIW for the entire duration of the Treatment Period. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain a Hb level of approximately 11 g/dL, the dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc.

Roxadustat will be dispensed to subjects with instructions for self-administration of the tablets orally on each dosing day, according to the dosing schedule. The tablets are to be swallowed whole.

First dose of roxadustat should be administered on Day 1 after completion of all procedures including laboratory draws. Roxadustat doses should be administered at least 2 days apart, and no more than 4 days apart. Dosing should occur at approximately at the same time of day. Roxadustat can be taken with or without food.

## 6.4.2 Epoetin Alfa

During the Treatment Period, starting from Day 1, all subjects on HD randomized to epoetin alfa arm will receive epoetin alfa intravenously TIW irrespective of their baseline route of administration or frequency of ESA use. Epoetin alfa dose adjustments should be based on the country specific package insert or SmPC.

Subjects requiring ultra-low dose of EPO (eg,  $\leq 1000$  IU/per week), frequency of administration may be adjusted per local standard of care. For peritoneal dialysis subjects and home hemodialysis subjects, the route of administration (IV or SC) may remain the same as baseline. However, if the investigator decides to change the route of administration in PD subjects from SC to IV after randomization it should be done during the early part of the treatment phase (preferably prior to Week 16).

In case of a change in route of administration from subcutaneous to intravenous (TIW), the initial dose of IV epoetin alfa will be determined by the investigator per local standard of care.

All epoetin alfa administrations should be performed by the investigator or an authorized member of the site staff or other trained personnel. In PD and HHD subjects, epoetin alfa may also be self-administered subcutaneously by the subject or a caregiver after adequate training or, if in the opinion of the investigator, the subject or a caregiver is already adequately self-administering ESA prior to the study.

## 6.5 Overdose, Emergency Procedures and Management of Overdose

The maximum tolerated dose of roxadustat has not been established in humans. For the purpose of this study, the maximum allowed roxadustat dose is set at 400 mg or 3.0 mg/kg/dose, whichever is lower. Any dosing exceeding the maximum allowed roxadustat dose should be reported within 24 hours. The Medical Monitor should be contacted as soon as possible. Symptoms associated with overdosing, if any, will be reported as adverse events. An overdose without associated symptoms is not an AE and will be recorded on the overdose eCRF only.

In the event of suspected roxadustat overdose, the subject should receive supportive care and monitoring. The Sponsor's Medical Monitor should be contacted as applicable.

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

## 7 ASSESSMENT OF EFFICACY

### 7.1 Study Procedures by Visit

During study visits, unless otherwise indicated, it is preferred that all assessments including labs and physical examinations should be completed predialysis for subjects on HD. For subjects on PD or HHD, assessments may be completed at any time during the visit, but preferably approximately at the same time of the day at each study visit. Quality of life assessments should be administered approximately at the same time of the day. For example, in subjects on HD, these assessments should be completed approximately at the same time during dialysis and in subjects on PD or HHD approximately at the same time of the day. Weight measurement in HD subjects should be done after dialysis (dry weight). For dose adjustment if the post-dialysis weight of the current visit is not available, post-dialysis weight of the prior dialysis session or last recorded post-dialysis weight may be used. Blood pressure and HR should be assessed according to the guidelines described in Appendix 5.

#### 7.1.1 Screening Period

Subjects must be consented before any screening tests or assessments are performed. All screening procedures should be completed within 6 weeks. For subjects currently taking Mircer<sup>®</sup>, the screening period can be extended up to 8 weeks. During the screening period eligibility assessments will be performed.

Subjects in screening will continue their existing ESA therapy for the treatment of anemia associated with ESRD.

##### 7.1.1.1 Screening 1

- Signed written informed consent
- Inclusion/Exclusion criteria verification
- Demographics and medical history
- Height and weight (use dry weight in HD subjects)
- Vital signs (BP, HR, respiratory rate [RR], and temperature [Temp])
- Laboratory tests:
  - Complete blood count (CBC) with WBC differential
  - Serum chemistry
  - Serum lipid panel
  - Serum iron, ferritin, total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), transferrin saturation (TSAT)
  - Reticulocyte count and hemoglobin in reticulocytes (CHr)
  - Hemoglobin A1c (HbA1c)
  - Vitamin B<sub>12</sub> and folate
  - Enzyme-linked immunosorbent assay (ELISA) for HIV
  - Hepatitis B surface antigen (HBsAg)

- Anti-HCV Ab
- Review and record concomitant medications
- Review and record procedures and nondrug therapies
- Review and record AEs, if any (capture the event under medical history, if applicable)

#### **7.1.1.2 Screening 2 (≥ 2 days apart from Screening 1)**

Hemoglobin values must be obtained at least 2 days apart.

- Vital signs (BP, HR, RR, and Temp)
- Laboratory test:
  - Hemoglobin (Hb) only
  - Serum human chorionic gonadotropin (hCG) pregnancy test for female subjects of childbearing potential only [not required for females of no childbearing potential e.g. postmenopausal (per discretion of the PI), surgically sterile etc.]
- Complete physical examination
- Renal ultrasound - not required if results of a previous renal ultrasound or other imaging within 12 weeks prior to randomization to rule out renal cell carcinoma are available. If no results are available, a renal ultrasound must be performed during the screening period prior to randomization. Renal ultrasound can be done at any time between Screening 2 and randomization, as convenient. The report must be reviewed prior to randomization.
- Review and record concomitant medications
- Review and record procedures and nondrug therapies
- Review and record AEs, if any (capture the event under medical history, if applicable)

#### **7.1.1.3 Additional Screening Assessments**

If a subject's laboratory results do not meet the eligibility criteria, the laboratory assessment may be repeated within the Screening Period. The visits must be at least 2 days apart.

For example, an additional Hb value may be collected if necessary. The mean of the 2 most recent Hb values during the screening period, obtained at least 2 days apart, will be used to calculate the subject's eligibility. Liver function test (LFT) parameters may not be repeated if found exclusionary at Screening without a prior approval from the Medical Monitor unless the investigator has a valid reason to believe that the original lab result is due to an error (eg, possible sample mix-up). Such repeat should be communicated to the Medical Monitor as soon as possible.

A subject who fails screening may be rescreened if deemed appropriate by the investigator. Where possible, an approval should be obtained from the Medical Monitor prior to rescreening.

For all screen failures, the reason(s) will be documented.

#### **7.1.1.4 Randomization**

Eligible subjects will be randomized via IWRS based on stratification factors to receive roxadustat or epoetin alfa. Randomization must take place prior to administration of study drug.

### 7.1.2 Treatment Period

The Treatment Period begins on the first day of dosing with study treatment (Day 1/Week 0) which should correspond to the administration of the subject's next dose of their current ESA treatment. At the Day 1, subjects randomized to Roxadustat Arm will discontinue prior ESA therapy and initiate roxadustat therapy; subjects randomized to Epoetin-Alfa Arm will receive epoetin-alfa irrespective of their prior ESA use. All study procedures must be completed prior to administration of the 1<sup>st</sup> dose of study treatment.

Subjects on long-acting ESAs (Aranesp or Mircera) may not receive the 1<sup>st</sup> dose of study medication on the day of randomization due to ESA dosing schedule (e.g. once weekly or once bi-weekly); in these subjects, the 1<sup>st</sup> dose of study medication (roxadustat or epoetin-alfa) should be administered on the day when the next dose of current ESA would have been due. For all practical purposes, the date of 1<sup>st</sup> dose of study drug administration should be considered as Day 1.

During the Treatment Period, subjects will attend weekly study visits from Day 1 to Week 2, followed by every two weeks study visits from Weeks 4 to 24. Following Week 24, study visits will occur every four weeks until the EOT. A common closeout will occur when a predetermined number of CV events have been accrued.

#### 7.1.2.1 Day 1 (Week 0)

The following assessments must be completed prior to study drug administration.

- Inclusion/Exclusion criteria verification
- Complete physical examination
- Weight (dry weight in HD subjects)
- Vital signs (BP, HR, RR, and Temp)
- 12 Lead ECG
- Laboratory tests:
  - CBC with WBC differential
  - Serum chemistry
  - Serum lipid panel
  - Serum iron, ferritin, TIBC, UIBC, TSAT
  - Reticulocyte count, CHr
  - HbA1c
  - Special laboratory analytes: High-sensitivity C-reactive protein (hs-CRP) and hepcidin and
  - Archival serum and plasma samples
- Local Hb
- Health Related Quality of Life (HRQoL) Assessments (SF-36, Functional Assessment of Cancer Therapy-Anemia [FACT-An], and EQ-5D-5L).

- Review and record concomitant medications
- Review and record procedures and nondrug therapies

Review and record baseline conditions, AEs, if any (capture the event under medical history, if applicable).

Dispense study drug.

#### **7.1.2.2 Weeks 1 to 2 (Weekly, $\pm 2$ days)**

- Laboratory tests (must be performed prior to dosing):
  - Week 1, 2, : CBC with WBC differential
  - Week 2: Liver function test (LFTs) only
  - Weeks 1, 2: Reticulocyte count and CHr
  - Week 2: Dispense study drug

#### **All visit weeks:**

- Local Hb
- Vital Signs (BP, HR, RR, Temp)
- Review dose adjustment for excessive hematopoiesis.
- Review and record concomitant medications
- Review and record procedures and nondrug therapies
- Review and record AEs, if any
- Drug accountability

#### **7.1.2.3 Weeks 4 to 24 (Every 2 weeks, $\pm 4$ days)**

- Laboratory tests (must be performed prior to dosing):
  - Week 4, 8, 12, 20: CBC with WBC differential
  - Week 6 followed by every visit where no CBC is collected: Hb only
  - Week 4, 8, 12, 20: Serum chemistry
  - Weeks 6, 16, 24: LFTs only
  - Weeks 4, 8, 12, and 20: Lipid panel
  - Weeks 4, 8, 12, 20: Serum iron, ferritin, TIBC, UIBC, TSAT
  - Weeks 4, 6, 8, 12, 16, 20: Reticulocyte count and CHr
  - Weeks 12, 24: HbA1c
  - Weeks 4, 12, 20: Special laboratory analytes (hs-CRP, hepcidin)
  - Weeks 4, 12, 20: Archival serum and plasma samples
  - Weeks 12, 24: Serum hCG pregnancy test for women of childbearing potential only



- Weeks 12, 24: Targeted physical examination
- Dose adjustment review: At Week 4, followed by every 4 weeks.
- Weeks 24: 12-lead ECG
- Week 12: HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)\*

**All visit weeks:**

- Local Hb
- Vital signs (BP, HR, RR, and Temp)
- Review dose adjustment for excessive hematopoiesis.
- Review and record concomitant medications
- Review and record procedures and nondrug therapies
- Review and record AEs, if any
- Drug accountability and dispense study drug

**7.1.2.4 Weeks 28 to End of Treatment (EOT; Every 4 weeks,  $\pm 4$  days)**

- Laboratory tests (must be performed prior to dosing):
  - Weeks 28, 36, 44, followed by every 8 weeks: CBC with WBC differential
  - Week 32 followed by every visit where no CBC is collected: Hb only
  - Weeks 28, 36, 44, followed by every 8 weeks: Serum chemistry
  - Week 32: LFTs only
  - Weeks 28, 36, 48, followed by every 12 weeks: Lipid panel
  - Weeks 28, 36, 44, followed by every 8 weeks: Serum iron, ferritin, TIBC, UIBC, TSAT
  - Weeks, 28, 36, 52, followed by every 16 weeks: Reticulocyte count, CHr
  - Weeks 36, 52, followed by every 52 weeks: HbA1c\*
  - Weeks 36, 52: Special laboratory analytes (hs-CRP, hepcidin)
  - Weeks 36, 48, followed by every 12 weeks: Serum hCG pregnancy test for women of childbearing potential only
  - Weeks 36, 52, followed by every 24 weeks: Archival serum and plasma samples\*
- Weeks 36, 52, followed by every 24 weeks: Targeted physical examination\*
- Weeks 36, 52, followed by every 24 weeks: Weight (dry weight in HD subjects)
- Weeks 36, 52, followed by every 24 weeks 12-lead ECG
- Weeks 28, 52 HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)\*
- Dose adjustment review: At Week 28, followed by every 4 weeks

**All visit weeks:**

- Local Hb
  - Vital signs (BP, HR, RR, and Temp)
  - Review dose adjustment for excessive hematopoiesis
  - Review and record concomitant medications
  - Review and record procedures and nondrug therapies
  - Review and record AEs, if any
  - Drug accountability and dispense study drug
- \* If the indicated assessments fall on a study treatment visit that is within 2 weeks of the planned EOT visit then these specified assessments can be postponed until the EOT visit.

At each study visit during the Treatment Period, a Hb value will be measured (prior to dialysis in HD subjects) locally to determine the need for a dose adjustment or to assess for excessive hematopoiesis. In the event that the Hb value from the central laboratory is significantly different from that measured locally, and per Investigator that warrants a reversal of the dose adjustment decision made earlier based on locally measured Hb value, the Medical Monitor should be informed, if possible.

**7.1.2.5 End of Treatment (EOT) / Early Termination (ET) ( $\pm 7$  days)**

If a subject discontinues study medication permanently during the Treatment Period, perform the EOT assessments at the time of withdrawal from dosing or as soon as possible.

- Laboratory tests:
  - CBC with WBC differential
  - Serum chemistry
  - Lipid panel
  - Serum iron, ferritin, TIBC, UIBC, TSAT
  - Reticulocyte count and CHr
  - HbA1c
  - Special laboratory analytes (hs-CRP, hepcidin)
  - Archival serum and plasma samples
  - Serum hCG pregnancy test for women of childbearing potential only
- Complete physical examination
- Local Hb
- Vital signs (BP, HR, RR, and Temp)
- Weight (dry weight in HD subjects)
- HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)

- 12-lead ECG
- Review and record concomitant medications
- Review and record procedures and nondrug therapies
- Review and record AEs, if any
- Final drug accountability

## 7.2 Post-Treatment Follow-Up Period

### 7.2.1 End of Study (EOS): 4 weeks after EOT or ET ( $\pm 7$ days)

- Laboratory tests:
  - CBC with WBC differential
  - Serum chemistry
  - Lipid panel
  - Serum iron, ferritin, TIBC, UIBC, TSAT
  - Reticulocyte count and CHr
  - HbA1c
  - Special laboratory analytes (hs-CRP, hepcidin)
  - Archival serum and plasma samples
- Targeted physical examination
- Weight (dry weight in HD subjects)
- Vital signs (BP, HR, RR, and Temp)
- Review and record concomitant medications
- Review and record procedures and nondrug therapies
- Review and record AEs, if any. Reconcile all ongoing adverse events at this visit.

### 7.2.2 Long-Term Follow-Up of Subjects who Discontinued Study Medication Prematurely

Each subject enrolled in this study is free to permanently discontinue study medication at any time, without prejudice to further treatment. Subject discontinuation and withdrawal are discussed in detail in Section 5.3

Subjects who discontinue study medication prematurely will be followed up for vital status, CV events, and hospitalization until study closure, unless consent to participate is withdrawn. Upon completion of EOT and EOS visits, these subjects will be followed up every 3-6 month interval (depending on the availability of subjects) until study closure. These visits may occur either in-person or via telephone.

The choice of anemia treatment after ET is up to the discretion of the investigator. If the investigator decides to resume ESA treatment in roxadustat treated subjects, the first dose of ESA should be administered at least three days after the last dose of roxadustat.

### **7.3 Missed Visits**

Every attempt should be made to complete all study visits within the visit window as outlined in the Schedule of Assessments.

### **7.4 Unscheduled Visits**

Unscheduled visit(s) and laboratory assessments may be required at the discretion of the investigator. Please refer to the eCRF completion guidelines for additional information.

### **7.5 Laboratory Assessments**

Central laboratory results should be reviewed by the Investigator or another designated qualified study staff member as soon as it is received. Any abnormalities must be evaluated in clinical context and the investigator should determine if it is clinically significant. Subject management is dependent upon close review of the laboratory data.

### **7.6 Central Laboratory**

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

Unscheduled and repeat laboratory tests will also be performed by the central laboratory. However, if the turnaround time from the central laboratory is not sufficiently rapid for clinical management of the subject, local laboratory (ie, Stat Lab) test results may be used to make the necessary clinical judgments. Stat lab is to be used only for urgent lab test that is needed for immediate decision making related to the protocol, management of adverse events as determined by the Investigator. In all cases, a central laboratory specimen would also be drawn at the same time. A central laboratory manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Laboratory tests for this study are listed in Table 4.

**Table 4. Laboratory Tests**

<p><b>CBC:</b></p> <ul style="list-style-type: none"> <li>Basophils</li> <li>Eosinophils</li> <li>Erythrocyte count (RBC)</li> <li>Hct</li> <li>Hb</li> <li>Leukocyte count (WBC)</li> <li>Lymphocytes</li> <li>Mean corpuscular volume</li> <li>Mean corpuscular Hb</li> <li>Mean corpuscular Hb concentration</li> <li>Monocytes</li> <li>Neutrophils</li> <li>Neutrophils, immature (banded)</li> <li>Platelets</li> </ul> <p><b>Serum Lipid Panel:</b></p> <ul style="list-style-type: none"> <li>Total Cholesterol</li> <li>LDL</li> <li>HDL</li> <li>Triglycerides</li> </ul> <p><b>Serum Iron Profile</b></p> <ul style="list-style-type: none"> <li>Ferritin</li> <li>Iron</li> <li>TIBC</li> <li>UIBC</li> <li>TSAT</li> </ul> <p><b>Special Laboratory Analytes:</b></p> <ul style="list-style-type: none"> <li>Hepcidin</li> <li>High-sensitivity CRP</li> </ul>	<p><b>Chemistry Panel:</b></p> <ul style="list-style-type: none"> <li>Albumin</li> <li>Bicarbonate</li> <li>BUN</li> <li>Calcium</li> <li>Chloride</li> <li>Creatinine</li> <li>Creatine phosphokinase</li> <li>Glucose</li> <li>Lipase</li> <li>Lactate dehydrogenase</li> </ul> <p><i>Liver Function Tests</i></p> <ul style="list-style-type: none"> <li>ALP</li> <li>ALT</li> <li>AST</li> <li>Bilirubin, total and direct</li> <li>GGT</li> </ul> <ul style="list-style-type: none"> <li>Magnesium</li> <li>Phosphorus</li> <li>Potassium</li> <li>Total protein</li> <li>Uric acid</li> </ul> <p><b>HIV and viral Hepatitis Panel:</b></p> <ul style="list-style-type: none"> <li>Anti-HCV Ab tests</li> <li>HBsAg</li> <li>HIV ELISA</li> </ul> <p><b>Additional Laboratory Analytes:</b></p> <ul style="list-style-type: none"> <li>Vitamin B<sub>12</sub></li> <li>Folate</li> <li>HbA1c</li> <li>Reticulocyte count</li> <li>CHr</li> <li>Serum hCG pregnancy test (for women of childbearing potential only)</li> </ul>
---	--

---

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CHr = reticulocyte hemoglobin content; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; GGT = gamma-glutamyl transferase; Hb = hemoglobin; HbA1c = glycated hemoglobin; HBsAg = hepatitis B surface antigen; Hct = hematocrit; HCV = hepatitis C virus; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; LDL = low-density lipoprotein; RBC = red blood cell; TIBC = total iron binding capacity; UIBC=unsaturated iron binding capacity  
TSAT = transferrin saturation; WBC = white blood cell.

### **7.6.1 Archival Serum and Plasma Samples (Optional)**

At prespecified visits, a set of serum and plasma samples will be drawn and stored for the potential future analysis of relevant biomarkers linked with the efficacy or safety of the study drugs or with the progression of CKD. No genetic (DNA) testing will be performed using these samples for diagnosis of genetic disorders. Subjects may opt out of providing serum and plasma samples when providing consent for study participation or at any time during the course of the study. All details on the processing of the samples, storage and shipment conditions will be provided in the laboratory manual.

### **7.7 Electrocardiogram**

Local 12-lead (ECGs) will be performed on all subjects at specific time points as described in the Schedule of Assessments. The ECG should be taken after 5 minutes in the supine position. 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. ECG recordings will be kept as source documents. Abnormal ECG findings prior to administration of study drug on Day 1 will be considered baseline conditions.

### **7.8 Renal Ultrasound**

A renal ultrasound examination will be performed during screening if no record of a renal ultrasound or other imaging exists within 12 weeks prior to randomization. Renal ultrasound findings must be available prior to randomization to exclude subjects with a presence or suspicion of renal cell carcinoma. The date of assessment and findings must be documented as baseline findings.

### **7.9 Health Related Quality of Life Questionnaires**

All study subjects will be required to complete the following HRQoL questionnaires: SF-36, FACT-An, and EQ-5D-5L at baseline and during the study at prespecified visits. HRQoL assessments should be administered approximately at the same time of the day. For example, in subjects on HD, these assessments should be completed approximately at the same time during dialysis (preferably at the beginning of the dialysis session) and in subjects on PD approximately at the same time of the day at scheduled visits.

#### **7.9.1 36-Item Short Form Health Survey**

The 36-Item Short Form Health Survey (SF-36) is a quality of life (HRQoL) instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. It is aimed at both adults and adolescents ages 18 years and older. The SF-36 consists of 8 domains of health status: physical functioning (PF) (10 items), role physical (4 items), bodily pain (2 items), general health (5 items), vitality (VT) (4 items), social functioning (2 items), role emotional (3 items) and mental health (5 items). Two component scores, the Physical Component Scores 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.

### **7.9.2 FACT-An**

The Functional Assessment of Cancer Therapy-General (FACT-G; Version 4) contains 27 items that cover four dimensions of well-being: physical (7 items), functional (7 items), social/family (7 items), and emotional (6 items). A subscale of 13 fatigue specific items plus 7 additional items related to anemia were developed for use in conjunction with the FACT-G (Yellen et al, 1997). The 13 fatigue items plus the 7 additional items related to anemia comprise the Anemia Subscale. Administration of the FACT-G plus the Anemia Subscale 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, (ie, ‘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 HRQoL.

### **7.9.3 European Quality of Life Questionnaire in 5 Dimensions**

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analog scale. The EQ-5D-5L 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 visual analog scale 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-5L health states, defined by the EQ-5D-5L 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.

## 8 SAFETY

### 8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the study drug. Subjects will be asked nonleading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 3. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor all SAEs, regardless of whether the investigator believes they are related to the study drug.

The definitions of an AE, suspected adverse reaction, adverse reaction, and SAE are described below in accordance with the FDA Final Rule Vol 75, No 188, September 29, 2010; Article 18 of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 and the International Conference on Harmonization (ICH) E2A guidance.

### 8.2 Definitions

#### 8.2.1 Definition of an Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

An AE can be any unfavorable and unintended sign (eg, an abnormal and clinically significant laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. This includes any occurrence that is new in onset or aggravated in severity or frequency from the BL condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. An AE can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

#### 8.2.2 Definition of a Serious Adverse Event

A **serious adverse event** is any AE or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (ie, if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Other medically important events



Based upon appropriate medical judgment, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. These events must be reported to the sponsor similar to serious adverse events.

Safety events of interest (“Special Situations”) on the medicinal products administered to the subject as part of the study (eg, 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 (exceeding the maximum allowable per dose i.e 400 mg or 3.0 mg/kg, whichever is lower)
- 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, eg, name confusion)
- Drug-drug interaction

### **8.2.3 Definition of a Suspected Adverse Reaction**

Suspected adverse reaction means any AE for which there is a *reasonable possibility* that the drug caused the AE. The term “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than the term “adverse reaction.”

### **8.2.4 Definition of an Adverse Reaction**

An adverse reaction means any AEs caused by a drug.

## **8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events**

### **8.3.1 Adverse Event Reporting Period**

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends at End of Study / 4-Week post ET/EOT Visit, except for pregnancy reporting (Section 8.3.6).

Adverse events will be followed until resolved, stable, or until the subject’s last study visit or lost to follow-up. If an AE is not resolved or stabilized at the subject’s last visit, it is up to the discretion of the investigator and study medical monitor to determine if further monitoring of the event is warranted.

Adverse events collected prior to dosing of study drug will be considered “nontreatment emergent” while those reported after the first dose of study drug and up to 28 days after the ET/EOT Visit will be considered “treatment emergent” and be assessed for relationship to study drug. If an AE starts on Day 1, the investigator must assess as to whether the AE started prior to or after the administration of study medication and record accordingly.

### 8.3.2 Adverse Event Eliciting/Reporting

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. Conditions including signs and symptom present at baseline, unless significantly worsened, shouldn't be reported as adverse events during the study.

Whenever is 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 is obtained may qualify to be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, may also qualify to be recorded as AEs.

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

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- In the opinion of the investigator, the abnormality is clinically meaningful and significantly different from baseline.

The following attributes must be assigned to each AEs:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug (decision taken by the PI in response to an AE)
- Other action (treatment, nondrug therapy) required
- Determination of "seriousness"

### 8.3.3 Assessing Adverse Event Severity

The Investigator should grade the AEs using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

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

#### 8.3.4 Assessing Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. Moreover, appropriately deciding whether the AE meets the definition of a suspected adverse reaction is usually the most difficult determination, but it is critical to avoid the miscategorization of the product's safety profile.

Due to the historical tendency for assessment of relationship to default as possibly related, the FDA has issued new guidance that clarifies the intent of the phrase "reasonable possibility" in the definition of "associated with the use of the drug." Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the product safety profile.

The investigator must provide an assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered enough evidence to assess an event as possibly related or related to study drug.

- **Related (Adverse Reaction):**
  - Any event for which there is evidence to conclude that the study drug caused the event
- **Possibly Related (Suspected Adverse Reaction):**
  - A single occurrence of an event that is uncommon and *known to be strongly associated with drug exposure*, such as angioedema, anaphylaxis, rhabdomyolysis, Stevens-Johnson syndrome, etc.
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug, such as tendon rupture

- **Not Related:**

- The event represents the underlying disease (eg, disease-related symptoms, disease progression)
- The event represents a comorbid condition present at the time the subject entered the study
- The event represents a known adverse reaction associated with a co-medication received by the study subject
- The event is common for the study population (eg, CV events in an elderly population)
- The event has no plausible relationship to study drug
- The event is a study endpoint (eg, mortality, major morbidity)

The investigator must provide an assessment of the relationship of the event to study drug, as this information is very important to monitor the real-time safety of the study drug. However, as the manufacturer of the study drug, FibroGen is responsible for making the final causality assessment for individual reports, and for reporting suspected adverse reactions and adverse reactions to appropriate Health Authorities.

While the investigator must provide an assessment of the relationship of the event to study drug, in most cases only aggregate data review will be used to make the determination of the relationship of the study drug to a given AE.

### **8.3.5 Reporting Serious Adverse Events on the SAE Report Form**

All SAEs must be reported immediately to the Sponsor and/or its designated safety management vendor.

To report an SAE, the investigator must fax an SAE Report Form to Sponsor's designated safety management vendor within 24 hours of becoming aware of the serious event. In case of emergency or doubt, the Investigator shall call Sponsor's Medical Monitor for guidance. Follow-up reports must be submitted in a timely manner as additional information becomes available.

Full details of the SAE should also be recorded on the medical records and onto the eCRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly (within seven days) as necessary.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

### **8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee**

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. Sponsor, or its safety representative, will provide to the investigator a copy of any expedited safety reports that it intends to file with a regulatory authority.

### **8.3.5.2 Deaths**

For any death occurring during the subject's study participation, regardless of attribution, the investigator will report the death immediately to the Sponsor's Medical Monitor and their designated safety management vendor.

The investigator should notify Sponsor and their designated safety management vendor of any death or other SAE occurring after a subject has discontinued or terminated study participation that may reasonably be related to the study.

The investigator must submit the SAE Report Form and complete the appropriate eCRF for the event that led to the subject's death.

When reporting a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the primary event term on the SAE Report Form.

### **8.3.6 Pregnancies: Reporting and Follow-up of Subjects**

A pregnancy in a female subject must be confirmed by positive serum  $\beta$ -hCG test. If  $\beta$ -hCG test is found positive in a female subject of childbearing potential, study drug should be placed on hold temporarily until pregnancy is ruled out via a repeat test  $\geq 3$  days. If a female subject becomes pregnant while the subject is receiving study treatment or within 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to Sponsor (by way of its designated safety management vendor) within 24 hours of the investigator learning of the pregnancy. The investigator should report the information to the sponsor on the designated forms. If applicable, a pregnant subject is immediately withdrawn from receiving study treatment. The investigator must follow the pregnancy to completion to ascertain both its outcome and whether any AEs occurred.

Pregnancy itself is not an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Pregnancies are followed up to outcome even if the subject was discontinued from the study. The outcome of the pregnancy must be reported by the investigator, which should be sent to the Sponsor and/or its designated safety management vendor within 24 hours of the investigator learning of the outcome. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented as described. To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome

(should be handled on a case by case basis with IRB/IEC approval); the male patient should not be asked to provide this information.

### **8.3.7 Abnormal Laboratory Findings**

Laboratory values will be collected throughout the study to assess for safety. The investigator must review and assess all laboratory results in a timely manner, and determine whether the abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms.

An abnormal laboratory finding should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- In the opinion of the investigator, the abnormality is clinically meaningful and significantly different from baseline

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

A decrease in Hb value without any significant clinical symptoms should not be reported as an adverse event. In this case, worsening of anemia as evidenced by drop in Hb value may be considered as lack of efficacy as opposed to AE as the subject fails to respond adequately to study drug.

### **8.3.8 Disease Progression**

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Gradual worsening of ESRD should be considered disease progression and should not be reported as an AE during the study.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 Sample Size Determination

At least 600 subjects will be enrolled in this study. During the course of this study, which is being conducted in parallel with other Phase 3 studies, up to 1200 subjects may be enrolled for safety evaluation of roxadustat in comparison to epoetin alfa including adjudicated and prespecified safety events of interest (ie, all-cause death, MI, stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, DVT, pulmonary embolism, vascular access thrombosis, and hypertensive emergency). The final number of patients to be enrolled will be based on the enrollment rate of other studies within the same indication, in order to optimize stopping these studies at comparable time frame

With at least 600 subjects, the study will provide at least 99% power to demonstrate statistical noninferiority of roxadustat versus ESA in the primary endpoint for US (FDA) submission (ie, specifically, Hb change from baseline to the average level during the evaluation period defined as Week 28 until Week 52).

The study will provide at least 99% power to demonstrate statistical noninferiority of roxadustat versus ESA in the primary endpoint outside of the United States (ie, specifically, Hb change from BL in the averaged Hb over Weeks 28 to 36).

This assumes a difference (roxadustat minus ESA) of 0.30 g/dL, a noninferiority margin for this difference of 0.75 g/dL and a standard deviation of 1.25 g/dL.

### 9.2 Randomization

Randomization will be stratified by the following three factors:

- Mean qualifying screening hemoglobin ( $\leq 10.5$  vs.  $> 10.5$  g/dL)
- History of CV, cerebrovascular, or thromboembolic diseases (yes vs. no)
- Mean prescribed weekly epoetin alfa dose (or, equivalent epoetin dose for nonpoetin subjects) in the 4 weeks prior to randomization ( $\leq 150$  vs.  $> 150$  IU/kg/week)
- Geographical region (US vs. Ex-US regions)

### 9.3 Analysis Populations

For US regulatory submission, efficacy and safety analyses will be based on all subjects stratified by the protocol amendments, on subjects enrolled during the original protocol but before the amendment 1, and on subjects enrolled after the amendments separately.

For EU regulatory submission, efficacy and safety analyses will be based on subjects enrolled during the original protocol before the amendments, as the subjects enrolled after the amendments may be considered as a sub-study for EU regulatory purpose.

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

#### 9.3.1 Intent to Treat Population (ITT)

The ITT population consists of all randomized subjects.

### **9.3.2 Full Analysis Set (FAS)**

The FAS consists of all randomized subjects who receive at least one dose of study drug and have at least one postdose Hb assessment. If treatment received differs from the randomized treatment, the randomized treatment arm will be used.

### **9.3.3 Per-Protocol Set (PPS)**

The PPS consists of all randomized subjects who received at least 8 weeks of study treatment, have at least one postdose Hb assessment and are without major protocol violations.

### **9.3.4 Safety Analysis Set (SAF)**

The SAF will consist of all randomized subjects who received at least one dose of study medication. If treatment received for the duration of the study differs from the randomized treatment, the actual treatment arm will be used.

## **9.4 Statistical Analysis**

Safety and efficacy data will be summarized and presented by treatment group in summary tables. Descriptive statistics including number of subjects (N), means, standard deviations, medians, and minimum and maximum values will be presented for continuous variables. Counts and percentages will be presented for categorical variables. For efficacy endpoints, the standard error and 95% confidence intervals (CI) will be presented as part of the descriptive summaries.

### **9.4.1 Subject Enrollment and Disposition**

The number of randomized subjects (ITT), treated subjects, FAS and PPS subjects and subjects who discontinued along with the reason for early termination will be summarized by treatment group and overall.

### **9.4.2 Demographics and Baseline Characteristics**

Demographics (age, race, sex), BL characteristics including stratification factors, and subject disease characteristics will be summarized.

Descriptive statistics will be calculated for continuous variables (eg, age, weight, BL Hb, body mass index) and frequency counts and percentages will be tabulated for categorical variables (eg, sex, race, Hb category, iron status, and history of CV disease or cerebrovascular disease) by treatment group and overall.

### **9.4.3 Efficacy Analyses**

Efficacy analysis for superiority will be conducted on the ITT population for US (FDA) submission and on FAS population for EU regulatory submission.

Efficacy analysis for non-inferiority will be conducted on the ITT population for US (FDA) submission and on the PPS for EU regulatory submission.

Hb results obtained from the central laboratory will be used for all efficacy analyses. Baseline Hb value for efficacy analysis is defined as the mean of four central laboratory Hb values, three of the latest screening Hb values plus the pre-dose Hb value collected on Day 1 for subjects who enrolled under original protocol and Amendment 1. Subjects enrolled under Amendment 2, baseline Hb value for efficacy analysis is defined as the mean of three central laboratory Hb values, two of the latest screening Hb values plus the pre-dose Hb value collected on Day 1.



In subjects with missing Day 1 Hb value, the mean of three (two, for Amendment 2) latest screening laboratory Hb values will be considered as BL Hb value.

#### 9.4.3.1 Primary Efficacy Analysis

The primary efficacy endpoint for the US (FDA) submission is defined as the Hb change from baseline to the average level during the evaluation period defined as Week 28 until Week 52. The analysis will be based on the all ITT population, Sensitivity analyses will be performed on ITT Population enrolled under the original protocol, and the ITT population enrolled under amended protocols, separately.

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

$H_0$ : Hb mean change from baseline to the average level from Week 28-to Week 52 in the roxadustat group  $\leq$  Hb mean change from baseline in the epoetin alfa group minus 0.75 g/dL

Versus:

$H_1$ : Hb change from baseline to the average level of Week 28 to Week 52 in the roxadustat group  $>$  Hb mean change from baseline in the epoetin alfa group minus 0.75 g/dL

A Multiple Imputation Analysis of Covariance (MI-ANCOVA) model will be used. The model will contain terms for baseline Hb measurement as covariate, treatment arm, and randomization stratification factors except Screening Hb values ( $\leq 10.5$  g/dL vs.  $> 10.5$  g/dL) as fixed effects. Detailed analysis of the primary endpoint will be outlined in the SAP.

In addition, as a sensitivity analysis, the primary efficacy endpoint will be analyzed using the analysis of MMRM model. The MMRM model will contain terms for baseline Hb measurement as covariate, treatment arm, visit, visit by treatment arm, and randomization stratification factors except Screening Hb values ( $\leq 10.5$  g/dL vs.  $> 10.5$  g/dL) as fixed effect. The primary efficacy analysis (for both, US [FDA] and EU regulatory submissions) will be based on the estimated difference between the two treatments overall mean effects throughout the evaluation period based on the primary analysis models.

Due to the large amount of visits to include in the MMRM model, the unstructured covariance pattern model will be tested against the less parameterized heterogeneous Toeplitz structure using the likelihood ratio test for nested models. If the algorithm for unstructured covariance pattern does not converge or the likelihood ratio test is not statistically significant then heterogeneous Toeplitz structure will be used. If this second model does not converge either then the (homogeneous) Toeplitz structure will be tried and finally compound symmetry as a covariance structure to achieve convergence.

Pattern Mixture models will be used as additional sensitivity analyses. The details will be described in the SAP.

Hb values under the influence of a rescue therapy will not be censored in the primary analysis.

The null hypothesis will be rejected if the two-sided 95% CI for the difference between the two least squares means of the roxadustat group and the epoetin alfa group throughout the evaluation lies entirely above  $-0.75$  g/dL

The primary efficacy endpoint for EU regulatory submission is defined as the Hb change from BL to the average Hb of Weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period and will be based on the PPS population enrolled under original protocol only. This primary efficacy analysis will be based on the estimated difference between the two treatments overall mean effects throughout the evaluation period based on the same MMRM model as the sensitivity analysis of primary efficacy endpoint for US regulatory submission.

For subjects who discontinued the study prior to Week 28, the last Hb value will be used in the assessment of the primary endpoint.

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

H<sub>0</sub>: Hb mean change from BL to the average of Weeks 28 to 36 in the roxadustat group  $\leq$  Hb mean change from BL in the epoetin alfa group minus 0.75 g/dL

Versus:

H<sub>1</sub>: Hb change from BL to the average of Weeks 28 to 36 in the roxadustat group  $>$  Hb mean change from BL in the epoetin alfa group minus 0.75 g/dL

For subjects who require rescue therapy, the Hb value after to the initiation of the rescue therapy will be set to missing up to 6 weeks from the last date of the rescue therapy. This null hypothesis will be rejected if the two-sided 95% CI for the difference between the two treatment groups using MMRM model lies entirely above  $-0.75$  g/dL.

The analysis will be repeated using the FAS as a sensitivity analysis.

#### 9.4.3.2 Secondary Efficacy Analyses

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

- For US (FDA) submission: Proportion of subjects with mean Hb level during the evaluation period defined as Week 28 until Week 52  $\geq 10.0$  g/dL.
- EU regulatory submission: Hemoglobin (Hb) response, defined as mean Hb during Weeks 28 to 36 within the range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

The hypothesis to be tested for the first secondary efficacy analysis is:

H<sub>0</sub>: Hb response rate for subjects in the roxadustat group - Hb responder rate for subjects in the epoetin alfa group  $\leq -15\%$

Versus

H<sub>1</sub>: Hb response rate for subjects in the roxadustat group - Hb responder rate for subjects in the epoetin alfa group  $> -15\%$ .

A 2-sided 95% CI for the difference of two responder rates (roxadustat-ESA) based on the Miettinen and Nurminen approach adjusting for treatment group and other stratification factors will be calculated and H<sub>0</sub> will be rejected if the lower bound of the 95% CI is greater than  $-15\%$ .

- The average monthly iron use during Weeks 1 to 36 will be compared between the 2 treatment groups using an ANCOVA model with BL iron replete as a covariate, and treatment arm and randomization stratification factors as fixed effects. Superiority will be declared if the lower bound of the 2-sided 95% CI of the difference between epoetin alfa and roxadustat exceeds 0.
- The change in low-density lipoprotein (LDL) cholesterol averaged over Weeks 12 to 28 from BL will be analyzed using an MMRM model with BL LDL cholesterol as a covariate and treatment arm, visit, interaction of treatment arm and visit, and randomization stratification factors as fixed effects. Superiority will be declared if the lower bound of the 2-sided 95% CI of the difference between epoetin alfa and roxadustat exceeds 0.
- Time to exacerbation of BP will be analyzed using the Cox Proportional Hazards model adjusting for treatment arm and randomization stratification factors. Superiority of roxadustat vs. epoetin alfa will be declared if the upper bound of the 2-sided 95% CI of the hazard ratio is  $< 1$ .
- The change in MAP averaged over Weeks 20 to 28 from BL will be analyzed and compared between the 2 groups using an MMRM model with BL MAP as a covariate and treatment arm, visit, interaction of treatment arm and visit, and randomization stratification factors as fixed effects. Superiority will be declared if the lower bound of the 2-sided 95% CI of the difference between roxadustat and epoetin alfa is below 0.
- The change from BL in SF-36 Physical Functioning (PF) subscore to the average PF subscore of Weeks 12 to 28 will be analyzed using an MMRM model using BL PF subscore as a covariate and treatment arm, visit, interaction of treatment arm and visit, and randomization stratification factors as fixed effects. Non-inferiority of roxadustat vs. epoetin alfa will be tested. The noninferiority margin is fixed as a difference of 2 points.
- Change from BL in SF-36 VT subscore to the average VT subscore of Weeks 12 to 28 will be analyzed using an MMRM model using BL VT subscore as a covariate and treatment arm, visit interaction of treatment arm and visit, and randomization stratification factors as fixed effects. Non-inferiority of roxadustat vs. epoetin alfa will be tested. The noninferiority margin is fixed as a difference of 2 points.

Statistical methods for additional efficacy endpoints are described in the Statistical Analysis Plan (SAP).

#### 9.4.4 Safety Analyses

The Safety analyses will be performed using the safety analysis set (SAF).

Safety parameters include adverse events, SAEs, laboratory parameters, vital signs, ECG parameters, and PE.

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

The CV safety assessment of roxadustat will also be based on pooled analysis of composites of adjudicated CV events pooled across multiple global Phase 3 clinical studies which includes this study, according to the regional pooled SAPs for meeting regional regulatory requirements.

For US (FDA) submission only: The primary safety endpoint in this study is the MACE (Major Adverse Cardiac Event) composite endpoint, defined as time to first occurrence of death from all causes, MI, or stroke, only for the purpose of being pooled across multiple similar studies in the Phase 3 program. None of the individual studies are powered to meet the MACE primary safety endpoint individually. The pooled MACE analysis is only for purposes of supporting a US FDA regulatory filing of roxadustat.

Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be conducted by an independent DSMB.

For each safety parameter, the last assessment made prior to the first dose of study medication will be used as the BL for all analyses of that safety parameter.

#### **9.4.4.1 Adverse Events**

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

An AE (classified by preferred term) occurring during the Treatment Period will be considered a treatment emergent AEs (TEAE) if it was not present prior to the first dose of study medication, or if it was present prior to the first dose of study medication but increased in severity during the Treatment Period. An AE that occurs more than 28 days after the ET/EOT Visit date will not be counted as a TEAE.

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

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

The proportion of subjects with TESAE, fatal SAEs (ie, events that caused death), and AEs leading to permanent discontinuation of study medication will be summarized by System Organ Class (SOC), preferred term and treatment group

Treatment emergent adverse events of interest will also be reported in terms of incidence rate per Patient Exposure Year (PEY).

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

#### **9.4.4.2 Clinical Laboratory Parameters**

Descriptive statistics for laboratory values and changes from BL at each assessment time point will be presented by treatment group for each laboratory parameter. To assess potentially clinically meaningful laboratory abnormalities, the number and percentage of subjects with post-BL lab values outside a predefined range or limit of change will be tabulated by treatment group.

### 9.4.4.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, respiration rate) and their changes from BL at each visit and, the EOS will be presented by treatment group.

### 9.4.4.4 Electrocardiogram

Descriptive statistics for ECG parameters (eg, HR, PR interval, QRS interval, QT interval, QTc interval) at BL and changes from BL at each assessment time point will be presented by treatment group. To assess potentially clinically meaningful ECG abnormalities, the number and percentage of subjects with post-BL ECG values outside a predefined range or limit of change will be tabulated by treatment group, as well as shift tables for results of ECG interpretation (normal, abnormal not significant, abnormal significant).

## 9.5 Interim Data Cut

There are currently no plans to conduct an interim data cut.

Safety data and dosing decisions will be monitored on an ongoing basis. Additional ongoing review of safety data will be conducted by an independent DSMB (see Section 4.8).

## 9.6 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will provide details of the data analyses. As an open-label study the SAP will be finalized prior to accumulation of a substantial amount of data to ensure lack of bias. Any significant changes to the analyses described in this protocol will be highlighted in the SAP and detailed in the Clinical Study Report.

## 9.7 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.

Due to the unique nature of this study, following issues are not to be considered as protocol deviations:

- Given the complexity in EPO dose adjustments and the need to take into account the various clinical parameters in EPO dose titration, one would not consider it a protocol deviation when patients are dosed according to local standard of care whether or not it is concordant with package insert/SmPC
- Given the complexity in Roxadustat dose adjustments and the need to take into account the various clinical parameters in Roxadustat dose titration, one would not consider it a protocol deviation when subjects are dosed based on their clinical circumstances whether or not it is concordant with the Roxadustat dose adjustment guidelines unless it was related to “excessive hematopoiesis” (Hb  $\geq$ 13 g/dL, requires a dose-hold) or “Overdose” (prescribed  $>$ 3.0 mg/kg per dose or 400 mg per dose, whichever is lower)

- ESA administrations in Roxadustat subjects during hospitalization are not to be reported as protocol deviation, if the roxadustat dosing were not allowed or available during that hospitalized period
- IV iron administrations in study subjects during hospitalization are not be reported as protocol deviation

For the purposes of this protocol, protocol deviations requiring notification to the Sponsor will be defined and detailed in the study monitoring plan.

## 10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by Sponsor or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, eCRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and ICH E6 guideline.

The purpose of study monitoring is to verify the following:

- The rights and well-being of human subjects are protected
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to Sponsor or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (eg, laboratory, safety, IWRS, clinical databases)
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)

The investigator must also permit the FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the FDA or other applicable regulatory authorities, the investigator must notify Sponsor immediately.

## **11 QUALITY CONTROL AND QUALITY ASSURANCE**

### **11.1 Data Quality Assurance**

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements.

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- Electronic case report form (eCRF) and query review against source documents

### **11.2 Audit and Inspection**

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

### **11.3 Database Audit**

A database audit will be conducted to ensure data quality and integrity.



## **12 ETHICS**

### **12.1 Ethical Considerations**

The study will be conducted in accordance with FDA regulations, the International Conference on Harmonisation (ICH) E6 Guideline for GCP, the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

### **12.2 Communication with the Institutional Review Board or Independent Ethics Committee**

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

### **12.3 Informed Consent Form**

No study procedure may be implemented prior to obtaining a signed, written Informed Consent Form (ICF) from the subject or the subject's legally authorized representative. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be reconsented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

## **12.4 Subject Confidentiality**

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

## **13 DATA HANDLING AND RECORD KEEPING**

### **13.1 Source Documents**

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data entered into the electronic database and used to resolve queries.

### **13.2 Data Collection, Handling, and Verification**

All required data will be entered into an electronic database by authorized site personnel. Data will be entered into a validated, clinical database compliant with 21 Code of Federal Regulation (CFR) Part 11 regulations. The database will be a secured, password-protected system with full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (eg, MedDRA and World Health Organization Drug [WHODrug] Dictionary).

The investigator is responsible for reviewing, verifying, and approving all subject data (ie, eCRFs and queries prior to study completion), ensuring that all data is verifiable with source documents.

## **14 FINANCING AND INSURANCE**

Financing and insurance are addressed in a separate document.

## **15 PUBLICATION POLICY**

A detailed explanation of the Sponsor's publication policy is described in the Clinical Trial Agreement.

## 16 INVESTIGATOR REQUIREMENTS

The investigator must be medically qualified to directly supervise the conduct of the study at his or her site. The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

### 16.1 Study Drug Accountability

The investigational product (roxadustat) required for completion of this study will be provided by Sponsor. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

The investigational product, including partial and empty bottles, must be maintained at the study site until Sponsor or its designee verifies drug accountability and provides instruction for destruction or the return of the investigational product to Sponsor's drug distribution depot.

Accurate records of all study drug received, dispensed, returned, and disposed of by the study site according to the Study Reference Manual or Pharmacy Manual should be recorded using the Drug Inventory Log.

### 16.2 Disclosure of Data

Data records generated by this study must be available for inspection upon request by representatives of the FDA or other regulatory agencies, national and local health authorities, Sponsor's monitors/representatives and collaborators, auditors, and the IRB/IEC for each study site.

The Investigators should promptly notify the Sponsor and/or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

### 16.3 Retention of Records

The investigator shall retain records required to be maintained under 21 CFR 312.62(c) for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the investigator shall retain these records until 2 years after the investigation is discontinued and the FDA is notified.

If the investigator moves or retires, he or she should identify in writing, the designee who will be responsible for record keeping. Archived data may be retained on electronic records or similar medium provided that a back-up exists and a hard copy is obtainable if required. No records will be destroyed without the prior written consent of Sponsor.

## 17 REFERENCES

- Besarab, A., et al. "The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin." *N Engl J Med* 339.9 (1998): 584-90.
- Besarab, A., S. Frinak, and J. Yee. "What is so bad about a hemoglobin level of 12 to 13 g/dL for chronic kidney disease patients anyway?" *Advances in Chronic Kidney Disease* 16.2 (2009): 131-42.
- Bradbury BD, Danese MD, Gleeson M, Critchlow CW "Effect of Epoetin alfa dose changes on hemoglobin and mortality in hemodialysis patients with hemoglobin levels persistently below 11 g/dL". *Clin J Am Soc Nephrol* 4 : 630– 637, 2009
- Buchler, P., et al. "Hypoxia-inducible factor 1 regulates vascular endothelial growth factor expression in human pancreatic cancer." *Pancreas* 26.1 (2003): 56-64.
- Collins, A. J., et al. "Trends in anemia treatment with erythropoietin usage and patient outcomes." *American Journal of Kidney Diseases* 32.6 Suppl 4 (1998): S133-S141.
- Coresh, J., et al. "Prevalence of chronic kidney disease in the United States." *JAMA* 298.17 (2007): 2038-47.
- Drueke, T. B., et al. "Normalization of hemoglobin level in patients with chronic kidney disease and anemia." *N Engl J Med* 355.20 (2006): 2071-84.
- Epstein AC, Gleadle JM, McNeill LA, et al. "C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation." *Cell*. 2001;107(1):43-54.
- Eschbach, J. W., et al. "Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial." *Annals of Internal Medicine* 111.12 (1989): 992-1000.
- Eschbach, J. W., et al. "Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial." *N Engl J Med* 316.2 (1987): 73-78.
- Eschbach, J. W., et al. "Treatment of the anemia of progressive renal failure with recombinant human erythropoietin." *N Engl J Med* 321.3 (1989): 158-63.
- Fan, C., et al. "Gene expression and phenotypic characterization of mouse heart after chronic constant or intermittent hypoxia." *Physiol Genomics* 22.3 (2005): 292-307.
- FDA. "Guidance for Industry on Complicated Urinary Tract Infections: Developing Drugs for Treatment." *Federal Register* 77.37 (2012).
- Fishbane, S. and A. Besarab. "Mechanism of increased mortality risk with erythropoietin treatment to higher hemoglobin targets." *Clinical Journal of the American Society of Nephrology* 2.6 (2007): 1274-82.
- Gladziwa U, Wagner S, Riehl J, Sieberth HG (1993) "Prevalence of cholelithiasis in haemodialysis patients". *Nephrology, Dialysis, Transplantation* 8: (12): 1397-1400

- Go, A. S., et al. "Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization." *N Engl J Med* 351.13 (2004): 1296-305.
- Gray, M. J., et al. "HIF-1alpha, STAT3, CBP/p300 and Ref-1/APE are components of a transcriptional complex that regulates Src-dependent hypoxia-induced expression of VEGF in pancreatic and prostate carcinomas." *Oncogene* 24.19 (2005): 3110-19.
- Greijer, A. E., et al. "Up-regulation of gene expression by hypoxia is mediated predominantly by hypoxia-inducible factor 1 (HIF-1)." *J.Pathol.* 206.3 (2005): 291-304.
- Hu, C. J., et al. "Differential roles of hypoxia-inducible factor 1alpha (HIF-1alpha) and HIF-2alpha in hypoxic gene regulation." *Mol Cell Biol* 23.24 (2003): 9361-74.
- Jungers PY, Robino C, Choukroun G, Nguyen-Khoa T, Massy ZA, Jungers P (2002) "Incidence of anaemia, and use of epoetin therapy in pre-dialysis patients: a prospective study in 403 patients." *Nephrol Dial Transplant* 17: (9):1621-1627
- Kilpatrick RD, Critchlow CW, Fishbane S, Besarab A, Stehman-Breen C, Krishnan M, Bradbury BD: "Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients." *Clin J Am Soc Nephrol* 3 : 1077– 1083, 2008
- Krapf, R. and H. N. Hulter. "Arterial hypertension induced by erythropoietin and erythropoiesis-stimulating agents (ESA)." *Clinical Journal of the American Society of Nephrology* 4.2 (2009): 470-80.
- Langsetmo, I., Nichols, B., Seeley, T., Stephenson, B., Klaus, S., Lin, A., and Liu, D. (2005) "FG-2216 Corrects Anemia and Improves Iron Utilization in a Rat Model of Anemia of Chronic Disease: Comparison to Darbepoetin." Abstract #F-PO674, *J Am Soc Nephrol* 16: 481A.
- Li Vecchi M, Soresi M, Cusimano R, et al. (2003) "Prevalence of biliary lithiasis in a Sicilian population of chronic renal failure patients." *Nephrology, Dialysis, Transplantation* 18: (11): 2321-2324
- Ma JZ, Ebben J, Xia H, Collins AJ (1999) "Hematocrit level and associated mortality in hemodialysis patients." *J Am Soc Nephrol.* 10: (3):610-619
- NKF KDOQI. "KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: update of hemoglobin target." *American Journal of Kidney Diseases* 50.3 (2007): 471-530.
- Peyssonnaud, C., V. Nizet, and R. S. Johnson. "Role of the hypoxia inducible factors HIF in iron metabolism." *Cell Cycle* 7.1 (2008): 28-32.
- Regidor DL, Kopple JD, Kovesdy CP, et al. (2006) Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol.* 17: (4):1181-1191
- Scortegagna, M., et al. "HIF-2a regulates murine hematopoietic development in an erythropoietin-dependent manner." *Blood* 105.8 (2005): 3133-40.
- Semenza, G. L. "Hypoxia-inducible factor 1: master regulator of O<sub>2</sub> homeostasis." *Curr.Opin.Genet.Dev.* 8.5 (1998): 588-94.

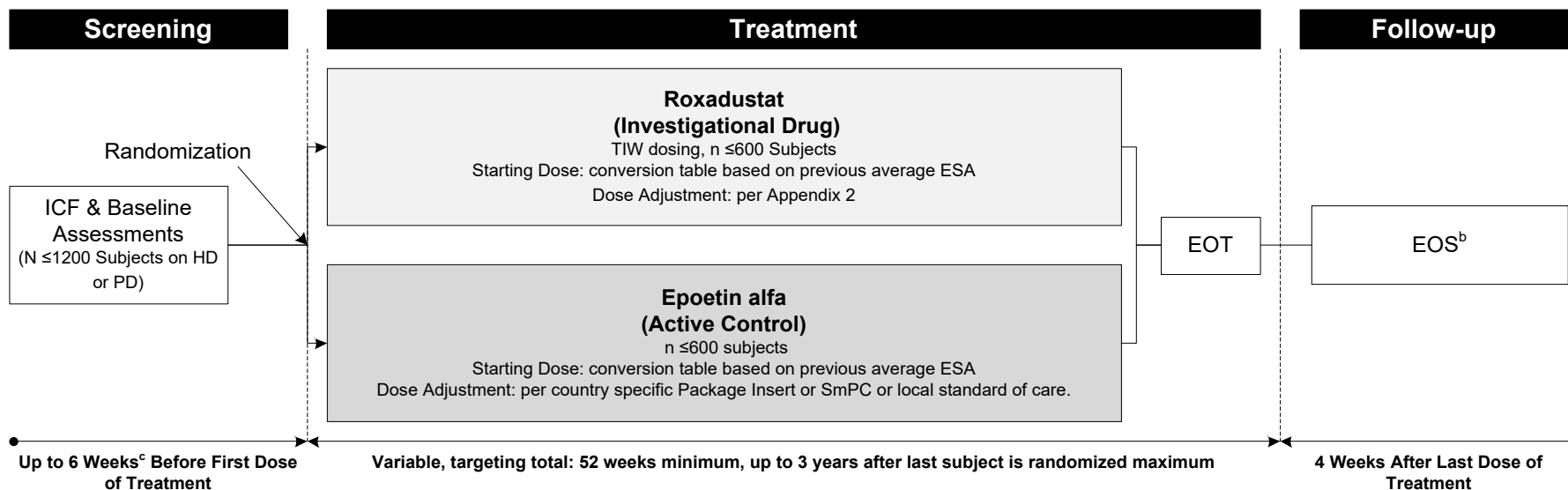


- Semenza GL (2000) HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol* 88: (4):1474-1480
- Szcezech LA, Barnhart HX, Inrig JK, et al. (2008) Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 74: (6):791-798
- Singh, A. K., et al. "Correction of anemia with Epoetin alfa in chronic kidney disease." *N Engl J Med* 355.20 (2006): 2085-98.
- Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med*. 2010;363(12):1146-1155.
- Thilly N, Stengel B, Boini S, Villar E, Couchoud C, Frimat L (2008) Evaluation and determinants of underprescription of erythropoiesis stimulating agents in pre-dialysis patients with anaemia. *Nephron Clin Pract* 108: (1):c67-c74
- Tonelli, M., et al. "Chronic kidney disease and mortality risk: a systematic review." *J Am Soc Nephrol* 17.7 (2006): 2034-47.
- Unger, E. F. FDA Perspectives on ESAs for Anemia of Chronic Renal Failure: Hemoglobin Target and Dose Optimization. 9-11-2007. FDA Department of Health and Human Services. Joint Meeting of the Cardiovascular and renal Drugs Advisory Committee and the Drug Safety and risk Management Advisory Committee. 10-16-2007.
- Unger EF, Thompson AM, Blank MJ, Temple R (2010) Erythropoiesis-stimulating agents time for a reevaluation. *N Engl J Med* 362: (3):189-192
- U.S. Renal Data System, 2000 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.
- U.S. Renal Data System, 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.
- U.S. Renal Data System, 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.
- U.S. Renal Data System, 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.
- U.S. Renal Data System, 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.
- U.S. Renal Data System, 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.
- U.S. Renal Data System, 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

- Wang, G. L., et al. "Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O<sub>2</sub> tension." *Proc Natl Acad Sci USA* 92.12 (1995): 5510-14.
- Warnecke, C., et al. "Differentiating the functional role of hypoxia-inducible factor (HIF)-1 $\alpha$  and HIF-2 $\alpha$  (EPAS-1) by the use of RNA interference: erythropoietin is a HIF-2 $\alpha$  target gene in Hep3B and Kelly cells." *The FASEB Journal* 18.12 (2004): 1462-64.
- Winearls, C. G., et al. "Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis." *Lancet* 2.8517 (1986): 1175-78.
- Yellen, S. B., et al. "Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system." *J Pain Symptom.Manage.* 13.2 (1997): 63-74.
- Zhang, Y., et al. "Epoetin requirements predict mortality in hemodialysis patients." *American Journal of Kidney Diseases* 44.5 (2004): 866-76.
- Zoccali C, Kramer A, Jager KJ. Epidemiology of CKD in Europe: an uncertain scenario. *Nephrol Dial Transplant.* 2010;25(6):1731-3.

## **18 APPENDICES**

**Appendix 1 Study Schema (Original Protocol)**



Abbreviations: EOS=end of study; EOT=end of treatment; ESA=erythropoiesis-stimulating agent; HD=hemodialysis; n=number of subjects; PD=peritoneal dialysis; SmPC=summary of product characteristics; TIW=three times a week.

- a EOT/ET + 4 weeks ±7 days
- c For subjects currently taking Mircera<sup>®</sup>, the screening period can be extended up to 8 weeks

## Appendix 2 Roxadustat Dose Adjustment Rules

At each study visit during the Treatment Period, Hb will be measured (prior to dialysis in HD subjects) locally to determine the need for a dose adjustment or to assess for excessive hematopoiesis. This local Hb measurement may be made with the use of a point-of-care device (eg, HemoCue<sup>®</sup>, CritLine<sup>®</sup>) or by local laboratory (ie, Stat Lab\*) testing if the point-of-care device is not available or the result is considered unreliable. In the event that the Hb value of the visit as determined by the study central laboratory is significantly different from that measured locally, and per Investigator that warrants a reversal of the dose adjustment decision made earlier based on locally measured Hb value, the Medical Monitor should be informed, if possible.

In this study, a rate of rise of Hb > 2 g/dL in 4 weeks or a Hb level of  $\geq$  13 g/dl at any time would be considered as excessive haematopoiesis and would require either dose reduction or temporary dose hold.

The dose of roxadustat will remain constant during the first 4 weeks of the Treatment Period unless a dose reduction is required for excessive hematopoiesis.

Roxadustat dose adjustments are permitted from Week 4 onwards, and every 4 weeks thereafter (eg, Week 4, Week 8, Week 12); however, the dose may be adjusted between two prespecified windows (eg, anytime between Week 4 and Week 8 visits, Week 8 and Week 12 visits) if all of the following criteria are met:

- No dose adjustment has been made in last 4 weeks
- Hb < 9.0 g/dL.

Any dose adjustment will reset the dose-adjustment window to every 4 weeks thereafter (eg, dose adjustment for a qualified reason at Week 6 leads to next dose adjustment at Week 10). Dose adjustment must not be done sooner than 4 weeks unless discussed with and preapproved by the medical monitor. Dose adjustments for roxadustat are described in the table below.

Subjects randomized to roxadustat will take doses TIW for the entire duration of the Treatment Period. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain a Hb level of approximately 11 g/dL, the dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc. The Medical Monitor should be notified as soon as possible of such dose change.

## Roxadustat Dose Adjustment Rules

Change in Hb over past 4 weeks (g/dL)	Hb (g/dL) at Dose Adjustment Review Visit			
	< 10.5	10.5 to < 12.0	12.0 to < 13.0	≥ 13.0
< -1.0	↑	↑	No change	Hold dosing, check Hb weekly or per PI's discretion via central lab, then resume dosing when Hb < 12.0 g/dL, at a dose that is reduced by one dose step
-1.0 to 1.0	↑	No change	↓	
> 1.0	No change	↓	↓	

Abbreviations: ↑ = increase; ↓ = decrease; Hb = hemoglobin.

### Notes:

#### *Dose Increases and Reductions:*

- Dose increases (↑) and reductions (↓) are preset.
- The dose steps are as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg. For example, a subject previously receiving 70 mg of roxadustat requiring a dose increase would have his dose changed to 100 mg of roxadustat. A subject previously receiving 150 mg of roxadustat requiring a dose reduction would have his dose changed to 100 mg of roxadustat. If < 20 mg /dose is required, dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc.
- The maximum dose is capped at 400 mg or 3.0 mg/kg/dose (whichever is lower).

#### *Dose Adjustment for Excessive Hematopoiesis:*

- If Hb increases by > 2.0 g/dL at any time within 4 weeks, the dose should be reduced by one dose step.
- Only one dose reduction for excessive hematopoiesis is recommended within a period of 4 weeks.
- Temporary dose holds for excessive hematopoiesis should be confirmed based on central lab Hb assessments. If the Hb is ≥ 13 g/dL, withhold dosing, check Hb weekly or per PI's discretion via central lab, then resume dosing when Hb < 12.0 g/dL, at a dose that is reduced by one dose step. The subsequent Hb follow-up assessments should also be done by a central lab.

\* A "Stat lab" is to be used only for urgent lab test that is needed for immediate decision making related to protocol, management of adverse events as determined by the Investigator.

**Appendix 3 Schedule of Assessments**

Study Period:	Screening (up to 6 to 8 Wks <sup>a</sup> )		Treatment Period (≥ 52 Wks)					Follow-up Period (4 Wks)	Unscheduled Visit	
	Visits:	S1	S2	± 2 days		± 4 days	± 4 days	± 7 days		
				Weekly (Wks 1-2)		Every 2 Wks (Wks 4-24)	Every 4 Wks (from Wk 28)	EOT/ET		EOS (EOT/ET +4 wks) <sup>c</sup>
	1	2	Day 1 <sup>b</sup>							
Written ICF	X									
Randomization			X							
Eligibility criteria	X		X							
Demographics	X									
Height (screening only), weight (dry weight [post dialysis] in HD subjects)	X		X				Wks 36, 52 + every 24 wks	X	X	
Medical history	X									
Physical examination		X	X			Wks 12 <sup>d</sup> , 24 <sup>d</sup>	Wks 36 <sup>d</sup> , 52 <sup>d</sup> + every 24 wks <sup>d</sup>	X	X <sup>d</sup>	O
Vital Signs: BP <sup>e</sup> , HR <sup>e</sup> , RR <sup>f</sup> , Temp	X	X	X	X	X	X	X	X	X	X
Local Hb Assessments			X	X	X	X	X	X		X
CBC with WBC diff	X		X	X	X	Wks 4, 8, 12, 20	Wks 28, 36, 44 + every 8 wks	X	X	O
Hemoglobin <sup>g</sup>		X				X <sup>g</sup>	X <sup>g</sup>			X
Reticulocyte count and CHr	X		X	X	X	Wks 4, 6, 8, 12, 16, 20	Wks 28, 36, 52 + every 16 wks	X	X	O
12-lead ECG			X			Wk 24	Wks 36, 52 + every 24 wks	X		O
Renal ultrasound <sup>h</sup>	X									
Serum chemistry	X		X			Wks 4, 8, 12, 20	Wks 28, 36, 44 + every 8 wks	X	X	O
LFTs					X	Wks 6, 16, 24	Wk 32			O
Serum Lipid panel	X		X			Wks 4, 8, 12, 20	Wks 28, 36, 48 + every 12 wks	X	X	O
Serum iron, ferritin, TIBC, UIBC, TSAT	X		X			Wks 4, 8, 12, 20	Wks 28, 36, 44 + every 8 wks	X	X	O
HbA1c	X		X			Wks 12, 24	Wks 36, 52 + every 52 wks	X	X	O
Vitamin B <sub>12</sub> , folate	X									

Study Period:	Screening (up to 6 to 8 Wks <sup>a</sup> )		Treatment Period (≥ 52 Wks)						Follow-up Period (4 Wks)	Unscheduled Visit
	S1	S2	Day 1 <sup>b</sup>	± 2 days		± 4 days	± 4 days	± 7 days	EOS (EOT/ET +4 wks) <sup>c</sup>	
				Weekly (Wks 1-2)		Every 2 Wks (Wks 4-24)	Every 4 Wks (from Wk 28)	EOT/ET		
Visits:			1	2						
HIV ELISA, HBsAg, anti-HCV Ab	X									
Serum (hCG) pregnancy test (every 12 weeks) <sup>i</sup>	X					Wks 12, 24	Wks 36, 48 + every 12 wks	X		O
hs-CRP, hepcidin			X			Wks 4, 12, 20	Wks 36, 52	X	X	
Archival serum & plasma samples for biomarkers			X			Wks 4, 12, 20	Wks 36, 52 + every 24 wks	X	X	
HRQoL Questionnaires <sup>j</sup>			X			Wks 12	Wks 28, 52	X		
Study drug: dispensing and/or accountability <sup>k</sup>			X	X	X	X	X	X		
Dose adjustment review <sup>l</sup>				X	X	X	X			
AE <sup>m</sup> and concomitant medication recording	X	X	X	X	X	X	X	X	X	X
Procedure and nondrug therapy recording	X	X	X	X	X	X	X	X	X	X

Abbreviations: Ab = antibody; AE = adverse event; BP = blood pressure; CBC = complete blood count; CHR = reticulocyte hemoglobin content; CV = cardiovascular; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; EOT = End of Treatment; ET=Early Termination; EOS = End of Study; HbA1c = glycated hemoglobin; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HD = hemodialysis; HIV = human immunodeficiency virus; HR = heart rate; HRQoL = health-related quality of life questionnaire; hs-CRP = high-sensitivity C-reactive protein; ICF = informed consent form; LFTs = liver function tests; O = optional test/assessment; PE = physical examination; RBC = red blood cell; RR = respiratory rate; TIBC = total iron binding capacity; UIBC = unsaturated iron binding capacity; TSAT = transferrin saturation; WBC = white blood cells; Wk(s) = week(s); X = mandatory test/assessment.

Notes: In subjects on HD, all lab sampling is to be performed prior to the dialysis session.

Subjects who discontinue study medication prematurely will be followed up until the end of the study, unless consent to participate is withdrawn. Upon completion of EOT and EOS visits, these subjects will be followed up every 3-6 month interval for vital status, CV events, and hospitalization (depending on the availability of subjects) until study closure. These visits may occur either in-person or via telephone.

- a All screening procedures should be completed within 6 weeks. For subjects currently taking Mircera®, the screening period can be extended up to 8 weeks.
- b Day 1 is a due treatment date per the existing ESA treatment schedule. All study assessments are to be performed prior to first study drug administration. In subjects on HD study assessments with the exception of HRQoL and body-weight measurement should also be performed prior to or at initiation of dialysis; HRQoL assessments should be done approximately during dialysis (preferably at the beginning) and weight measurement after dialysis.



- c Subjects discontinuing study medication prematurely will complete EOT and EOS. Unless consent is withdrawn, CV events, vital status and hospitalizations will be collected every 3 to 6 months (phone or in-person clinic visit) for these subjects until study closure
- d Targeted PE (general appearance, CV, respiratory and abdomen)
- e BP and HR should be measured in triplicate (preferred) using automated calibrated instruments at pre dialysis in subjects on HD and preferably approximately at the same time in subjects on PD or HHD Measurement to occur prior to study drug administration (if applicable); BP and HR should be assessed per guidelines provided in Appendix 5
- f Respiratory rate should be measured at predialysis in subjects on HD and preferably approximately at the same time in subjects on PD. Measurement should occur prior to study drug administration (if applicable)
- g Separate Hb samples should be collected at all the visits where a CBC is not collected (ie, Hb at Weeks 6, 10, 14, 16, 18, 22, 24, 32, 40, 48, etc)
- h Not required if result of a renal ultrasound or other imaging report within 12 weeks prior to randomization is available
- i Collect from female subjects of childbearing potential only can be collected at Screen 1, Screen 2 or as an unscheduled visit. Must be reviewed prior to randomization.
- j Including SF-36, FACT-An, EQ-5D 5L, HRQoL assessments should be administered approximately at the same time of the day. Example: in HD subjects, questionnaires to be completed by subject approximately at the same time during dialysis and in PD subjects approximately at the same time of the day
- k Initial dosing of roxadustat and epoetin alfa per Table 1 and Table 2, respectively. Dose adjustment per Appendix 2 (roxadustat subjects) or epoetin package insert or SmPC (epoetin subjects); dose review for excessive hematopoiesis at every visit. All subjects on HD will receive epoetin alfa TIW intravenously (IV). For peritoneal dialysis and home hemodialysis subjects, the route of administration (IV or SC) of epoetin alfa may remain the same as baseline (per discretion of the Investigator)
- l Subjects randomized to roxadustat: dose adjustment begins at Week 4 refer to Appendix 2
- m AEs and SAEs reporting period begins after informed consent is obtained and ends at End of Study / 4-week post ET/EOT Visit or EOS/Disposition date for subjects who did not complete the ET/EOT visit

## Appendix 4 Liver Safety Monitoring Assessment

The guidelines described in this Section are intended to enable early detection and action following abnormal liver function test (LFT) results. Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to  $> 3 \times$  upper limit of normal (ULN), or bilirubin  $> 2 \times$  ULN, should undergo detailed testing (including at least alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TBL]) for further evaluation and follow-up. Alerts will be generated by the central lab to inform the investigator, study monitor and study team. Testing should be repeated within 48-72 hours of notification. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

### Definition of Liver Abnormalities

Confirmed abnormalities should be characterized as follows:

	<b>ALT or AST</b>		<b>Total Bilirubin</b>
<b>Moderate</b>	$> 3 \times$ ULN	or	$> 2 \times$ ULN
<b>Severe<sup>a</sup></b>	$> 3 \times$ ULN	and	$> 2 \times$ ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

- a Hy's Law: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant)." The two "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated subjects to be discriminating"). 2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3x ULN and no evidence of intra- or extrahepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006 Apr;15(4):241-3.]

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

- ALT or AST  $> 8 \times$  ULN
- ALT or AST  $> 5 \times$  ULN for more than 2 weeks
- ALT or AST  $> 3 \times$  ULN and international normalized ratio (INR)  $> 1.5$  (if INR testing is applicable/evaluated).
- ALT or AST  $> 3 \times$  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

Subjects with confirmed abnormal liver function results should be closely monitored and followed as described below. If close monitoring for LFTs in a subject is not possible, study drug should be discontinued.

Repeat LFTs 2-3 times weekly, then weekly or less until abnormalities stabilize or return to within normal limits. LFTs should include ALT, AST, TBL and ALP

In addition, evaluate the subject for potential causes, which may include the following:

- Detailed history of symptoms and prior or concurrent diseases
- Concomitant drug use, including nonprescription medications, herbal and dietary supplements, alcohol or recreational drug use, or special diets
- Exposure to environmental chemical agents
- Rule out acute viral hepatitis Types A,B,C,D,E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; biliary tract disease
- Obtain additional tests as appropriate: eg, INR, GGT or direct bilirubin; ultrasound or other imaging to assess biliary tract disease
- Consider gastroenterology or hepatology consultations

In general, in the absence of an explanation for increased LFTs, such as viral hepatitis, preexisting or acute liver disease or exposure to other agents associated with liver injury, the study drug should be discontinued.

Discontinuation of treatment should be considered if:

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

Once LFTs return to normal, and depending on whether there is an explanation for the LFT elevations, study drug dosing may resume, after discussion with the Medical Monitor

*Ref: FDA Guidance for Industry, titled: "Drug-Induced Liver Injury: Premarketing Clinical Evaluations", issued July 2009*

## **Appendix 5 Blood Pressure and Heart Rate Measurement Guidelines**

### **Blood Pressure**

Blood pressure (BP) measurement should 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 should 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 device. The same device should preferably be used for the subject during the course of the study, timing as indicated in the Schedule of Assessments. Also the same arm should be used consistently for readings throughout the study.

Blood pressure should be measured in triplicate (preferred) with at least one minute interval between the measurements. In subjects on HD, BP should be measured a prior to the start of the dialysis procedure that day (predialysis), preferably using the nondialysis arm. In subjects on PD, BP should be measured approximately at the same time of the day at each visit.

### **Heart Rate**

Heart rate measurement should be done at rest in a sitting position wherever possible. It can be performed with an electronic automated device as used for BP measurement. The same device should preferably be used for the subject during the course of the study, timing as indicated in the schedule of assessments. Heart rate (HR) should be measured in triplicate (preferred) with at least one minute interval between the measurements. In subjects on HD, HR should be measured at predialysis and in subjects on PD and should be measured approximately at the same time of the day at each visit.

## Appendix 6 Recommended Intravenous Iron Therapy

### Recommended List of IV Iron Preparations:

- If none of the following IV iron preparation is available or can be used for any reasons, the Medical Monitor should be contacted prior to administration, if possible.

Iron Preparations (generic names)
Iron gluconate
Iron sucrose complex
Iron dextran complex
Iron isomaltoside
Iron polymaltose complex