NCT # NCT02052310

CLINICAL STUDY PROTOCOL

STUDY TITLE:	A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of FG-4592 in the Treatment of Anemia in Incident-dialysis Patients
PROTOCOL NUMBER:	FGCL-4592-063
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	74,454
STUDY DRUG:	Roxadustat (FG-4592)
INDICATION:	Anemia associated with end-stage renal disease
FIBROGEN MEDICAL MONITOR (US):	Name: [redacted] Title: Telephone: Mobile: E-mail: [redacted]
FIBROGEN MEDICAL MONITOR (Ex-US):	Name: [redacted] Title: Telephone: Mobile: E-mail: [redacted]

ORIGINAL PROTOCOL:	31 May 2013
PROTOCOL VERSION & DATE:	Amendment 1: 20 Oct 2014 Amendment 2 (United States only): 24 Nov 2015 Amendment 3 (United States only): 12 Aug 2016 Amendment 4: 20 Sep 2017

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

A Phase 3, Multicenter, Randomized, Open-Label Active-Controlled Study of the Efficacy and Safety of FG-4592 in the Treatment of Anemia in Incident-dialysis Patients

FGCL-4592-063

Amendment 4

20 September 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 4 (Global)

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

Description of Change	Rationale for Change	Section(s) Affected [a]
Inclusion Criteria: Inclusion criteria # 3 has been modified by removing "native kidney" – the revised verbiage reads as follows: *Incident dialysis subjects receiving dialysis for ESRD for ≥ 2 weeks but ≤ 4 months at the time of randomization* Inclusion criteria # 6, 7, 8, 9 were modified as follows (added text is italicized): 6. Ferritin ≥ 100 ng/mL (≥ 220pmol/L). *Subjects with ferritin level < 100 ng/mL (<220pmol/L) during screening qualify after receiving iron supplementation (per local standard of care) without the need to retest ferritin prior to randomization.* 7. Transferrin saturation ≥ 20%. *Subjects with a TSAT level < 20% during screening qualify after receiving iron supplementation (per local standard of care), without the need to retest TSAT prior to randomization.* 8. Serum folate level, performed within 8 weeks prior to randomization ≥ lower limit of normal (LLN). *Subjects with a serum folate level < LLN during screening qualify after receiving folate supplement (per local standard of care), without the need to retest folate prior to randomization.* 9. Serum vitamin B_{12} level, performed within 8 weeks prior to randomization ≥ LLN. *Subjects with a Vitamin B_{12} level < LLN at screening qualify after receiving vitamin B_{12} supplement (per local standard of care), without the need to retest vitamin B_{12} prior to randomization.*	To allow subjects who restarted dialysis recently due to transplanted kidney end-stage renal disease (see revised Exclusion # 17 below) Revised TSAT/ferritin/Vit.B12/folate criteria: Subjects with TSAT/ferritin/folate/Vit.B12 levels below the screening values are eligible, upon receiving the respective supplementations, without the need for re-testing during screening. This will improve the screening success rate without altering the patient population intended for inclusion in this study, and will help shorten the screening period by minimizing the need for additional visits to retest these parameters.	Synopsis; Section 4.1
Exclusion Criteria: Exclusion criteria 2, 3, 4, 6, 9, 13, 17, 19, and 25 were modified to read as follows (added text is italicized, revised text is bolded and italicized): 2. Intravenous iron: *there is no restriction regarding IV iron use during screening, provided it is administered in accordance with local standard of*	These exclusion criteria have been modified to allow more incident subjects to be eligible, who are otherwise good study candidates , in order to retain a representative sample of real-life incident dialysis patients. Easing the restriction on the amount of IV iron allowed during screening will help	Synopsis; Section 4.2

Description of Change	Rationale for Change	Section(s) Affected [a]
care. 3. Red blood cell (RBC) transfusion within ***4*** weeks prior to randomization. *4.* Active, clinically significant infection that could be manifested by white blood cell (WBC) count >ULN, and/or fever, in conjunction with clinical signs and symptoms of infection *at the time of randomization.* 6. New York Heart Association Class III or IV congestive heart failure *at screening.* 9. Renal ***imaging*** performed within 12 weeks prior to randomization indicative of a diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category 2 or higher) of renal cell carcinoma. 13. Known, untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration, or retinal vein occlusion. *(Subjects who are already blind for the above reasons qualify to participate).* *17. Organ transplant: subjects with any of the following:* *a) experienced rejection of transplanted organ within 6 months of transplantation* *b) currently on high doses of immunosuppressive therapy (per discretion of the Investigator)* *c) scheduled for organ transplantation. Note: being on a waiting list for kidney transplant is not exclusionary* 19. ***Active*** or chronic gastrointestinal bleeding 25. Subject has a history of alcohol or drug abuse within ***6 months*** prior to screening	accrue subjects meeting TSAT/ferritin eligibility criteria (see also updates to eligibility criteria related to TSAT and ferritin levels). This will improve the screening success rate without altering the patient population intended for inclusion in this study, and will help shorten the screening period by minimizing the need for additional screening visits to retest these parameters RBC transfusion was updated to state within 4 weeks instead of 8 weeks prior to randomization. It is not expected to impact baseline Hb and there are no additional safety concerns. "at the time of randomization" has been added to clarify the timing of exclusion #4 due to this criterion. "at screening" has been added to clarify the timing of exclusion #6 due to this criterion. Changing from renal ultrasound to renal imaging will allow all acceptable imaging options eg, ultrasound, CT scans, MRI etc. 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. 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) "Known" was removed to clarify exclusion criterion #19 applies to only active gastrointestinal bleeding. Potential subjects with no history of alcohol or drug abuse was updated from within 2 years to within 6 months to allow more subjects to qualify and does not pose any additional safety risk.	

Description of Change	Rationale for Change	Section(s) Affected [a]
Treatment Period (added text is italicized, revised text is bolded and italicized): Treatment duration is variable for individual subjects. *In order to complete the Treatment Period simultaneously for all study subjects, the minimum treatment duration may be less than 52 weeks,* with a maximum treatment duration of up to approximately 3 years after the last subject is randomized. *Subjects will be informed at least 4 weeks prior to their treatment period end.*	In order to complete the Phase 3 program in a timely manner and simultaneously for all study subjects, the minimum treatment duration of subjects enrolled after March 2017 (as part of Amendment 4) may be less than 52 weeks. Such subjects will be informed at least 4 weeks in advance if such a decision is made.	Synopsis, Section 3.1
Procedures for Handling Incorrectly Enrolled Subjects The following section was added: *Subjects who fail to meet all eligibility criteria should not be enrolled. If it is discovered in retrospect that a subject did not meet all eligibility criteria, the Investigator should inform the Medical Monitor immediately, and a discussion should occur regarding whether or not to discontinue the study subject. All decisions from such a discussion should be appropriately documented.*	This language was added to align the protocol with a new SOP for protocol templates	Section 3.3
Excessive Hematopoiesis The following section was added: *For subjects randomized to roxadustat, the following scenarios are defined as "excessive hematopoiesis";* • *Hb increases by > 2.0 g/dL at any time within a 4 week period: reduce the dose by one dose step.* • *Hb reaches or exceeds 13 g/dL: hold dosing, check Hb weekly. Resume dosing when Hb < 12.0 g/dL (for US subjects central lab Hb value preferred), at a dose that is reduced by two dose steps.* *For subjects on prolonged dose hold with stable (not dropping) Hb, the Investigator may use discretion to schedule less frequent visits.* *Anytime Hb is assessed via HemoCue®/CritLine®/local lab, a central lab Hb should be obtained as well.*	Instructions have been added to the body of the protocol, specifying when to reduce or hold dosing in case of excessive Hb rate of rise, in order to further emphasize these specific dosing instructions; in addition, these instructions also allow for PI discretion to determine the frequency of visits, in case of prolonged dose-hold, with stable (not dropping) Hb	Section 3.5.3.4, Appendix 2
Investigational Product The following text was added (revised text is bolded and italicized): ***If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain Hb levels in the Maintenance Phase, the dosing frequency should be reduced in a step-wise fashion eg, TIW to BIW, BIW to QW, QW to Q-2 Week***	To provide further guidance on roxadustat dosing, if a subject requires further dose reductions from 20 mg TIW, given 20 mg is the lowest tablet strength available. Roxadustat subjects: various factors, such as discrepancies between HemoCue® Hb and Central lab Hb value, Investigator	Synopsis; Sections 3.5.2.1, 3.5.3.2, 3.5.3.3, 5.3.1, Appendix 2

Description of Change	Rationale for Change	Section(s) Affected [a]
etc. The following paragraphs were added to clarify: *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 study 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" (eg, Hb ≥ 13 g/dL, requiring a dose hold) or "Overdose" (prescribed >3.0 mg/kg per dose or 400 mg per dose whichever is lower)* *ESA administration in roxadustat subjects during hospitalization is not considered a protocol deviation if roxadustat is not allowed or available during that hospitalization.* *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 study subjects are dosed according to local standard of care whether or not it is concordant with package insert/SmPC*	decision etc. can influence dose titration decisions at the time of the visit or after the visit. As a result, the dose prescribed may not exactly match the dose per the dose adjustment algorithm. However, as the stable dose would be achieved through titration, dosing discrepancy when subjects are dosed based on their clinical status is not considered a protocol deviation unless it is related to excessive hematopoiesis (≥13.0 g/dL, requiring a dose-hold) or overdose (>3.0 mg/kg/dose). Roxadustat subjects may receive ESA while hospitalized, in part due to lack of access to roxadustat while in hospital, and/or as part of hospital standard-of-care of anemia treatment; therefore, ESA administration in such circumstances is not considered a protocol deviation. EPO subjects; To allow flexibility with EPO dosing where investigators/sites are not able to follow epoetin-alfa package insert guidelines due to various factors including local standard of care, and clinical status of the subjects.	
Supplemental Iron Use: Text was modified as follows (added text is italicized, revised text is bolded and italicized) : In this study, oral iron ***should*** be allowed as first-line iron supplementation without restrictions, for both study arms. All subjects ***should*** be encouraged to take oral iron as the first-line iron supplementation during the Treatment Period, *except for subjects not tolerating oral iron.* *Intravenous iron supplementation is permitted if in the opinion of the Investigator the subject's Hb has not responded adequately and the subject is considered iron deficient.* *IV iron administration in study subjects during hospitalization is not considered a protocol deviation.*	Many ESRD patients cannot tolerate oral iron therapy due to GI adverse effects including GI bleeding. The modified text allows for that. 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. The original IV iron administration guidelines are considered overly restrictive and not in line with the current standard of care. Therefore, this section has been revised to allow IV iron per discretion of the PI. 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. Therefore, IV iron administered in study subjects while hospitalized is not considered a protocol deviation.	Synopsis; Sections 3.6.2.1, 3.6.2.2, Appendix 6

Description of Change	Rationale for Change	Section(s) Affected [a]
Rescue Therapy and Emergency Procedures: Text was modified as follows: From: Subjects who receive an ESA inadvertently (and do not meet the criteria above) may be allowed to continue on study, if considered safe by the Investigator and Medical Monitor. To: *Inadvertent ESA administration, including ESA administration by hospital staff in roxadustat subjects, should not be counted as rescue, unless above criteria are met; these subjects may be allowed to continue on study, if considered safe by the Investigator and Medical Monitor.* The following paragraph was updated to (added text is italicized): Subjects may receive one course of ESA rescue during the Treatment Period. Erythropoiesis-stimulating agent rescue should stop after 4 weeks or once Hb exceeds 9 g/dL, whichever occurs first. *If a subject requires more than 4 weeks of ESA rescue therapy due to inadequate Hb response, the Medical Monitor should be contacted.*	ESA therapy is the only standard of care to treat anemia in ESRD patients. It is a common practice to administer ESA during dialysis session. Clarification has been added that inadvertent ESA administration, or ESA administration by 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.	Synopsis; Section 3.6.3.2
Contraception The following section was added: *In female subjects of childbearing potential, a serum pregnancy test will be done per the Schedule of Assessments (Appendix 3) to rule out pregnancy. A pregnancy test is not required for female subjects of no childbearing potential eg, postmenopausal (determination whether a woman is post-menopausal is at the discretion of the Investigator), surgically sterile, etc.*	This language was added to align the protocol with a new SOP for protocol templates	Section 3.6.6
Additional Screening Section was updated as follows (added text is italicized, revised text is bolded and italicized): *Screening procedures that are not done at the scheduled visit must be completed prior to randomization.* If subjects fail screening, they may be re-screened once as deemed appropriate ***by the investigator. Where possible, an approval should be obtained from the Medical Monitor prior to rescreening.***	To allow further flexibility for subjects during the screening period. This would allow further subjects to participate.	Section 6.1.1.3

Description of Change	Rationale for Change	Section(s) Affected [a]
Treatment Period **Section 6.1.2.3 was changed from:** Weeks 6 to 24 (Every 2 weeks, ± 2 days) To: Weeks 6 to 24 (Every 2 weeks, ± ***4*** days) **Section 6.1.2.4 was changed from:** Weeks 28 to End of Therapy (Every 4 weeks, ±3 days) To: Weeks 28 to End of Therapy (Every 4 weeks, ±***4*** days) **Section 6.1.2.5 was changed from:** End of Treatment (± 3 days) To: End of Treatment (± *7* days) Appendix 3 was updated to align with the above sections	The increased visit window update was made to avoid unnecessary protocol deviations given dialysis sessions are scheduled in general every other day, the 4-day window will allow subjects who miss one dialysis session to be within the visit window.	Section 6.1.2.3, 6.1.2.4, 6.1.2.5, Appendix 3
Subject Discontinuation Adverse Events was added as a possible reason for subject discontinuation from the study.	The schedule of Assessments already includes this assessment at the discontinuation visit. The text was updated to match the table.	Section 6.1.3.2
HemoCue®/CritLine® Section was updated as follows: ***Anytime an Hb is obtained via such a point-of-care device, a central lab Hb should be obtained as well, either as part of the regular visit labs, or anytime when a point-of-care Hb is obtained at unscheduled visits, such as during dose-hold for excessive hematopoiesis.***	Instructions were added to obtain a central laboratory Hb anytime a HemoCue®/CritLine® or other local Hb is obtained, for proper documentation in the central laboratory database, and to improve Sponsor oversight	Section 6.4.1
Protocol Deviation: Text has been added to pre-specify issues that are not considered protocol deviations. Added text reads as follows: *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 to, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.* *Guidelines related to roxadustat, epoetin-alfa, and IV iron administration deviations are described in the respective sections.*	This section was added to align the protocol with a new SOP for protocol templates.	Section 8.4.6

Description of Change	Rationale for Change	Section(s) Affected [a]
Adverse Event Eliciting/Reporting Added clarification regarding action taken with study drug (added text is bolded and italicized): *Action taken regarding study drug (**action taken by PI in response to an AE**)*	To clarify that "Action taken regarding the study drug" refers to PI's decision in response to an AE (eg, 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)	Section 9.3.2
Pregnancies: Reporting and Follow-up of Subjects Added clarification regarding confirmation of pregnancy (added text is italicized and bolded) A pregnancy in a female subject or a male subject's female partner must be confirmed by positive serum β-hCG test(s). ***If pregnancy is suspected, study drug may need to be interrupted until pregnancy is ruled out.***	Text is added to reflect the current clinical practice to confirm pregnancy in this patient population (known to have high false positive pregnancy results). Also, to minimize exposure to the fetus as a precaution (in case pregnancy is confirmed).	Section 9.3.6
Disease Progression The following section was added: *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.*	This language was added to align the protocol with a new SOP for protocol templates	Section 9.3.8
Blood Pressure and Heart Rate Measurement Guidelines Revised BP and HR measurement guidelines (added text is bolded and italicized): Blood pressure ***should*** be measured in triplicate (***preferred***) with at least one minute interval between the measurements. Heart rate (HR) ***should*** be measured in triplicate (***preferred***) with at least one minute interval between the measurements.	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.	Appendix 5
Sample Size Determination The following section was added: *(ie, the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment).*	The analysis of EMA primary endpoint is to be more specifically described in the section.	Section 8.1

Description of Change	Rationale for Change	Section(s) Affected [a]
Potential EMA Interim Analysis Potential EMA interim analysis description part was removed.	Minimum 52-week treatment was not a requirement anymore per FDA response. Hence, no such Potential EMA interim analysis.	Section 8.3
Analysis Model Description a) Other stratification factors changed to randomization stratification factors in the model terms. b) Factors were updated to fixed effects in the model terms. c) LOCF was removed from MMRM models. d) Visit and interaction of visit and treatment arm were removed from MI ANCOVA models and added to MMRM models	Changes a and b are making the wording more precise. Changes c and d are corrections.	Synopsis; Section 8.4.3.1, 8.4.3.2, 8.4.3.3
The Evaluation Period of Ex-US Submission Ex-US submission: Mean Hb change from baseline to the average level during the Evaluation Period, defined as "Week 28 until Week 36". It was Week 28 to Week 52. **Evaluation period for additional efficacy** Evaluation time frame for hemoglobin maintenance has been revised to Weeks 28 to 52 Evaluation time frame for mean change in Hb has been revised to "96 to 104 weeks of treatment"	EMA only required following up to Week 36. To align with other similar protocols under this Phase 3 program	Synopsis, Section 7.3, 8.4.3.2
Baseline Hb value calculation Added text regarding baseline Hb value calculation for subjects enrolled under Amendment 4. Revised text reads as follows (added text is italicized, revised text is bolded and italicized): *Baseline Hb is defined as the mean of **at least three** central laboratory Hb values: the last **two** screening Hb values prior to randomization plus the one pre-dose Hb value on Day 1of the Treatment Period.*	To align with the revised Inclusion Criteria #5	Section 8.4.3

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LIST OF ABBREVIATIONS

Abbreviation	Definition
~	approximately
Ab	antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance model
AST	aspartate aminotransferase
AV	arteriovenous
BIW	twice weekly
BP	blood pressure
CBC	complete blood count
CERA	continuous erythropoietin receptor activator
CFR	Code of Federal Regulations
CHr	reticulocyte hemoglobin content
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CYP	cytochrome P450
dBP	diastolic blood pressure
DD-CKD	dialysis-dependent chronic kidney disease
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	Ethics committee
ECG	electrocardiogram
eEPO	endogenous erythropoietin
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOT	end of treatment
EPO	erythropoietin

Abbreviation	Definition
EQ-5D-5L	European Quality Of Life questionnaire in 5 Dimensions, 5 Levels
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
HHD	Home-hemodialysis
HDL	high-density lipoprotein
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl hydroxylase
HIF-PHI	hypoxia-inducible factor 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 Harmonisation
IEC	independent ethics committee
IND	investigational new drug
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
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
MAA	Marketing Authorization Application
MACE	major adverse cardiac event
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MI ANCOVA	Multiple imputation Analysis of ANCOVA model
MMRM	Mixed Model Repeated Measures
N	sample size
n	subsample size
NDD-CKD	nondialysis-dependent chronic kidney disease
PD	peritoneal dialysis
PE	physical examination
PEY	patient-exposure-year
PK	pharmacokinetics
PPS	Per Protocol Set
QW	once weekly
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
sBP	systolic blood pressure
SF-36	The 36-Item Short Form Health Survey
SmPC	Summary of Product Characteristics
Tbili	total bilirubin

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIBC	total iron binding capacity
TIW	three times weekly
TSAT	transferrin saturation
ULN	upper limit of normal
USRDS	United States Renal Data System
VEGF	vascular endothelial growth factor
WBC	white blood cell

PROTOCOL SYNOPSIS

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of FG-4592 in the Treatment of Anemia in Incident-dialysis Patients
Protocol Number:	FGCL-4592-063
Investigational Product:	Roxadustat (FG-4592)
Target Population:	Incident dialysis patients with anemia due to end-stage renal disease (ESRD)
IND Number:	74,454
Study Phase:	Phase 3
Study Centers Planned:	Up to approximately 400 study centers worldwide
Number of Subjects Planned:	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) • Epoetin alfa (active control, up to approximately 600 subjects)
Primary Objectives:	Evaluate the efficacy and safety of roxadustat in the treatment of anemia in incident-dialysis subjects compared with Active Control.
Secondary Objectives:	• Evaluate the utilization of intravenous (IV) iron with roxadustat compared with Active Control • Evaluate effect of roxadustat on serum lipid parameters compared with Active Control • Evaluate the effect of roxadustat on blood pressure (BP) compared with Active Control • Evaluate time to achieve a hemoglobin (Hb) response compared with Active Control
Study Design:	This is a Phase 3, multicenter, randomized, open-label, active-controlled study to evaluate the efficacy and safety of roxadustat in the treatment of anemia in incident-dialysis subjects. The study periods are as follows: • **Screening Period:** Up to 6 weeks

- **Treatment Period:** Treatment duration is variable for individual subjects. In order to complete the Treatment Period simultaneously for all study subjects, the minimum treatment duration may be less than 52 weeks with a maximum treatment duration of up to approximately 3 years after the last subject is randomized. Subjects will be informed at least 4 weeks prior to their treatment period end.

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

A total of up to approximately 1200 subjects will be randomized to receive either roxadustat or Active Control (epoetin alfa) in a 1:1 ratio (Appendix 1).

Randomization is stratified by geographical region, screening Hb values, and cardiovascular/cerebrovascular/thromboembolic medical history.

Scheduled Visits During Treatment

During the Treatment Period, subjects will attend weekly study visits from Weeks 0 to 4, followed by every other week study visits starting Week 6 until Week 24. Starting with Week 28, subjects will attend study visits every 4 weeks until the end of the Treatment Period.

After the Treatment Period, subjects will proceed to the 4-week Post-Treatment Follow-up Period.

Starting Dose of Study Drug

Roxadustat Arm

For subjects receiving roxadustat, the initial dose (per dose amount) is based on a tiered, weight-based dosing scheme (Table S1). Roxadustat will be dosed orally three times weekly (TIW) throughout the Treatment Period, except if a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain an Hb levels in the Maintenance Phase, the dosing frequency should be reduced in a step-wise fashion eg, TIW to BIW, BIW to QW, QW to Q-2 Week etc..

Epoetin Alfa Arm

- Subjects on hemodialysis (HD) receiving epoetin alfa will initiate IV epoetin alfa treatment according to the epoetin alfa US Package Insert (USPI) or Summary of Product Characteristics (SmPC).
- For subjects on home-hemodialysis (HHD) or peritoneal dialysis (PD), epoetin alfa will be administered according to the epoetin USPI or SmPC, or local standard-of-care.

Table S1. Initial Study Drug Dosing

Study Drug (Dose Frequency)	Low Wt (≤ 70 kg)	High Wt (> 70 to160 kg)
Roxadustat (TIW)	70 mg	100 mg
Epoetin alfa HD (TIW)	IV dosing according to epoetin alfa USPI or SmPC	
Epoetin alfa PD/HHD	Epoetin alfa should be administered according to the USPI or SmPC or local standard of care.	

Abbreviations: HD = hemodialysis; HHD= home-hemodialysis; IV = intravenous; PD = peritoneal dialysis; SmPC = summary of product characteristics; TIW = three times a week; USPI = United States Package Insert; wt = weight.

Note: Weight in HD subjects = subject's dry weight.

Dose Adjustments for Roxadustat

Dose adjustments will occur in two separate dosing phases: the Correction Phase and the Maintenance Phase. Each of these phases will follow unique dose adjustment rules according to Appendix 2. All subjects in the roxadustat arm will be dosed orally TIW during the Treatment Period. The maximum roxadustat dose is 3.0 mg/kg per dose or 400 mg, whichever is lower.

All dose adjustments as well as assessments of excessive hematopoiesis are based on Hb values using a point-of-care device such as HemoCue® or CritLine®. In the event that the central lab Hb value of the site visit is significantly different and the dose adjustment decision based on the HemoCue® or CritLine® value is being reconsidered, the Medical Monitor should be contacted, if possible.

The determination of Hb response and transition from the Correction to the Maintenance Phase of the study is based on the central laboratory Hb value.

Correction Phase of Dosing for Roxadustat

The aim of the Correction Phase is to increase Hb levels from baseline to the target Hb level by using the dose adjustment algorithm in Appendix 2. This phase is variable in length for each subject.

Dose adjustment reviews will occur on Week 4, and at intervals of every 4 weeks thereafter (Weeks 8, 12, 16, etc.) except in the event of excessive hematopoiesis, in which case doses may be adjusted at any time. In such cases, dose adjustment reviews are resumed at 4-week

	intervals. For example, if the subject's Hb increases >2.0 g/dL from Week 1 to Week 3, the subject's dose is reduced by one dose step at Week 3. The next dose adjustment review should occur 4 weeks later at Week 7 and at 4-week intervals thereafter. If the dose adjustment interval falls on a non-study visit week (starting Week 4), the dose adjustment review should be performed at the next scheduled clinic visit, if a dose adjustment was not required at the previous visit. For example, if a subject's visit is scheduled for Weeks 6 and 8, and the dose adjustment would occur at Week 7, then the dose adjustment should be evaluated at the Week 8 visit. .M**aintenance Phase of Dosing for Roxadustat** The aim of the Maintenance Phase is to maintain Hb levels after the initial correction by using the dose adjustment algorithm in Appendix 2. **Dosing and Dose Adjustment for Active Control Arm (Epoetin alfa)** Subjects on epoetin alfa should maintain their Hb levels within the target range accepted by their health authorities, specifically: • Hb 10 to 11 g/dL in the United States • Hb 10 to 12 g/dL in countries outside the United States Subjects receiving HD on epoetin alfa will be dosed IV TIW, with starting doses and dose adjustment rules according to the epoetin alfa USPI or SmPC. HD subjects requiring ultra-low dose of EPO (eg, ≤1000 IU/per week), frequency of administration may be adjusted per local standard of care. Subjects receiving PD or HHD on epoetin alfa will be dosed according to the epoetin alfa USPI or SmPC, or local standard of care. For countries using prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest calculated weekly dose. **Excessive Hematopoiesis** For subjects randomized to Roxadustat, the following scenarios are defined as "excessive hematopoiesis" ; • Hb increases by > 2.0 g/dL at any time within a 4 week period: reduce the dose by one dose step. • Hb reaches or exceeds 13 g/dL: hold dosing, check Hb weekly. Resume dosing when Hb < 12.0 g/dL (for US subjects central lab Hb value preferred), at a dose that is reduced by two dose steps. For subjects on prolonged dose-hold, with stable (not dropping) Hb, the Investigator may use discretion to schedule less frequent visits.

Anytime Hb is assessed via HemoCue®/CritLine®/local lab, a central lab Hb should be obtained as well.

Supplemental Iron Use

In a Phase 2 study of roxadustat, in which study subjects were randomized to either receive no iron, oral iron or IV iron, there was no significant difference in Hb levels in subjects receiving oral iron compared to subjects receiving IV iron. Therefore, based on the mechanism of action of roxadustat and the Phase 2 study results, in subjects randomized to roxadustat, oral iron may be sufficient for iron supplementation.

In this study, oral iron should be allowed as first-line iron supplementation without restrictions, for both study arms.

In addition to the scheduled assessments (Appendix 3), 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.

a) *Oral Iron Supplementation*

All subjects should be encouraged to take oral iron as the preferred first-line iron supplementation during the Treatment Period, except subjects not tolerating oral iron. The dose and frequency are at the discretion of the Investigator. Oral iron supplementation should be started before the subject becomes iron depleted.

b) *Intravenous Iron Supplementation*

Intravenous iron supplementation is permitted if in the opinion of the Investigator the subject's Hb has not responded adequately, and the subject is considered iron-deficient.

Treatment with study medication will continue during IV iron administration. Discontinuation of IV iron is recommended once the subject is no longer deemed iron deficient (eg, ferritin ≥ 100 ng/ml [≥ 220 pmol/L], TSAT ≥ 20%) and has evidence of a hematopoietic response.

Rescue Therapy Guidelines

Rescue therapy guidelines are provided to standardize the use of rescue therapy.

Red Blood Cell Transfusion

Red blood cell (RBC) transfusion should be considered if rapid correction of anemia is required to stabilize the subject's condition (eg, acute hemorrhage) and the Investigator is of the opinion that the blood transfusion is a medical necessity. Study drug treatment may continue

	during RBC transfusion administration. *Erythropoiesis Stimulating Agents (Roxadustat Arm only)* The use of erythropoiesis-stimulating agents (ESAs) is not permitted during the Treatment Period, except if all of the following criteria are met: • A subject's Hb level has not responded adequately despite two or more consecutive roxadustat dose increases or the roxadustat dose has reached the maximum dose limit • Other causes for lack of response or declining Hb, such as iron deficiency, bleeding, acute inflammatory conditions, have been ruled out • Reducing risk of alloimmunization in transplant eligible patients is a goal. Roxadustat and ESA may not be co-administered. Treatment with an approved ESA may be initiated ≥ 3 days after the last roxadustat dose. If the situation permits, the Investigator should inform the Medical Monitor prior to initiation of ESA therapy. Subjects may receive **one course** of ESA rescue during the Treatment Period. Erythropoiesis-stimulating agent rescue should stop after 4 weeks or once Hb exceeds 9 g/dL, whichever occurs first. If a subject requires more than 4 weeks of ESA rescue therapy due to inadequate Hb response, the Medical Monitor should be contacted. Treatment with roxadustat may resume after the following intervals: • Two days after stopping epoetin alfa • One week after stopping darbepoetin alfa • Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera®) If more than one course of ESA rescue is required during the Treatment Period, the subject must be discontinued permanently from the study, and is considered a Treatment Failure. Inadvertent ESA administration including ESA administered by hospital staff in Roxadustat subjects should not be counted as rescue unless, above criteria are met; these ssubjects may be allowed to continue on study, if considered safe by the Investigator and Medical Monitor. **Therapeutic Phlebotomy** If there are clinical concerns of excessive elevation of Hb levels, the Investigator may decide to perform a therapeutic phlebotomy in addition to a dose hold. This should be discussed with the Medical

	Monitor and documented.
Inclusion Criteria:	1. Age ≥ 18 years. 2. 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. 3. Receiving HD or PD for end-stage renal disease (ESRD) for a minimum of 2 weeks and a maximum of 4 months, prior to randomization. 4. Hemodialysis access consisting of an arteriovenous (AV) fistula, AV graft, or tunnelled (permanent) catheter; or PD catheter in use. 5. Mean of the two most recent Hb values during the Screening Period, obtained at least 2 days apart, must be ≤ 10.0 g/dL, with a difference of ≤ 1.3 g/dL between the highest and the lowest values. The last Hb value must be drawn within 10 days prior to randomization. 6. Ferritin ≥ 100 ng/mL (≥ 220 pmol/L); subjects with ferritin level < 100 ng/mL (<220pmol/L) during screening qualify after receiving iron supplementation (per local standard of care), without the need to retest ferritin prior to randomization. 7. Transferrin saturation ≥ 20%; subjects with TSAT level < 20% during screening qualify after receiving iron supplementation (per local standard of care), without the need to retest TSAT prior to randomization. 8. Serum folate level, performed within 8 weeks prior to randomization ≥ lower limit of normal (LLN); subjects with serum folate level < LLN during screening qualify after receiving folate supplement (per local standard of care), without the need to retest folate prior to randomization. 9. Serum vitamin B_{12} level, performed within 8 weeks prior to randomization ≥ LLN; subjects with vitamin B12 level < LLN during screening qualify after receiving Vitamin B12 supplement (per local standard of care), without the need to retest Vitamin B12 prior to randomization. 10. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN), and total bilirubin (Tbili) ≤ 1.5 x ULN. 11. Body weight up to 160 kg (HD subjects: dry weight).

Exclusion Criteria:	1. Total duration of prior effective ESA use must be ≤3 weeks within the preceding 12 weeks at the time informed consent is obtained. **Specific dosing guidance, depending on the type of ESAs, injected IV or SC within 12 weeks prior to start of screening are as follows:** <u>Short-acting ESAs (EPO-alfa or equivalents)</u> • IV: Up to 9 doses; last EPO dose must be ≥2 days prior to start of screening • SC: Up to 3 doses; last EPO dose must be ≥1 week (7 days) prior to start of screening <u>Darbepoetin</u> • IV: Up to 3 doses; last darbepoetin dose must be ≥1 week (7 days) prior to start of screening • SC: Up to 2 doses; last darbepoetin dose must be ≥2 weeks (14 days) prior to start of screening <u>Continuous erythropoietin receptor activator (CERA)</u> • IV or SC: Up to 2 doses; last CERA dose must be ≥2 weeks (14 days) prior to start of screening 2. Intravenous iron: there is no restriction regarding IV iron use during screening, provided it is administered in accordance with local standard of care.. 3. Red blood cell transfusion within 4 weeks prior to randomization. 4. Active, clinically significant infection that could be manifested by white blood cell (WBC) count > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection at the time of randomization. 5. History of chronic liver disease (eg, chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver). 6. New York Heart Association Class III or IV congestive heart failure at screening. 7. Myocardial infarction (MI), acute coronary syndrome, stroke, seizure, or a thromboembolic event within a major vessel (excluding vascular dialysis access) (eg, deep vein thrombosis [DVT] or pulmonary embolism) within 12 weeks prior to randomization. 8. Uncontrolled hypertension, in the opinion of the Investigator, (eg, that requires change in anti-hypertensive medication) within 2 weeks prior to randomization.

	9. Renal imaging performed within 12 weeks prior to randomization indicative of a diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category 2 or higher) of renal cell carcinoma. 10. History of malignancy, except for the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps. 11. Positive for any of the following: human immunodeficiency virus (HIV); hepatitis B surface antigen (HBsAg); or anti-hepatitis C virus antibody (anti-HCV Ab). 12. Chronic inflammatory disease that could impact erythropoiesis (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission. 13. Known, untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration, or retinal vein occlusion (subjects who are already blind for the above reasons qualify to participate). 14. Known history of myelodysplastic syndrome or multiple myeloma. 15. 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). 16. Known hemosiderosis, hemochromatosis, coagulation disorder, or a hypercoagulable condition. 17. Organ transplant: subjects with any of the following. a) Experienced rejection of a transplanted organ within 6 months of transplantation b) Currently on high doses of immunosuppressive therapy (per discretion of the investigator) c) Scheduled for organ transplantation. Note: being on the waiting list for kidney transplant is not exclusionary 18. Anticipated elective surgery, except for vascular access surgery or dialysis catheter placement, that is expected to lead to significant blood loss, or anticipated elective coronary revascularization. 19. Active or chronic gastrointestinal bleeding. 20. Any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). 21. Use of iron-chelating agents within 4 weeks prior to randomization. 22. Known hypersensitivity reaction to any ESA. 23. Use of an investigational drug or treatment, participation in an

	investigational study, or presence of an expected carryover effect of an investigational treatment, within 4 weeks prior to randomization. 24. Anticipated use of dapsone or androgens at any dose amount or chronic use of acetaminophen or paracetamol > 2.0 g/day during the study. 25. History of alcohol or drug abuse within 6 months prior to randomization. 26. Females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception. 27. Pregnant or breastfeeding females. 28. Any medical condition, that in the opinion of the Investigator, may pose a safety risk to a subject in this study, may confound efficacy or safety assessment, or may interfere with study participation. Subjects who fail to meet the above eligibility criteria should not be randomized or receive study medication. If Day 1 lab values (collected prior to administration of study medication) are found to be of significant safety risk, in the opinion of the Investigator or Medical Monitor, the subject may be discontinued from the study.
Study Procedures:	See Schedule of Study Assessments (Appendix 3)
Roxadustat Formulation, Dose, and Mode of Administration:	Roxadustat tablets are available in 20, 50, and 100 mg doses for oral administration. All tablets must be administered whole. ***Initial Doses*** Subjects will receive tiered, weight-based initial doses (Table S1) ***Dosing Frequency*** Subjects will be dosed TIW throughout the Treatment Period. Dosing frequency may be reduced if a subject requires < 60 mg/week to maintain Hb levels in the Maintenance Phase. ***Dose Adjustment Rules*** Refer to Section 3.5.3, and Appendix 2.
Reference Therapy:	Active Control: Epoetin alfa for injection Hemodialysis subjects: Initial dose and dose adjustments rules according to the epoetin alfa USPI or SmPC. For countries using prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest calculated total weekly dose. Peritoneal Dialysis and HHD subjects: Epoetin alfa should be administered according to the epoetin alfa USPI or SmPC, or local

	standard of care. For countries using prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest calculated total weekly dose.
Efficacy Endpoints and Assessments:	In the endpoint definitions below, rescue therapy for roxadustat-treated subjects is defined as either ESA rescue or RBC transfusion; rescue therapy for epoetin alfa-treated subjects is defined as RBC transfusion. All endpoints using Hb are based on central lab. ***Primary:*** • **US (FDA) submission**: Mean Hb change from baseline (using central laboratory values) to the average level during the Evaluation Period, defined as Week 28 until Week 52. This analysis will be based on the intent-to-treat (ITT) population. Hemoglobin values under the influence of rescue therapy will not be censored for the primary analysis. • **Ex-US submission**: The proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response in the Per Protocol Set (PPS). A Hb response is defined, using central laboratory values, as: o Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or o Increase in Hb ≥ 2.0 g/dL in subjects whose baseline Hb ≤ 8.0 g/dL ***Secondary:*** • **US (FDA) submission**: The proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response. A Hb response is defined, using central laboratory values, as o Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or o Increase in Hb ≥ 2.0 g/dL in subjects whose baseline Hb ≤ 8.0 g/dL • **Ex-US submission**: Mean Hb change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 36. This analysis will be based on the PPS population. US and ex-US:

	• Average monthly IV iron use per subject during the Treatment Period • Mean change in low-density lipoprotein (LDL) cholesterol averaged over Weeks 12 to 24 • Blood pressure effects: o Proportion of subjects with exacerbation of hypertension, meeting at least one of the following criteria: - Increase in blood pressure: An increase from baseline in systolic blood pressure (sBP) of ≥ 20 mm Hg and sBP > 170 mmHg, or an increase from baseline in dBP of ≥ 15 mm Hg and diastolic blood pressure (dBP) > 100 mmHg. Increases from baseline in BP must be confirmed by repeat measurement - Time to an increase in BP as defined above - Mean change in mean arterial pressure (MAP) averaged over Weeks 8 to 12 • Time to achieve first Hb response as defined by the primary endpoint, (ex-US) (which is the secondary endpoint for the US [FDA] submission).
Safety Assessments and Endpoints:	Study-specific safety will be assessed by evaluating the following: • Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), and clinically significant laboratory values from baseline • Vital signs, electrocardiogram (ECG) findings 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: • Death from any cause, MI, stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, hypertensive emergency, deep venous thrombosis, 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 pooled Statistical Analysis Plan (SAP). **For US (FDA) Only**: The primary safety endpoint in this study is the Major Adverse Cardiac Event (MACE) 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. • 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.
Statistical Methods:	***Sample Size Estimation*** The sample size calculation is based on the primary endpoint for both the United States and Ex-US. 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 pre-specified 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 a comparable time frame. With at least 600 subjects, the study will provide at least 99% power to demonstrate statistical non-inferiority 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). This assumes a difference (roxadustat minus ESA) of 0.30 g/dL, a non-inferiority margin for this difference of 0.75 g/dL and a standard deviation of 1.25 g/dL. This endpoint will be analyzed using the ITT population for the US FDA submission. The study will provide at least 99% power to demonstrate statistical non-inferiority of roxadustat versus ESA in the primary endpoint outside of the United States (ie, the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment). This assumes an 80% responder rate for both roxadustat and epoetin alfa, in order to support the primary efficacy analysis (ie, a

non-inferiority comparison in responder rate between roxadustat and epoetin alfa) and assuming a non-inferiority margin of -15% for this difference (roxadustat minus epoetin alfa). This endpoint will be analyzed using the PPS population for the European Medicines Agency (EMA) submission.

Statistical Analysis

1. Efficacy analysis for superiority will be conducted on the ITT population for US (FDA) submission and on the full analysis set (FAS) population, for Ex-US submission.
2. Efficacy analysis for non-inferiority will be conducted on the ITT population for US (FDA) submission and on the PPS population, for Ex-US submission.
3. Hemoglobin results obtained from the central laboratory will be used for all efficacy analyses. Baseline Hb is defined as the mean of at least three central laboratory Hb values: at least the last two screening Hb values prior to randomization plus the one predose Hb value on Day 1 of the Treatment Period.

Primary Efficacy Analysis

US (FDA) submission: The primary efficacy endpoint for submission in the United States is defined as the mean 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 ITT population. Hb values under the influence of rescue therapy will not be censored for the primary efficacy analysis.

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 arm ≤ Hb mean change from baseline in the epoetin alfa arm 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 arm > Hb mean change from baseline in the epoetin alfa arm minus 0.75 g/dL

A multiple imputation Analysis of Ancova Model (MI ANCOVA) will be used for the primary endpoint.

The model will contain terms for treatment arm, baseline measurement, and randomization stratification factors (except screening Hb values (≤ 8g/dL vs. >8g/dL). The primary efficacy analysis will be based on the estimated difference between the two treatments overall mean effects throughout the study based on the MI ANCOVA model.

In addition, as a sensitivity analysis, the primary efficacy endpoint will be analyzed using the analysis of the mixed model for repeat measures

	(MMRM). 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 (≤ 8g/dL vs. >8g/dL) as fixed effects. Due to the large amount of visits included in the 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. This null hypothesis will be rejected if the two-sided 95% confidence interval (CI) for the difference of least square means from the mixed model lies entirely above –0.75 g/dL. **Ex-US Submission**: The primary efficacy endpoint for Ex-US submission is defined as the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response. • A Hb response is defined, using central laboratory values, as: Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or • Increase in Hb ≥ 2.0 g/dL in subjects whose baseline Hb ≤ 8.0 g/dL. Rescue therapy for roxadustat treated subjects is defined as ESA rescue or RBC transfusion, and rescue therapy for epoetin alfa treated subjects is defined as RBC transfusion. The hypothesis to be tested for the primary efficacy analysis is: *H_0: Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm ≤ -15%.* *Versus* *H_1: Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm > -15%.* A two-sided 95% CI for the difference of 2 responder rates (roxadustat minus epoetin alfa) based on the Miettinen and Nurminen approach adjusting for treatment and other stratification factors will be calculated and the null hypothesis will be rejected if the lower bound of the 95% CI is greater than -15%. ***Safety:***

	All subjects who have received any dose of study treatment will be included in the safety analyses. All safety data will be tabulated using descriptive statistics. Safety parameters include adverse events (AEs), serious adverse events (SAEs), laboratory parameters, vital signs, ECG parameters, and physical examinations (PE's). For each safety parameter, the last assessment made prior to the first dose of study medication will be used as the baseline for all analyses of that safety parameter. The analytical methods for the MACE endpoint, as well as other composite safety endpoints of interest, will be described in a region-specific pooled statistical analysis plan (PSAP) to reflect the nature of the pooling of these endpoints across comparable studies in the Phase 3 program and the region-specific safety endpoints. Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be conducted by an independent Data Safety Monitoring Board (DSMB).

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

1 INTRODUCTION

Roxadustat (FG-4592) is an investigational novel small molecule drug for oral administration that has not been marketed in any country. The drug is in global Phase 3 clinical development. It is being developed for the treatment of anemia associated with chronic kidney disease (CKD), including end-stage renal disease (ESRD).

1.1 Background Information

1.1.1 Epidemiology of CKD and ESRD

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

The number of patients suffering from ESRD also continues to increase worldwide. The US has one of the highest prevalence rates of ESRD in the world: in 2010, the US had over 1700 ESRD patients per million population, a 23% increase compared with 10 years prior (United States Renal Data System (USRDS, 2011) Vol 2, Ch 1, p188). In 2009 (point prevalence Dec 31), there were approximately 570,000 ESRD patients in the US, of whom 370,000 were receiving hemodialysis (HD), 27,000 were receiving peritoneal dialysis (PD), and 173,000 had a functioning kidney transplant (USRDS, 2011) [Vol 2, Ch 1, p184]. The average expected life expectancy of a dialysis patient is 5.9 years, compared with 16.4 years for a transplant patient, and 25.2 years for someone of comparable age in the general population (USRDS, 2011) [Vol 2, Ch 2, p 181]. The prevalence of ESRD is projected to grow to 774,000 by the year 2020 (USRDS, 2009) [Vol 2, Ch 2].

1.1.2 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 erythropoietin (EPO), a hormone produced primarily in the kidneys, is considered an important etiologic factor. The impaired ability of the body to absorb and utilize iron is likely a second important etiologic factor.

Anemia may present in 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 CKD who have not yet progressed to dialysis (Coresh, 2007; Go, 2004). Over 90 % of patients undergoing dialysis are anemic. Half of new dialysis patients (50.1%) have hemoglobin (Hb) levels below 10 g/dL and approximately 28% have Hb levels below 9 g/dL (USRDS, 2003) [Ch 3, Figure 3.11].

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

Anemia contributes to the excess morbidity and mortality in CKD and ESRD. In patients with CKD, the severity of anemia correlates directly with the risk of hospitalization, cardiovascular

disease, and death (Collins, 1998). Patients with the lowest Hb have worse outcomes, as was discussed in the post hoc analysis of mortality by Hb quintiles for the Normal Hematocrit and Correction of Hb and Outcomes in Renal Insufficiency (CHOIR) studies in the FDA briefing document for the October 2007 Cardiovascular and Renal Advisory Committee (Unger, 2007). Similar observations are found in USRDS mortality data stratified by Hb. All-cause mortality stratified by Hb (1993–1996) showed significantly higher first-year death rates in patients with Hb levels < 9, compared with 11 to 12 g/dL. This trend continued to worsen, as reflected in 1998–1999 data, where the death rate rose by ~75% compared with the 1993–1996 period (USRDS, 2000) Ch 8, Fig 8.16; (USRDS, 2001) [Ch 9, Fig 9.14]. 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) [Ch 9, Table 9b]. The relative risk of cardiovascular hospitalization increases significantly to 1.26 in patients with Hb levels < 9 g/dL compared with those with Hb at 11 to 12 g/dL (USRDS, 2001) [Ch 5, Fig 5.27].

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

1.2 Treatment of 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 treatment of anemia in patients with CKD (Winearls, 1986; Eschbach, 1989; Eschbach, 1987), despite the documented safety risks. These safety risks include hypertension, thrombosis and cerebrovascular events and may be associated with the 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 ESRD and CKD nondialysis patients have shown higher mortality or trends in that direction in the higher-dosed ESA-treated cohorts when the protocol objective was to treat to high target Hb levels (Besarab, 1998, Drueke, 2006; Singh, 2006). An ESA dose relationship to mortality has been reported in a review of the USRDS database (Zhang, 2004) of ESRD patients who received higher ESA doses. Additionally, ESA therapy for anemia in ESRD patients on HD usually requires concomitant intravenous (IV) iron supplementation. IV iron is associated with its own set of risks, including anaphylaxis.

There is currently an unmet medical need for an oral treatment that can correct anemia in CKD nondialysis and dialysis patients while avoiding supraphysiologic levels of circulating plasma EPO levels, and also minimizes the use of IV iron.

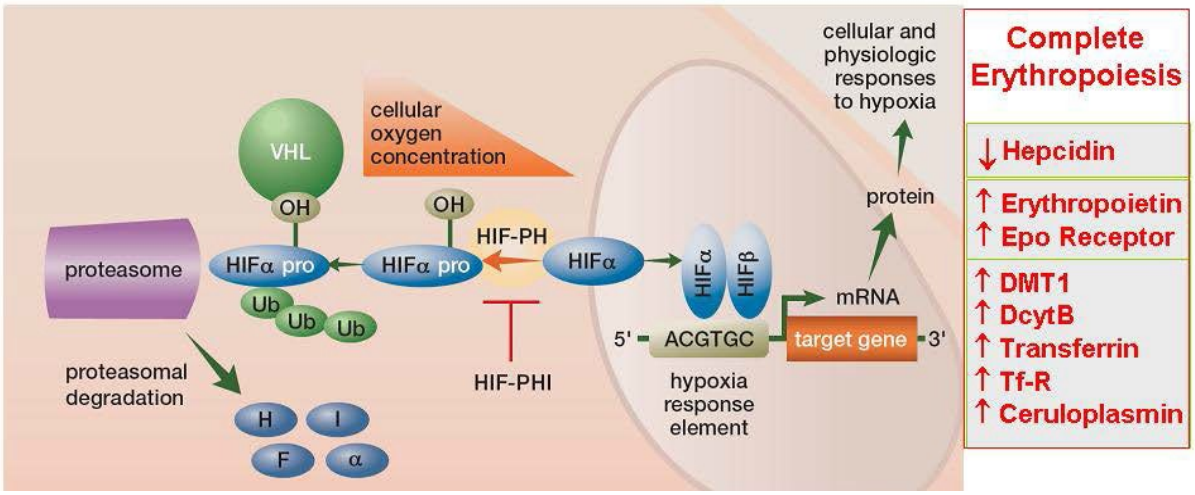
Roxadustat is an oral medication that could potentially deliver effective treatment for CKD-related anemia with less need for IV iron supplementation and without producing supraphysiologic levels of circulating EPO, which may translate into an improved safety profile.

1.3 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 (HIF) 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, 2005). Hypoxia-inducible factor is a heterodimeric transcription factor family comprising three oxygen-sensitive isoforms (HIF-1α, HIF-2α and HIF-3α), and a constitutively expressed HIF-1β subunit, with each heterodimeric isoform responsible for the induction of specific sets of genes (Greijer, 2005; Hu, 2003). For example, HIF-1α has been shown to regulate vascular endothelial growth factor (VEGF) expression (Gray, 2005; Buchler, 2003), while HIF-2α is critical for the induction of the EPO gene and erythropoiesis (Wamecke, 2004).

Figure 1 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. Cell, 2001 Oct 5; 107(1)

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

Although HIF-α isoforms are constitutively produced, their accumulation under normoxic conditions is prevented by recruitment and binding by the von Hippel-Lindau (VHL) protein, which targets HIF-α isoforms for degradation through the ubiquitin-proteasome pathway. The molecular mechanism for oxygen-dependent degradation of HIF-α is based on the hydroxylation of specific proline residues, as catalyzed by a family of hypoxia-inducible prolyl hydroxylases

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

Roxadustat is a potent and reversible hypoxia inducible 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. Hypoxia inducible prolyl factor induces expression of not only EPO, but also the EPO receptor and proteins that promote iron absorption and recycling (Peyssonnaux, 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 No. 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 anemias caused by inflammation-induced functional iron deficiency, which are typically hyporesponsive to ESAs. In these conditions, iron availability for erythropoiesis is reduced due to a number of inflammatory mediators, all of which increase Hepcidin levels, impairing iron transport to the bone marrow. 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, 2005).

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

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

1.4 Clinical Experience with Roxadustat

Roxadustat is currently being studied in dialysis and nondialysis CKD subjects with anemia. Seventeen clinical studies with roxadustat have been completed. Information from these studies is provided below and in the current Investigator's Brochure (IB).

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 subjects with nondialysis-dependent chronic kidney disease (NDD-CKD), and 298 dialysis-dependent subjects with chronic kidney disease (DD-CKD). 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 weekly (TIW) 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 subjects on dialysis 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 subjects with incident 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 subjects on incident-dialysis.

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

1.4.1 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 subjects on dialysis compared with healthy subjects.

A relative bioavailability study was conducted in 24 healthy volunteers comparing capsule formulation, which was used in Phase 1 and Phase 2, with tablet formulation, which was developed for Phase 3. The study demonstrated bioequivalence to bridge the 2 formulation. With an intermittent dose regimen (once weekly [QW], twice weekly [BIW], or TIW), no or limited accumulation in mean AUC or 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 Ki value was observed for CYP 2C8 (16 μM). In a clinical drug-drug interaction study with rosiglitazone, a probe drug for CYP 2C8, roxadustat did not show any inhibitory potential on CYP 2C8 in vivo.

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 erythropoietin (eEPO) (starting from single doses of 0.3 mg/kg), increases in reticulocytes (starting from doses of 2 mg/kg), and Hb responses (starting at 3 mg/kg). The mean peak level of plasma EPO following the Day 26 dose of 2.0 mg/kg TIW (the high therapeutic dose studied) was 326.3 ± 197.0 mIU/mL.

In pharmacodynamic studies conducted with roxadustat in CKD subjects not on dialysis (Study FGCL-4592-017), the mean maximum EPO increase from baseline ranged from 82 to 443 mIU/mL and 492 to 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 United States and in Japan (Study CL-1517-203) 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 PK profile. Also, comparable dose-dependent increases in EPO levels were observed with both predialysis and postdialysis dosing. These increases in eEPO were transient, peaked at around 10 hours postdose with eEPO levels returning to baseline 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 > 10,000 mIU/mL (Besarab, 2009). In a clinical study with subjects on dialysis, 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, 2007). This is approximately 10-fold higher than the physiologic range.

1.4.2 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 IB.

1.4.2.1 Studies in Subjects with NDD-CKD

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 ≥ 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 ≥11 g/dL as well as

increasing by ≥ 1.0 g/dL, the Hb responder rate with roxadustat 2.0 mg/kg was 89% and 91% in 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, 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 to 13 g/dL in 96 subjects and 10.5 to 12.0 g/dL in 48 subjects). Dose-response trends suggested that starting doses of 1.0 to1.6 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.

1.4.2.2 Studies in Subjects with DD-CKD

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 36-Item Short Form Health Survey (SF-36) Physical Functioning, Role physical, and Vitality scores, as well as in the Functional Assessment of Cancer Therapy-Anemia (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 low-density lipoprotein (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 with subjects randomized to continue epoetin alfa. Other serum iron parameters were not significantly different between the treatment arms.

1.4.2.3 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 subjects with CKD over 52 to 76-week treatment as of 07 September 2013.

1.4.3 Safety

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 cardiovascular events with roxadustat, or any effect on adverse event (AE) rates related to either increasing Hb levels or on the rate of change of Hb levels.

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 United States or Eastern Europe. In general, the most commonly reported AEs (≥ 4% and ≥ 1% above placebo rate) in healthy volunteers were headache and dizziness. The most commonly reported AEs (≥ 5%) in subjects with NDD-CKD were diarrhea, nausea, urinary tract infection, nasopharyngitis, peripheral edema, hyperkalemia, headache, and hypertension (none were ≥ 8%), The most commonly reported AEs (≥ 3%) in subjects with DD-CKD were diarrhea, nausea, hypertension, and upper respiratory tract infection (none were ≥ 5%). Adverse event rates of hypertension (1% in Study FGCL-SM4592-017and 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, 2009). No safety risks were associated with rate of rise of Hb levels or with achieving an 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

cardiovascular 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, 5 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 5 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 IB.

Of note, cholelithiasis is reported to be more common in subjects with CKD compared with 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 with 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. For detailed safety information, please refer to the most current version of the IB.

1.5 Summary

In summary, roxadustat is an orally active HIF-PHI with erythropoietic effects. Intermittent dosing of roxadustat results in transient activation of HIF, intermittent induction of endogenous

physiologic-range EPO, and dose-dependent erythropoiesis, suggesting 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 with anemia treated up to 60 weeks.

1.6 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 < 70 kg), medium (70 to 100 kg), or heavy (> 100 kg); and using an absolute starting dose regardless of body weight. The tiered weight-based approach has been chosen for the development of roxadustat in the Phase 3 program to provide a practical starting dose strategy for a controlled Correction to target Hb values, based on the observed relationship between body weight, PK, and Hb response, and the requirements of oral dosing.

The tiered, weight-based starting doses selected for this study consist of the following roxadustat doses: 70, and 100 mg, for low weight (≤ 70 kg), and high weight (> 70 to 160 kg) subjects, respectively. These dose tiers are based primarily on the interim safety and efficacy data generated in the CKD nondialysis Correction of anemia study (FGCL-4592-041) and confirmed by the dialysis study. These doses will be administered at a frequency of TIW. Using this dosing scheme, subjects will receive starting roxadustat doses between 0.9 mg/kg TIW for the heaviest subject, and 1.6 mg/kg TIW for the lightest subject. This is comparable to the starting doses of 1.0 to 1.6 mg/kg, which were the doses that effectively corrected Hb levels in studies FGCL-4592-041 and FGCL-4592-053. Further dose adjustment to achieve Correction and subsequent Maintenance is based upon regular monitoring of Hb.

Based on the Phase 2 data, it is expected that subjects who receive these starting doses to correct anemia will be able to maintain Hb levels with a total weekly dose reduction of the order of 22 to 35%. This dose reduction can be achieved by adjusting the per dose amount towards the protocol-defined Hb target range. The 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. Pre-specified 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.

1.7 Risks/Benefits of Roxadustat Treatment

The primary benefit of roxadustat is the treatment 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 cardiovascular risk may be lower than with ESAs.

An established dose adjustment algorithm will be used during the study to titrate roxadustat doses to enable subjects to achieve and maintain optimal Hb levels, while closely monitoring the rate of rise of Hb levels. Roxadustat doses may be held and/or the use of therapeutic phlebotomy is allowed in the event of excessive hematopoiesis. Adverse and serious adverse events (SAEs),

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 cardiovascular, cerebrovascular and thromboembolic events. In addition, an independent Data and Safety Monitoring Board (DSMB) will perform regular, periodic assessments of safety data 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.

2 OBJECTIVES

2.1 Primary Objectives

Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Incident-Dialysis Subjects, Compared with Active Control.

2.2 Secondary Objectives

The secondary objectives in this study are to:

- Evaluate the utilization of IV iron with roxadustat compared with Active Control
- Evaluate the effect of roxadustat on serum lipid parameters compared with Active Control
- Evaluate the effect of roxadustat on BP compared with Active Control
- Evaluate time to achieve a Hb response compared with Active Control

3 STUDY DESIGN

3.1 Description of the Study

This is a Phase 3, multicenter, randomized, open-label, and active-controlled study to evaluate the efficacy and safety of roxadustat in the treatment of anemia in incident-dialysis subjects.

The study periods are as follows:

- **Screening Period:** Up to 6 weeks
- **Treatment Period:** Treatment duration is variable for individual subjects. In order to complete the Treatment Period simultaneously for all study subjects, the minimum treatment duration may be less than 52 weeks, with a maximum treatment duration of up to approximately 3 years after the last subject is randomized. Subjects will be informed at least 4 weeks prior to their treatment period end.
- **Post-Treatment Follow-Up Period:** 4 weeks

3.2 Randomization and Treatment Assignment

A total of up to approximately 1200 subjects will be randomized in a 1:1 ratio to receive either open-label roxadustat or epoetin alfa (Appendix 1).

Randomization is stratified by the following factors:

- Geographical region
- Screening Hb values (≤ 8 g/dL vs. > 8 g/dL)
- Cardiovascular/cerebrovascular/thromboembolic medical history (Yes vs. No)

Randomization schedules will be prospectively prepared. Automated randomization and treatment assignments will be provided by an Interactive Voice and Web Response System (IXRS).

3.3 Procedures for Handling Incorrectly Enrolled Subjects

Subjects who fail to meet all eligibility criteria should not be enrolled.

If it is discovered in retrospect that a subject did not meet all eligibility criteria, the Investigator should inform the Medical Monitor immediately, and a discussion should occur regarding whether or not to discontinue the study subject. All decisions from such a discussion should be appropriately documented.

3.4 Replacement of Subjects

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

3.5 Study Treatment

3.5.1 Dose and Schedule

Eligible subjects will be randomized via IXRS to receive either roxadustat or epoetin alfa. The first study drug administration will be on Day 1 (Week 0).

3.5.2 Starting Dose of Study Drug

3.5.2.1 Roxadustat Arm

For subjects receiving roxadustat, the initial dose (per dose amount) is based on a tiered, weight-based dosing scheme (Table 1). Roxadustat will be dosed orally TIW throughout the Treatment Period, except if a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain Hb levels in the Maintenance Phase, the dosing frequency should be reduced in a step-wise fashion eg, TIW to BIW, BIW to QW, QW to Q-2 Week etc.

3.5.2.2 Active Control Arm (Epoetin alfa)

Subjects on HD will initiate intravenous (IV) treatment according to the epoetin alfa US Package Insert (USPI) or Summary of Product Characteristics (SmPC).

For subjects on HHD or PD, epoetin alfa will be administered according to the epoetin USPI, or SmPC or local standard-of-care.

For countries using prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest weekly dose.

Table 1 Initial Study Drug Dosing

Study Drug (Dose Frequency)	**Low Weight** (≤ 70 kg)	**High Weight** (> 70 to 160 kg)
Roxadustat (TIW)	70 mg	100 mg
Active Control HD (TIW)	IV dosing according to epoetin alfa Package Insert or SmPC.	
Active Control PD/HHD	Epoetin alfa should be administered according to the epoetin alfa Package Insert or SmPC or local standard of care.	

Abbreviations: HD = hemodialysis; HHD= home-hemodialysis; PD = peritoneal dialysis; SmPC = summary of product characteristics; TIW = three times a week.

Note: Weight in HD subjects = subject's dry weight.

3.5.3 Dose Adjustment for Roxadustat

Dose adjustments will occur in two separate study dosing phases: the Correction Phase and the Maintenance Phase. Each of these phases will follow unique adjustment rules according to Appendix 2.

All subjects will be dosed orally TIW during the Treatment period. The maximum roxadustat dose is 3.0 mg/kg per dose or 400 mg (whichever is lower).

All dose adjustments as well as assessments of excessive hematopoiesis are based on Hb values using a point-of-care device, such as HemoCue® or CritLine®. In the event that the central lab Hb value of the site visit is significantly different and the dose adjustment decision based on the HemoCue® / CritLine® value is being re-considered, the Medical Monitor should be contacted, if possible.

The determination of Hb response and transition from the Correction to the Maintenance Phase of the study is based on the central laboratory Hb value.

3.5.3.1 Correction Phase of Dosing for Roxadustat

- The aim of the Correction Phase is to increase Hb levels from baseline to the target Hb level by using the dose adjustment algorithm in Appendix 2.
- . This phase is variable in length for each subject.
- Dose adjustment reviews will occur on Week 4, and at intervals of every 4 weeks thereafter (Weeks 8, 12, 16, etc.), except in the event of excessive hematopoiesis, in which case doses may be adjusted at any time. In such cases, dose adjustment reviews are resumed at 4-week intervals. For example, if the subject's Hb increases > 2.0 g/dL from Week 1 to Week 3, the subject's dose is reduced by one dose step at Week 3. The next dose adjustment review should occur 4 weeks later at Week 7 and at 4-week intervals thereafter.
- If the dose adjustment interval falls on a non-study visit week (starting Week 4), the dose adjustment review should be performed at the next scheduled study visit if a dose adjustment was not required at the previous visit. For example, if a subject's visit is scheduled for Weeks 6 and 8, and the dose adjustment would occur at Week 7, then the dose adjustment should be evaluated at the Week 8 visit.

3.5.3.2 Maintenance Phase of Dosing for Roxadustat

- The aim of the Maintenance Phase is to maintain Hb levels after the initial correction by using the dose adjustment algorithm in Appendix 2.

Note: Note: 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 study 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" (eg, Hb ≥ 13 g/dL, requiring a dose hold) or "Overdose" (prescribed >3.0 mg/kg per dose or 400 mg per dose whichever is lower).

3.5.3.3 Active Control (Epoetin alfa) Subjects

Epoetin alfa subjects should maintain their Hb levels within the target range accepted by health authorities, specifically:

- Hb 10 to 11 g/dL in the United States (US)
- Hb 10 to 12 g/dL in countries outside the US

Hemodialysis subjects will be dosed IV TIW, with starting doses and dose adjustment rules according to the epoetin alfa USPI or SmPC. In subjects requiring ultra-low dose of EPO (eg, ≤1000 IU/per week), frequency of administration may be adjusted per local standard of care.

Home-hemodialysis and peritoneal dialysis subjects will be dosed according to the epoetin Package Insert or the SmPC or local standard of care.

For countries using prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest weekly dose.

Note: 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 study subjects are dosed according to local standard of care whether or not it is concordant with package insert/SmPC

ESA administration in roxadustat subjects during hospitalization is not considered a protocol deviation if roxadustat is not allowed or available during that hospitalization.

3.5.3.4 Excessive Hematopoiesis

For subjects randomized to Roxadustat, the following scenarios are defined as "excessive hematopoiesis"

- Hb increases by > 2.0 g/dL at any time within a 4 week period: reduce the dose by one dose step.
- Hb reaches or exceeds 13 g/dL: hold dosing, check Hb weekly. Resume dosing when Hb < 12.0 g/dL (for US subjects central lab Hb value preferred), at a dose that is reduced by two dose steps.

For subjects on prolonged dose-hold, with stable (not dropping) Hb, the Investigator may use discretion to schedule less frequent visits.

Anytime Hb is assessed via HemoCue®/CritLine®/local lab, a central lab Hb should be obtained as well.

3.6 Concomitant Medications, Procedures and Nondrug Therapies

3.6.1 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.

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

3.6.1.1 Use of Phosphate Binders During the Study (Roxadustat Subjects)

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.

3.6.1.2 Use of Hydroxymethylglutaryl Coenzyme A (HMG-CoA) Reductase Inhibitors (Statins) During the Study (Roxadustat Subjects)

When coadministered with roxadustat, in clinical pharmacolgical 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 Table 2 for subjects randomized to roxadustat.

Table 2 Recommended Maximum Daily Dose of Statins for Subjects Randomized to Roxadustat

Statin	Proposed Max Dose (mg/day)
Simvastatin	5
Atorvastatin	40
Rosuvastatin	5
Fluvastatin	40
Pitavastatin	2
Pravastatin	40
Pitavastatin	1
Lovastatin	20

Abbreviations: max = maximum.

3.6.2 Supplemental Iron Use

In a Phase 2 study of roxadustat, in which study subjects were randomized to either receive no iron, oral iron or IV iron, there was no significant difference in Hb levels in subjects receiving oral iron compared to subjects receiving IV iron. Therefore, based on the mechanism of action of roxadustat and the Phase 2 study results, in subjects randomized to roxadustat, oral iron may be sufficient for iron supplementation.

In this study, oral iron should be allowed as first-line iron supplementation without restrictions, for both study arms. In addition to the scheduled assessments (Appendix 3), 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.

3.6.2.1 Oral Iron Supplementation

All subjects should be encouraged to take oral iron as the first-line iron supplementation during the Treatment Period, except subjects not tolerating oral iron. The dose and frequency are at the discretion of the Investigator. Oral iron supplementation should be started before the subject becomes iron depleted.

3.6.2.2 Intravenous Iron Supplementation

Intravenous iron supplementation is permitted if in the opinion of the Investigator the subject's Hb has not responded adequately and the subject is considered iron deficient.

Treatment with study medication will continue during IV iron administration. Discontinuation of IV iron is recommended once the subject is no longer deemed iron deficient (eg, ferritin ≥ 100 ng/ml [≥ 220 pmol/L], TSAT ≥ 20%) and has evidence of a hematopoietic response.

Note: IV iron administration in study subjects during hospitalization is not considered a protocol deviation.

3.6.3 Rescue Therapy Guidelines

Rescue therapy guidelines are provided to standardize the use of rescue therapy.

3.6.3.1 Red Blood Cell Transfusion

Red blood cell transfusion should be considered if rapid correction of anemia is required to stabilize the subject's condition (eg, acute hemorrhage) and the Investigator is of the opinion that the blood transfusion is a medical necessity. Study drug treatment may continue during the RBC transfusion administration.

3.6.3.2 Erythropoiesis Stimulating Agents (Roxadustat Arm Only):

The use of ESAs is not permitted during the Treatment Period, except if all of the following criteria are met:

- A subject's Hb level has not responded adequately despite two or more consecutive roxadustat dose increases or the roxadustat dose has reached the maximum dose limit
- Other causes for lack of response or declining Hb, such as iron deficiency, bleeding, acute inflammatory conditions, have been ruled out
- Reducing risk of alloimmunization in transplant eligible patients is a goal.

Roxadustat and ESA may not be co-administered. Treatment with an approved ESA may be initiated ≥ 3 days after the last roxadustat dose.

If the situation permits, the Investigator should inform the Medical Monitor prior to initiation of ESA therapy.

Subjects may receive **one course** of ESA rescue during the Treatment Period. Erythropoiesis-stimulating agent rescue should stop after 4 weeks or once Hb exceeds 9 g/dL, whichever occurs first. If a subject requires more than 4 weeks of ESA rescue therapy due to inadequate Hb response, the Medical Monitor should be contacted.

Treatment with roxadustat may resume after the following intervals:

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

If more than one course of ESA rescue is required during the Treatment Period, the subject must be discontinued permanently from the study, and is considered a Treatment Failure.

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

3.6.4 Therapeutic Phlebotomy

If there are clinical concerns of excessive elevation of Hb levels, the Investigator may decide to perform a therapeutic phlebotomy in addition to a dose hold. This should be discussed with the Medical Monitor and documented.

3.6.5 Excluded Medications/Therapies/Substances

Subjects are not permitted to consume more than three alcohol-containing drinks per day during the Treatment or Follow-up Periods.

The following medications are prohibited from the day of randomization until completion of the study:

- Androgens and iron-chelating agents (eg, deferoxamine, deferiprone, or deferasirox therapy)
- Dapsone in any dose amount
- For subjects receiving roxadustat: chronic use of acetaminophen or paracetamol >2.0 g/day during the Treatment Period and up to 1 week after EOT.
- Use of herbal medicine is not prohibited but strongly discouraged.

3.6.6 Contraception

Female subjects of childbearing potential 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 with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (eg, condom) if not surgically sterile (ie, vasectomy). Contraceptive methods must be practiced upon entering the study and through 12 weeks after the last dose of study treatment. If a subject discontinues prematurely, the contraceptive method must be practiced for 12 weeks following final administration of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported (Section 9.3.6).

In female subjects of childbearing potential, serum pregnancy test will be done per Schedule of Assessments (Appendix 3) to rule out pregnancy. Pregnancy test is not required for female subjects of no childbearing potential eg, postmenopausal (determination whether a woman is post-menopausal is at the discretion of the Investigator), surgically sterile etc..

3.7 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 examinations (PEs), and electrocardiogram (ECGs). During the course of the study, vital signs, complete and targeted PEs, and laboratory tests will be performed at regular intervals. A comprehensive PE will be conducted during the Screening visit, Day 1 and at the End of Study (EOS) visit. A targeted PE (general appearance, cardiovascular, respiratory and abdomen) will be conducted throughout the study as described in Schedule of Assessments (Appendix 3).

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 medically significant 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 managed according to Drug-Induced Liver Injury (DILI) guidance (Appendix 4).

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, stable, or until the subject's EOS visit. See Section 9 for details on AE and SAE reporting.

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

3.8 Data Safety and Monitoring Board

A Data Safety Monitoring Board will review safety data periodically in collaboration with the Sponsor to ensure subject safety. A separate DSMB charter will establish the rules, meeting frequency, and scope of responsibilities of the DSMB.

4 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

1. Age ≥ 18 years.
2. 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.
3. Receiving HD or PD for ESRD for a minimum of 2 weeks and a maximum of 4 months, prior to randomization.
4. Hemodialysis access consisting of an arteriovenous (AV) fistula, AV graft, or tunnelled (permanent) catheter; or PD catheter in use.
5. Mean of the two most recent predialysis Hb values during the Screening Period, obtained at least 2 days apart, must be ≤ 10.0 g/dL, with a difference of ≤ 1.3 g/dL between the highest and the lowest values. The last Hb value must be drawn within 10 days prior to randomization.
6. Ferritin ≥ 100 ng/mL (≥ 220 pmol/L); subjects with ferritin level < 100 ng/mL(<220pmol/L) during screening, qualify after receiving iron supplement (per local standard of care), without the need to retest ferritin prior to randomization.
7. Transferrin saturation ≥ 20%; subjects with TSAT level < 20% during screening, qualify after receiving iron supplement (per local standard of care), without the need to retest TSAT prior to randomization.
8. Serum folate level, performed within 8 weeks prior to randomization ≥ lower limit of normal (LLN); subjects with serum folate level < LLN during screening, qualify after receiving folate supplement (per local standard of care), without the need to retest folate prior to randomization.
9. Serum vitamin B12 level, performed within 8 weeks prior to randomization ≥ LLN; subjects with vitamin B12 level < LLN during screening, qualify after receiving B12 supplement (per local standard of care), without the need to retest B12 prior to randomization.
10. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN), and total bilirubin (Tbili) ≤ 1.5 x ULN.
11. Body weight up to 160 kg (HD subjects: dry weight).

4.2 Exclusion Criteria

1. Total duration of prior effective ESA use must be ≤3 weeks within the preceding 12 weeks at the time informed consent is obtained.

   Specific dosing guidance, depending on the type of ESAs, injected IV or SC within 12 weeks prior to start of screening are as follows:

   <u>Short-acting ESAs (EPO-alfa or equivalents)</u>

   - IV: Up to 9 doses; last EPO dose must be ≥2 days prior to start of screening

- SC: Up to 3 doses; last EPO dose must be ≥1 week (7 days) prior to start of screening

Darbepoetin

- IV: Up to 3 doses; last darbepoetin dose must be ≥1 week (7 days) prior to start of screening
- SC: Up to 2 doses; last darbepoetin dose must be ≥2 weeks (14 days) prior to start of screening

Continuous erythropoietin receptor activator (CERA) IV and SC

- IV or SC: Up to 2 doses; last CERA dose must be ≥2 weeks (14 days) prior to start of screening

2. Intravenous iron: there is no restriction regarding IV iron use during screening, provided it is administered in accordance with local standard of care.

3. Red blood cell transfusion within 4 weeks prior to randomization.
4. Active, clinically significant infection that could be manifested by white blood cell (WBC) count > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection at the time of randomization.
5. History of chronic liver disease (eg, chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver).
6. New York Heart Association Class III or IV congestive heart failure at screening.
7. Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thromboembolic event within a major vessel (excluding vascular dialysis access) (eg, deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.
8. Uncontrolled hypertension, in the opinion of the Investigator, (eg, that requires a change in anti-hypertensive medication) within 2 weeks prior to randomization.
9. Renal imaging performed within 12 weeks prior to randomization indicative of a diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category 2 or higher) of renal cell carcinoma.
10. History of malignancy, except for the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps.
11. Positive for any of the following: human immunodeficiency virus (HIV); hepatitis B surface antigen (HBsAg); or anti-hepatitis C virus antibody (anti-HCV Ab).
12. Chronic inflammatory disease that could impact erythropoiesis (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission.
13. Known, untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration, or retinal vein occlusion (subjects who are already blind for the above reasons qualify to participate).

14. Known history of myelodysplastic syndrome or multiple myeloma.
15. Known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia, or other known causes for anemia other than CKD.
16. Known hemosiderosis, hemochromatosis, coagulation disorder, or a hypercoagulable condition.
17. Organ transplant: subjects with any of the following:
    a. Experienced rejection of a transplanted organ within 6 months of transplantation
    b. Currently on high doses of immunosuppressive therapy (per discretion of the Investigator)
    c. Scheduled for organ transplantation. Note: being on a waiting list for kidney transplant is not exclusionary
18. Anticipated elective surgery, except for vascular access surgery or dialysis catheter placement, that is expected to lead to significant blood loss, or anticipated elective coronary revascularization.
19. Active or chronic gastrointestinal bleeding.
20. Any prior treatment with roxadustat or a HIF-PHI.
21. Use of iron-chelating agents within 4 weeks prior to randomization.
22. Known hypersensitivity reaction to any ESA.
23. Use of an investigational drug or treatment, participation in an investigational study, or presence of an expected carryover effect of an investigational treatment, within 4 weeks prior to randomization.
24. Anticipated use of dapsone or androgens at any dose amount or chronic use of acetaminophen or paracetamol > 2.0 g/day during the study.
25. History of alcohol or drug abuse within 6 months prior to randomization.
26. Females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception.
27. Pregnant or breastfeeding females.
28. Any medical condition that, in the opinion of the Investigator, may pose a safety risk to a subject in this study, may confound efficacy or safety assessment, or may interfere with study participation.

Subjects who fail to meet the above eligibility criteria should not be randomized or receive study medication. If Day 1 lab values (collected prior to administration of study medication) are found to be of significant safety risk, in the opinion of the Investigator or Medical Monitor, the subject may be discontinued from the study.

5 INVESTIGATIONAL PRODUCT

5.1 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 2. All ingredients used for manufacture of roxadustat comply with US and European Union compendial 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.

5.2 Storage

Roxadustat tablets should be protected from light, and stored at 15º to 30ºC (59º–86ºF).

Epoetin alfa should be stored according to the USPI or SmPC.

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

Handling and disposition of unused study drug is described in the site Drug Accountability Binder.

5.3 Administration

5.3.1 Roxadustat

Roxadustat should be dispensed to subjects with instructions for self-administration of the tablets on each dosing day, according to the dosing schedule below. The tablets are to be swallowed whole with room-temperature drinking water. Dosing should occur at approximately the same time of day.

Study drug doses taken TIW must be administered at least 2 days apart, and no more than 4 days apart. Dosing days should remain consistent throughout the study. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain Hb levels in the Maintenance Phase, the dosing frequency should be reduced in a step-wise fashion eg, TIW to BIW, BIW to QW, QW to Q-2 Week etc.

5.3.2 Active Control-Epoetin Alfa

5.3.2.1 Hemodialysis Subjects

Epoetin alfa will be administered IV TIW according to the Package Insert or SmPC by appropriately trained personnel. In subjects requiring ultra-low dose of EPO (eg, ≤1000 IU/week), the frequency of administration may be adjusted by the PI per local standard of care. For countries provided with prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest calculated total weekly dose.

5.3.2.2 Home-hemodialysis and Peritoneal Dialysis Subjects

Epoetin alfa will be administered according to the Package Insert, or SmPC or local standard of care by appropriately trained personnel including subject or caregiver. For countries provided

with prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest calculated total weekly dose.

5.4 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 3.0 mg/kg/dose or 3.5 mg/kg/dose from the original protocol (based on dry weight in subjects on HD and normal weight in subjects on HHD and PD) or 400 mg per administration, 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 AEs. An overdose without associated symptoms is not an AE and will be recorded on the dosing case report form (CRF) 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 epoetin alfa USPI of SmPC.

6 STUDY PROCEDURES

6.1 Study Procedures by Visit

During study visits, unless otherwise indicated, it is preferred that all assessments including labs and PEs be completed predialysis for subjects on HD. For subjects on HHD and PD, 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 HHD/PD approximately at the same time of the day. Weight assessment in HD subjects should be done after dialysis (dry weight). Blood pressure and HR should be assessed according to the guidelines described in Appendix 5.

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6.1.1 Screening Period (Up to 6 Weeks)

Subjects must have a signed written informed consent before any screening tests or assessments are performed. For all screen failures, the reason(s) will be documented. Subjects will undergo at least two screening visits to determine eligibility, at least two days apart. All assessments and their timing are outlined in Appendix 3.

6.1.1.1 Screening 1

- Signed written informed consent
- Inclusion/Exclusion criteria verification
- Demographics and medical history
- Complete physical exam
- Height, weight (HD subjects: use dry weight)
- Blood pressure, HR
- Laboratory tests:
    - Complete blood count (CBC) with WBC differential
    - Serum chemistry
    - Lipid panel (fasting whenever possible)
    - Serum iron, ferritin, TIBC, TSAT
    - CHr
    - Hemoglobin A1c (HbA1c)
    - Vitamin B_{12} and folate (if no value available within 8 weeks prior to randomization)

  - Enzyme-linked immunosorbent assay (ELISA) for HIV
  - Hepatitis B surface antigen and anti-HCV Ab
  - Serum human chorionic gonadotropin (hCG) test for women of childbearing potential only (For definition, see Section 3.6.6).
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

6.1.1.2 Screening 2

Hemoglobin values must be obtained at least 2 days apart

- Blood pressure, HR
- Hemoglobin only
- Renal ultrasound - not required if results of a previous renal ultrasound or other renal imaging modality 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 screening.
- Adverse event recording.
- Concomitant medication recording
- Procedures and nondrug therapies recording

6.1.1.3 Additional Screening

If a subject's laboratory results do not meet the eligibility criteria at Screening, the laboratory assessment may be repeated within the Screening Period.

For example, additional Hb values may be collected if necessary. The mean of 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 prior approval from the Medical Monitor, unless the Investigator has a valid reason to believe that the original laboratory result is due to an error (eg, possible sample mix-up). Such a repeat should be communicated to the Medical Monitor as soon as possible.

Screening procedures that are not done at the scheduled visit must be completed prior to randomization.

If subjects fail screening, they may be re-screened once as deemed appropriate by the investigator. Where possible, an approval should be obtained from the Medical Monitor prior to rescreening.

6.1.2 Treatment Period

Eligible subjects will be randomized via IXRS to receive roxadustat or epoetin alfa. The Treatment Period begins on the first day of dosing with study treatment (Day 1/Week 0). A common closeout will occur when a predetermined number of adjudicated CV, cerebrovascular or thromboembolic events have been accrued across the entire Phase 3 program.

6.1.2.1 Day 1 (Week 0)

All assessments are to be completed prior to study drug administration

- Inclusion/Exclusion criteria verification
- Complete PE
- Weight (HD use dry weight)
- Blood pressure, HR, temperature, and respiratory rate (RR)
- Laboratory tests:
    - Complete blood count with WBC differential
    - Serum chemistry
    - Lipid panel (fasting, whenever possible)
    - Serum iron, ferritin, TIBC, TSAT
    - CHr
    - HbA1c
    - Reticulocyte count
    - Special laboratory analytes: Hepcidin and high sensitivity-C-reactive protein (hs-CRP)
    - Archival serum/plasma samples (optional donation, separate consent form)
- HemoCue®/CritLine® assessment
- 12-Lead ECG
- HRQoL questionnaires (SF-36, FACT-An, and European Quality of Life in 5 Dimensions, 5 Levels [EQ-5D-5L])
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording
- Dispense study drug

6.1.2.2 Weeks 1 to 4 (Weekly, ±2 days)

- Laboratory tests (must be performed prior to dosing):
    - Weeks 1, 2, 3, 4, CBC with WBC differential.
    - Week 2: LFTs only
    - Week 4: Serum chemistry
    - Week 4: Lipid panel (fasting whenever possible)
    - Week 4: Serum iron, ferritin, TIBC, TSAT.
    - Week 4: CHr
    - Weeks 1, 2: Reticulocyte count
    - Week 4: Special laboratory analytes
    - Week 4: Archival serum/plasma samples (optional donation, separate consent form)
- HemoCue®/CritLine® assessment.
- Dose adjustment review beginning Week 4 and at 4-weekly intervals thereafter (except in the event of excessive hematopoiesis). Refer to Section 3.5.3, and Appendix 2.
- All visit weeks: BP and HR
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording
- Dispense study drug every 2 weeks (Week 2 and Week 4)

6.1.2.3 Weeks 6 to 24 (Every 2 weeks, ± 4 days)

- Laboratory tests (must be performed prior to dosing):
    - Weeks 8, 12, 20: CBC with WBC differential
    - Week 6 followed by every visit where no CBC is collected; Hb only.
    - Weeks 8, 12, 20: Serum chemistry
    - Weeks 6, 16: LFTs and CPK
    - Weeks 8, 12, 24: Lipid panel (fasting whenever possible).
    - Weeks 8, 12, 20: Serum iron, ferritin, TIBC, TSAT.
    - Weeks 8, 12, 20: CHr
    - Week 12: HbA1c
    - Weeks 8, 20: Reticulocyte count
    - Weeks 12, 20: Special laboratory analytes

- Weeks 12, 20: Archival serum/plasma samples (optional donation, separate consent form)
- HemoCue®/CritLine® assessment
- Weeks 12, 24: Serum hCG pregnancy test for women of childbearing potential (for definition, see Section 3.6.6)
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- Week 24 followed by every 12 weeks: Targeted physical exam (eg, respiratory and cardiovascular system)
- Week 24 followed by every 24 weeks: 12-lead ECG, weight (HD subjects: dry weight)
- Dose adjustment review every 4 weeks (except in the event of excessive hematopoiesis or dose frequency conversion). Refer to Section 3.5.2, and Appendix 2.
- All visit weeks: BP and HR
- Week 12 HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording
- Dispense study drug

6.1.2.4 Weeks 28 to End of Therapy (Every 4 weeks, ±4 days)

- Laboratory tests (must be performed prior to dosing):
    - Week 28 followed by every 8 weeks: CBC with WBC differential
    - Week 32 followed by every visit where no CBC is collected; Hb only
    - Week 28 followed by every 8 weeks: Serum chemistry
    - Weeks 32, 40, 48, 60 followed by every 24 weeks: Lipid panel (fasting whenever possible)
    - Week 28 followed by every 8 weeks: Serum iron, ferritin, TIBC, TSAT
    - Week 28 followed by every 8 weeks: CHr
    - Weeks 28, 44, 60, followed by every 16 weeks: HbA1c
    - Week 44 followed by every 24 weeks: Reticulocyte count
    - Week 44, followed by every 24 weeks: Special laboratory analytes

- Week 44 followed by every 24 weeks: Archival serum/plasma samples (optional donation, separate consent form)
- All visit weeks: HemoCue®/CritLine® assessment.
- Week 36 followed by every 12 weeks: Targeted physical exam (eg, respiratory and cardiovascular system)
- Week 36, followed by every 12 weeks: Serum hCG test for women of childbearing potential (for definition, see Section 3.6.6)
- All visit weeks: Dose adjustment review (except in the event of excessive hematopoiesis or dose frequency conversion). Refer to Section 3.5.2, and Appendix 2.
- All visit weeks: BP and HR
- Weeks 36 and 52: HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording
- Dispense study drug

* If the indicated assessments fall on a study treatment visit that is within two weeks of the planned EOT visit, then these specified assessments can be postponed until the EOT visit.

6.1.2.5 End of Treatment (± 7 days)

- Laboratory tests:
    - Complete blood count with WBC differential
    - Serum chemistry
    - Lipid panel (fasting whenever possible)
    - Serum iron, ferritin, TIBC, TSAT
    - CHr
    - HbA1c
    - Reticulocyte count
    - Special laboratory analytes
    - Archival serum/plasma samples (optional donation, separate consent form)
- Complete physical exam.

- Serum hCG test for women of childbearing potential (for definition, see Section 3.6.6)
- Blood pressure, HR, temperature, respiration rate
- HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)
- 12-lead electrocardiogram
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

Erythropoiesis-stimulating agents may be started ≥ 3 days after the last dose of roxadustat.

6.1.2.6 Early Termination (ET)

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 (Section 6.1.2.5). Erythropoiesis-stimulating agents may be started ≥ 3 days after the last dose of roxadustat.

Unless consent is withdrawn, these subjects will be followed up for CV events of interest, vital status, and hospitalization until study closure.

These subjects will be followed up every 3 to 6 months (depending on the availability of the subjects) until study closure. These visits may occur either in person or via telephone.

6.1.3 Post-Treatment Follow-Up Period

6.1.3.1 End of Study: 4 weeks (± 7 days) after EOT or ET

- Laboratory tests:
  - Complete blood count with WBC differential
  - Serum chemistry
  - Lipid panel (fasting whenever possible)
  - Serum iron, ferritin, TIBC, TSAT
  - CHr
  - HbA1c
  - Reticulocyte count
  - Special laboratory analytes
  - Archival serum/plasma samples (optional donation, separate consent form)
- Targeted physical exam
- Serum hCG test for women of childbearing potential

- Blood pressure, HR
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

6.1.3.2 Subject Discontinuation

Subjects may discontinue from the study at any time. Discontinued subjects should be encouraged to complete the ET and the EOS visit procedures. The appropriate documentation must be entered on the CRF. Subjects should be discontinued from the study for any of the following reasons:

- Subject no longer consents to participate in the study
- 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 the Investigator or Sponsor
- Lack of Efficacy / Meets ESA withdrawal criteria (for subjects on roxadustat; see also Section 3.6.3.2)
- Subject is lost to follow-up
- Subject is no longer requiring dialysis due to kidney transplant
- Pregnancy
- Death
- Site terminated by Sponsor

Women of childbearing potential who withdraw from this study will continue contraception for 12 weeks following the last study drug administration. Male subjects with partners of childbearing potential must agree to use a medically acceptable method of contraception during the study and for 12 weeks following the last study drug administration.

6.2 Missed Visits

Every attempt should be made to complete all study visits as outlined in the Schedule of Assessments (Appendix 3). All missed study visits and visits outside the visit window are considered protocol deviations.

6.3 Unscheduled Visits

Unscheduled visit(s) and laboratory assessments may be required at the discretion of the Investigator. Please refer to the CRF Completion Guidelines located in the Study Reference Manual for additional information.

6.4 Laboratory Assessments

Central laboratory results should be reviewed by the Investigator or another qualified study staff member as soon as it is received. Subject management is dependent upon close review of the laboratory data.

6.4.1 HemoCue® / CritLine®

Hemoglobin values obtained by point-of-care devices such as HemoCue® or CritLine® are used to allow "real-time" dose adjustments for all subjects. HemoCue®/ CritLine® results will be collected in the CRF. Anytime an Hb is obtained via such a point-of-care device, a central lab Hb should be obtained as well, either as part of the regular visit labs, or anytime when a point-of-care Hb is obtained at unscheduled visits, such as during dose-hold for excessive hematopoiesis.

6.4.2 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" labs, USA) test results may be used to make the necessary clinical judgments. In all such cases, a central lab specimen should be obtained 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 parameters to be measured in this study are listed in Table 3.

Table 3 Laboratory Tests

CBC:	**Chemistry Panel:**
Basophils	Albumin
Eosinophils	Bicarbonate
Erythrocyte count (RBC)	BUN
Hb	Calcium
Hct	Chloride
Leukocyte count (WBC)	Creatinine
Lymphocytes	Glucose
Mean corpuscular volume	Lipase
Mean corpuscular Hb	Lactate dehydrogenase
Mean corpuscular Hb concentration	*Liver Function Tests*
Monocytes	ALP
Neutrophils	ALT
Neutrophils, immature (banded)	AST
Platelets	Bilirubin, total and direct
Reticulocyte count	CPK
	GGT
Serum Lipid Panel:	Magnesium
Total Cholesterol	Phosphorus
LDL	Potassium
HDL	Sodium
Triglycerides	Total protein
Serum Iron Profile	Uric acid
Ferritin	**HIV and Viral Hepatitis Panel:**
Iron	Anti-HCV Ab tests
Reticulocyte Hb content	HBsAg
TIBC	HIV ELISA
TSAT	
Special Laboratory Analytes:	**Additional Laboratory Analytes:**
Hepcidin	Vitamin B_{12}
High-sensitivity CRP	Folate
	HbA1c
	Serum β-HCG

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; GGT = gamma-glutamyl transferase; Hb = hemoglobin; HbA1c = glycated hemoglobin A1c; HBsAg = hepatitis B surface antigen; Hct = hematocrit; HCV = hepatitis C virus; HDL = high-density lipoprotein; HCG- human chorionic gonadotropin; HIV = human immunodeficiency virus; LDL = low-density lipoprotein; RBC = red blood cell; TIBC = total iron binding capacity; TSAT = transferrin saturation; WBC = white blood cell.

Archival serum/plasma samples: A set of serum and plasma samples may be drawn and stored for the future analysis of relevant select biomarkers. Donation of these samples is optional and will be sought through a separate informed consent form (ICF). No genetic testing will be performed for the diagnosis of genetic disorders on these samples.

6.5 Electrocardiogram

Local 12-lead ECGs will be performed on all subjects at specific time points as described in the Schedule of Assessments. ECG will be taken after the subject has been lying quietly in the supine position for 5 minutes. Any abnormalities must be evaluated in clinical context (based on subject's medical history and concomitant medication) and the Investigator should determine if it is clinically significant. Clinically significant abnormalities should be reported as an AE. 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.

6.6 Renal Ultrasound

A renal ultrasound examination will be performed during screening if no record of a renal imaging modality exists within 12 weeks prior to randomization. Findings of the renal ultrasound to exclude the presence or suspicion of renal cell carcinoma will be required for eligibility. Sites are reminded to schedule the renal ultrasound in a timely manner.

6.7 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.

6.7.1 36-Item Short Form Health Survey

The 36-Item Short Form Health Survey is a 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 (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.

6.7.2 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, 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 QoL.

6.7.3 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.

7 ENDPOINTS AND ASSESSMENTS

In the endpoint definitions below, rescue therapy for roxadustat treated subjects is defined as ESA rescue or RBC transfusion and rescue therapy for epoetin alfa-treated subjects is defined as RBC transfusion.

All endpoints related to Hb are based on central lab values

7.1 Primary Endpoint*:*

- **US (FDA) submission**: Mean Hb change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 52. This analysis will be based on the intent-to-treat (ITT) population. Hemoglobin values under the influence of rescue therapy will not be censored for the primary analysis.
- **Ex-US submission**: The proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response. This analysis is based on the Per Protocol Set (PPS) population.

  A Hb response is defined, using central laboratory values, as

  - Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or
  - Increase in Hb ≥2.0 g/dL in subjects whose baseline Hb ≤ 8.0 g/dL

7.2 Secondary Endpoints

- **US (FDA) submission**: The proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response.

  A Hb response is defined, using central laboratory values, as

  - Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or
  - Increase in Hb ≥ 2.0 g/dL in subjects whose baseline Hb ≤ 8.0 g/dL
- **Ex-US submission**: Mean Hb change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 36 without rescue therapy within 6 weeks prior to and during the evaluation period. This analysis will be based on the PPS population.

Both, US and ex-US Submissions:

- Average monthly IV iron use per subject during the Treatment Period. Mean change in low-density lipoprotein (LDL) cholesterol averaged over Weeks 12 to 24.

- Blood pressure effects:
  - Proportion of subjects with exacerbation of hypertension, meeting at least one of the following criteria:
    - Increase in BP: An increase from baseline of ≥ 20 mm Hg systolic BP and sBP >170 mmHg, or an increase from baseline of ≥ 15 mm Hg diastolic BP and dBP>100 mmHg. Increases from baseline in blood pressure must be confirmed by repeat measurement.
  - Time to an increase in BP as defined above.
  - Mean change in mean arterial pressure (MAP) averaged over Weeks 8 to 12.
- Time to achieve first Hb response as defined by the primary endpoint (ex-US) (which is the secondary endpoint for the US [FDA]).

7.3 Additional Evaluation of Efficacy

- **Hemoglobin Correction and Maintenance:**
  - Hemoglobin maintenance: Mean change in Hb averaged over 8 weeks of treatment at Weeks 28 to 52, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
  - Hemoglobin long-term Maintenance: Mean change 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 in Hb averaged over the 96 to 104 weeks of treatment, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period
  - Change in Hb at each of the selected time points
  - Change in Hb averaged over 8 weeks of treatment at Weeks 28 to 36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period, in subjects who have reached a Hb ≥ 11 g/dL prior to Week 28
  - Proportion of subjects with Hb within 10 to 12 g/dL in United States and 10 to 13 g/dL in Ex-US averaged over Weeks 28 to 36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period
- **Hospitalizations:**
  - Occurrence (number) of hospitalization(s)
  - Proportion of subjects hospitalized
  - Number of days of hospitalizations per patient-exposure year (PEY)
- Missed dialysis sessions

- **Rescue Therapy Use:**
  - Proportion of subjects who receive RBC transfusions
  - Number of RBC packs per patient-month exposure to study medication
  - The proportion of subjects requiring ESA rescue therapy will be summarized
- **Changes in Cholesterol Levels:**
  - Change at each of the selected treatment time points in:
    - Total cholesterol
    - LOL/HDL ratio
    - Non-HDL cholesterol.
  - Proportion of subjects achieving LDL target of < 100 mg/dL averaged over Weeks 12 to 24 of treatment.

Additional Blood Pressure Effects:

- Proportion of subjects achieving blood pressure treatment goal in ESRD subjects (pre dialysis systolic BP < 140 mmHg systolic and diastolic BP< 90 mmHg) averaged over Weeks 12 to 28

- **HRQoL and EQ-5D-5L Benefits of Anemia Therapy:**

  Mean change averaged over Weeks 12, 36 and 52 of treatment including those listed below.

  - *Vitality Subscale of SF-36:* In FAS subjects with baseline Vitality Subscore below 50
  - *Physical Component Scores of SF-36:*
    - In FAS subjects with baseline *physical component scores* below 40
    - In all FAS subjects
  - *Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scores:*
    - In FAS subjects with baseline subscale scores below 55 (generally associated with fatigue)
      - In all FAS subjects
  - *Total FACT-An Scores:*
    - In FAS subjects with baseline FACT-An scores below 135
    - In all FAS subjects
  - *EQ-5D-5L Scores:* In all FAS subjects

- **Hepcidin, Iron, and HbA1c:**
    - Change in serum hepcidin at each of the selected time points
    - Change in serum ferritin at each of the selected time points, total and sub-grouped by baseline values of < 100 ng/mL, 100 to 400 ng/mL, and >400 ng/mL
    - Change in TSAT at each of the selected time points, total and sub-grouped by baseline values of < 20%, 20% to 40%, and >40%
    - Change in HbA1c level at each of the selected time points in all subjects, in subjects with history of diabetes

7.4 Safety Assessments and Endpoints

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

- TEAEs, TESAEs, and clinically significant laboratory values from baseline
- Vital signs, ECG findings 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:

- Death from any cause, MI, stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, hypertensive emergency, deep venous thrombosis, 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 pooled SAPs.

For US (FDA) Only: The primary safety endpoint in this study is the Major Adverse Cardiac Event (MACE) 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.

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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size calculation is based on the primary endpoint for both the US (FDA) submission and Ex-US submission.

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 a 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). 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. This endpoint will be analyzed using the ITT population for the US (FDA) submission.

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, the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment). This assumes a 80% responder rate for both roxadustat and epoetin alfa, in order to support the primary efficacy analysis (ie, a noninferiority comparison in responder rate between roxadustat and epoetin alfa) and assuming a noninferiority margin of -15% for this difference (roxadustat minus epoetin alfa). This endpoint will be analyzed using the PPS population for the European Medicines Agency (EMA) submission.

Randomization will be stratified by the following three factors:

1. Geographical region (US vs. Ex-US)
2. Screening Hb values (≤ 8 g/dL vs. > 8 g/dL)
3. Cardiovascular/cerebrovascular/thromboembolic medical history (yes vs. no).

8.2 Analysis Populations

The following analysis populations will be used for the statistical analysis:

- Safety Population: The Safety Population consists of all subjects who received at least one dose of study treatment. All safety data will be tabulated using descriptive statistics. If treatment received during the study differs from the randomized treatment, the actual treatment arm will be used for the analysis.

- Intent-to-Treat population: The ITT population consists of all randomized subjects. The primary efficacy endpoint for the US (FDA) submission will be analyzed using this population. In addition, the superiority comparison of this endpoint for the US (FDA) submission will be performed using this population as well.

- Full Analysis Set: The FAS consists of all 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. Efficacy analysis for superiority will be conducted on the FAS population for the EMA submission.

- Per Protocol Set: The PPS consists of all randomized subjects who received at least 4 weeks of study treatment, have at least one postdose Hb assessment and are without major protocol violations. Criteria for PPS exclusion will be defined in the Statistical Analysis Plan (SAP). Non-inferiority analyses for the EMA submission will be based on the PPS.

8.3 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 (Section 3.8).

8.4 Statistical Analysis

Safety and efficacy data will be summarized and presented by treatment group and time point 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% CIs will be presented as part of the descriptive summaries.

8.4.1 Subject Enrollment and Disposition

A table will provide the number of randomized subjects (ITT), treated subjects (Safety population), FAS and PPS subjects and subjects who terminated the Treatment Period/study early along with the reason for ET.

8.4.2 Demographics and Baseline Characteristics

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

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

8.4.3 Efficacy Analyses

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

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

Hemoglobin results obtained from the central laboratory will be used for all efficacy analyses. Baseline Hb is defined as the mean of at least three central laboratory Hb values: the last two screening Hb values prior to randomization plus the one predose Hb value on Day 1 of the Treatment Period.

8.4.3.1 Primary Efficacy Analysis

US (FDA) Submission: The primary efficacy endpoint for US (FDA) submission is defined as the mean 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 ITT population. Hb values under the influence of rescue therapy will not be censored for the primary efficacy analysis.

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 arm ≤ Hb mean change from baseline in the epoetin alfa arm 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 arm > Hb mean change from baseline in the epoetin alfa arm minus 0.75 g/dL*

A Multiple Imputation Analysis of Covariance (MI ANCOVA) model will be used for the primary endpoint (change from baseline in Hb from Week 28 to Week 52).

The model will contain terms for treatment arm, baseline Hb measurement, and randomization stratification factors, except for Screening Hb values (≤ 8g/dL vs. > 8g/dL). Detailed analysis of the primary [efficacy] endpoint will be outlined in the SAP. The primary efficacy analysis for US [FDA] and sensitivity analysis for the first secondary endpoint for ex-US submissions will be based on the estimated difference between the two treatment arms of the overall mean effects throughout the evaluation period based on the MI ANCOVA model.

In addition, as a sensitivity analysis, the primary efficacy endpoint for US [FDA] and primary analysis for the first secondary endpoint for ex-US submissions will be analyzed using the analysis of a model for repeat measures (MMRM). The MMRM model will contain terms for baseline Hb, as covariate, treatment arm, visit, visits by treatment arm, and randomization stratification factors (except for Screening Hb values (,≤ 8g/dL vs > 8g/dL) as fixed effects. Additional analysis using pattern mixture approaches would be detailed in the SAP.

Due to the large amount of visits to include in the 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.

This null hypothesis will be rejected if the two-sided 95% CI for the difference (roxadustat minus epoetin alfa) of two least square means from the mixed model lies entirely above –0.75 g/dL.

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

Ex–US Submission: The primary efficacy endpoint for Ex-US submission is defined as the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response.

- A Hb response is defined, using central laboratory values, as: Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or
- Increase in Hb ≥ 2.0 g/dL in subjects whose baseline Hb ≤ 8.0 g/dL

Rescue therapy for roxadustat treated subjects is defined as ESA rescue or RBC transfusion, and rescue therapy for epoetin alfa treated subjects is defined as RBC transfusion.

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

> *H_0: Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm ≤ -15%*
>
> *Versus*
>
> *H_1: Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm > -15%*

A two-sided 95% CI for the difference of 2 responder rates (roxadustat minus epoetin alfa) based on the Miettinen & Nurminen approach adjusting for treatment and other stratification factors will be calculated and this null hypothesis will be rejected if the lower bound of the 95% CI is greater than -15%.

The stratification factors to be used in efficacy analyses are:

1. Geographical region
2. Screening Hb values (≤ 8 g/dL vs. > 8 g/dL)
3. Cardiovascular/cerebrovascular/thromboembolic medical history (Yes vs. No)

8.4.3.2 Secondary Efficacy Analyses

Once the null hypothesis has been rejected for the primary endpoint (for both, US [FDA] and ex-US submissions), the secondary endpoints below will be tested using a fixed sequence testing procedure, in order to maintain the overall two-sided Type I error rate at 0.05. If p-value from a test is < 0.05, the claim of superiority (or noninferiority) will be considered met and the test will progress to the next comparison in sequence as follows:

- **US (FDA) Submission**: The first secondary endpoint for US (FDA) submission is defined as the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response.

  A Hb response is defined, using central laboratory values, as:

  - Hb ≥ 11.0 g/dL and a Hb increase from baseline by ≥ 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or
  - Increase in Hb ≥ 2.0 g/dL in subjects whose baseline Hb ≤ 8.0 g/dL

The hypothesis to be tested for this efficacy analysis is:

H_0: Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm ≤ 15%

Versus

H_1: Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm > 15%

A two-sided 95% CI for the difference of 2 responder rates (roxadustat minus epoetin alfa) based on the Miettinen & Nurminen approach adjusting for treatment and other stratification factors will be calculated and H_0 will be rejected if the lower bound of the 95% CI is greater than -15%.

- **Ex-US Submission**: The first secondary endpoint for Ex-US submission is the mean change in Hb levels from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 36. This analysis will be based on the PPS population.

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

  H_0: Hb mean change from baseline to the average level from Week 28 to Week 36 in the roxadustat arm ≤ Hb mean change from baseline in the epoetin alfa arm minus 0.75 g/dL

  Versus:

  H_1: Hb change from baseline to the average level of Week 28 to Week 36 in the roxadustat group > Hb mean change from baseline in the epoetin alfa group minus 0.75 g/dL

  This efficacy endpoint will be analyzed using a mixed model of repeated measures (MMRM) with Hb baseline value as covariate and treatment group and randomization stratification factors as fixed effects and MI ANCOVA as sensitivity analysis for Ex-US submission.

  This null hypothesis will be rejected if the two-sided 95% CI for the difference of least square means from the mixed model is above –0.75 g/dL.

  Hb values under the influence of a rescue therapy within 6 weeks prior to and during this 8-week evaluation period will be censored in the analysis.

- The average monthly iron use will be compared between the 2 treatment groups using an ANCOVA model with baseline iron replete as a covariate, and treatment group and randomization stratification factors as fixed effects. Superiority will be declared if the lower bound of the two-sided 95% CI of the difference between epoetin alfa and roxadustat exceeds zero.

- Mean change from baseline in LDL cholesterol averaged over Weeks 12 to 24 will be analyzed using an MMRM model with baseline LDL cholesterol as a covariate and treatment group, visit, visits by treatment arm, and randomization stratification factors as fixed effects. Superiority will be declared if the lower bound of the two-sided 95% CI of the difference between epoetin alfa and roxadustat exceeds zero.

- Proportion of subjects with exacerbation of hypertension, meeting at least 1 of the following criteria will be analyzed using CMH model adjusting for treatment group and stratification factors

    - Increase in blood pressure: An increase from baseline in systolic blood pressure (sBP) of ≥ 20 mm Hg and sBP > 170 mmHg or an increase from baseline in diastolic blood pressure (dBP) of ≥ 15 mm Hg and dBP > 100 mmHg. Increases from baseline in blood pressure must be confirmed by repeat measurement.

Noninferiority of roxadustat vs. epoetin alfa will be tested. Non-inferiority will be declared if the upper bound of the two-sided 95% CI of the hazard ratio is less than 1.3.

- Time to an increase in blood pressure (defined as an increase from baseline of ≥ 20 mm Hg systolic BP and sBP >170 mmHg or an increase from baseline of ≥ 15 mm Hg diastolic BP and dBP > 100 mmHg). Time to an increase in blood pressure will be analyzed using the Cox Proportional Hazards model adjusting for treatment group and randomization stratification factors. Superiority of roxadustat vs. epoetin alfa will be tested.

- Mean change in mean arterial pressure (MAP) averaged over Weeks 8 to 12 will be analyzed using an MMRM model with baseline MAP as a covariate and treatment group, visit, visits by treatment arm, and randomization stratification factors as factors. Superiority will be declared if the lower bound of the two-sided 95% CI of the difference between epoetin alfa and roxadustat exceeds zero.

The time to achieve the first Hb response defined as the primary endpoint (for ex-US submission) will be analyzed using the Cox Proportional Hazards model adjusting for treatment group and other stratification factors. Non-inferiority of roxadustat vs. epoetin alfa will be tested. Non-inferiority will be declared if the upper bound of the two-sided 95% CI of the hazard ratio is less than 1.3.

8.4.3.3 Additional Efficacy Analyses

- Hemoglobin maintenance: The mean change in Hb averaged over 8 weeks of treatment at Weeks 28 to 52 without rescue therapy within 6 weeks prior to and during this 8-week evaluation period. The mean change in Hb will be analyzed using an MMRM model with baseline Hb as a covariate and treatment group, visit, visits by treatment arm, and randomization stratification factors as fixed effects. Non-inferiority between roxadustat compared with epoetin alfa will be declared if the lower bound of the two-sided 95% CI of the difference between roxadustat and epoetin alfa exceeds -0.75 g/dL. All subjects will be included in the analysis

- HRQoL benefit of roxadustat will be assessed using SF-36 vitality and physical functioning subscales. Change from baseline at Weeks 12, 36, and 52 will be computed for each treatment group. A paired t-test will be used to assess within treatment effect. Between treatment difference will be assessed using an MMRM model with baseline subscore as a

covariate and treatment group visit, visits by treatment arm, and randomization stratification factors as factors. Noninferiority of roxadustat vs. epoetin alfa will be tested. The non-inferiority margin is fixed as a difference of 2 points.

The additional efficacy analyses will use the FAS population.

Additional efficacy analyses of continuous endpoints will use an MMRM model with baseline value, visit, visits by treatment arm, and randomization stratification factors as covariates.

Additional efficacy analyses of proportions will use the CMH model adjusting for treatment group and randomization stratification factors.

Additional efficacy analyses of time-to-event endpoints will use the Cox Proportional Hazards model adjusting for treatment and randomization stratification factors.

8.4.4 Safety Analyses

Safety analyses will be performed using the Safety Population. Safety parameters include AEs, laboratory parameters, vital signs, ECG parameters, and PEs. For each safety parameter, the last assessment made prior to the first dose of study medication will be used as the baseline for all analyses of that safety parameter.
The analytical methods for the MACE endpoint, as well as other composite safety endpoints of interest, will be described in a region-specific pooled statistical analysis plan to reflect the nature of the pooling of these endpoints across comparable studies in the Phase 3 program and the region-specific safety endpoints.

8.4.4.1 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 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 EOT/ET 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, preferred term, and relationship. 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 TESAEs, fatal SAEs (ie, events that caused death), and AEs leading to discontinuation of study medication will be summarized by SOC, preferred term and treatment group

Treatment emergent adverse events of interest will also be reported in terms of incidence rate per PEY.

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

8.4.4.2 Clinical Laboratory Parameters

Descriptive statistics for laboratory values and changes from baseline at each assessment time point will be presented by treatment group for each laboratory parameter.

8.4.4.3 Vital Signs

Descriptive statistics for vital signs (sBP and dBP, pulse rate, respiration rate) and their changes from baseline at each visit and, the end of study will be presented by treatment group.

8.4.4.4 Electrocardiogram

Descriptive statistics for ECG parameters (eg, HR, PR interval, QRS interval, QT interval, and QTc interval) at baseline and changes from baseline at each assessment time point will be presented by treatment group.

8.4.5 Statistical Analysis Plan

The Statistical Analysis Plan 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 the Clinical Study Report.

8.4.6 Protocol Deviation

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. Guidelines related to roxadustat, epoetin-alfa, and IV iron administration deviations are described in the respective sections.

9 SAFETY

9.1 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 2001and the ICH E2A guidance.

9.2 Definitions

9.2.1 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 baseline 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 9.3.1).

9.2.2 Definition of a Serious Adverse Event

An **SAE** is any AE or suspected adverse reaction that results in any of the following outcomes:

- Death
- A life-threatening AE (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
- An important medical event (based on appropriate medical judgment, the event jeopardizes the subject and may require medical or surgical intervention to prevent one of the above-listed outcomes)

9.2.3 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."

9.2.4 Definition of an Adverse Reaction

An adverse reaction means any AE caused by a drug.

9.2.5 Special situations

Certain safety events called "Special Situations" that occur in subjects while on the medicinal products administered as part of the study require reporting may include, but are not limited to:

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

9.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

9.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 28 days after the ET/EOT Visit Date (ie, completion of 4-week ET Follow-up visit for the Early Terminated subjects and completion of End of Study (EOS) visit for the Completed subjects) except for pregnancy reporting (Section 9.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded.

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 last dose of study drug will be considered "treatment emergent" and be assessed for relationship to study drug.

9.3.2 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 baseline or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

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

The following attributes must be assigned to each AE:

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

9.3.3 Assessing Adverse Event Severity

The Investigator should use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For terms not specified as part of NCI-CTCAE, the following guidelines should be used to determine grade:

- **Grade 1, Mild**: Asymptomatic or mild symptoms 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** related to AE.

9.3.4 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.

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. The following are examples of adverse events and their relationship 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, but is a typical drug toxicity and ***known to be strongly associated with drug exposure,*** such as 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.

Not Related:

- The event represents the underlying disease (eg, disease-related symptoms, disease progression) and the presentation of the event is typical.
- The event represents a comorbid condition present at the time the subject entered the study that has not worsened.
- 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, cardiovascular events in an elderly population).

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 Health Authorities.

9.3.5 Reporting Serious Adverse Events on the Serious Adverse Event 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 or email 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 in the CRF. 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 7 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).

9.3.5.1 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.

9.3.5.2 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 CRF page 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.

9.3.6 Pregnancies: Reporting and Follow-up of Subjects

A pregnancy in a female subject or a male subject's female partner must be confirmed by positive serum β-HCG test(s). If pregnancy is suspected, study drug may need to be interrupted until pregnancy is ruled out. If a female subject or the female partner of a male 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. 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 occur.

Pregnancy itself is not an AE. However, the Investigator should report the information to the sponsor on the designated forms. Pregnancies are followed up to outcome. The outcome of the pregnancy must be reported by the Investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety management vendor within 24 hours of the Investigator learning of the outcome.

9.3.7 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 or not clinically significant, and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs.

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. 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.

An abnormality identified during a medical test (eg, laboratory parameter, vital sign, ECG data, PE) 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.

9.3.8 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.

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, CRFs, 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, IXRS, 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 the 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.
- CRF 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.

Ethics

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with FDA regulations, ICH E6 Guideline for GCP, the Declaration of Helsinki, any other applicable regulatory requirements, and 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 IB, 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. Institutional Review board/IEC 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 re-consented 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 US 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, if applicable.

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 records 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 records must be adequate to reconstruct all data transcribed onto the CRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will be entered onto CRFs 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, AEs, 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, CRFs 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 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 REFERENCE LIST

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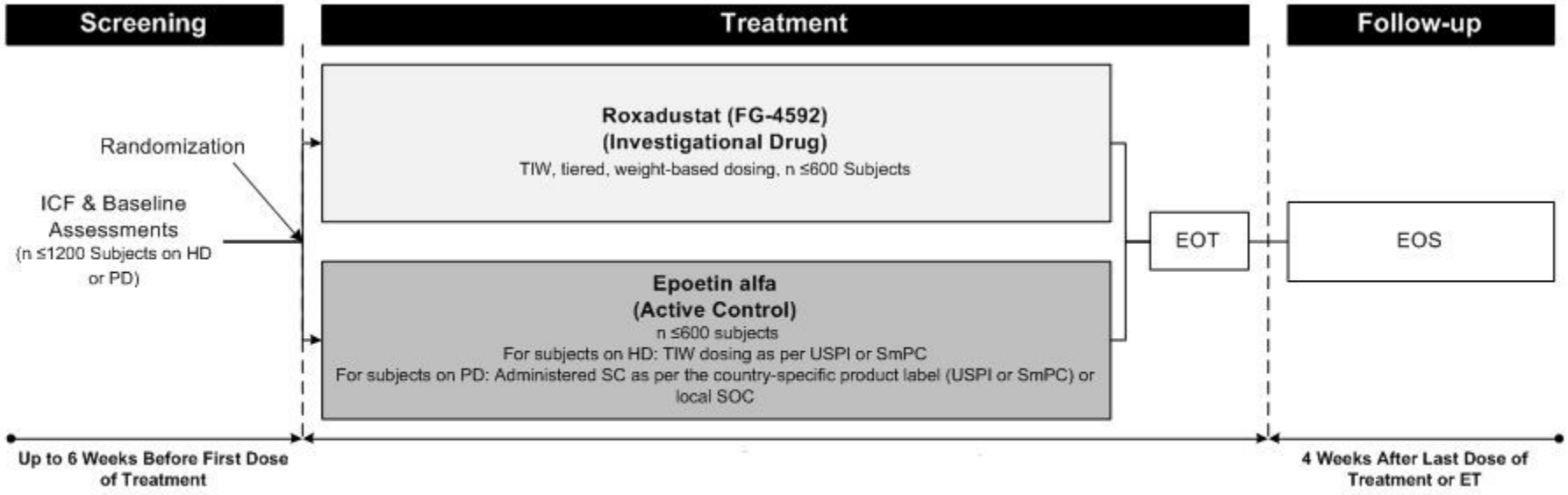
18 APPENDICES

Appendix 1 Study Schema



Abbreviations: EOS=end of study; EOT=end of treatment; ESA=erythropoesis-stimulating agent; ET=early termination; HD=hemodialysis; ICF=informed consent form; n=number of subjects; IV=intravenous; PD=peritoneal dialysis; SC=subcutaneous; SmPC=summary of product characteristics; SOC=standard of care; TIW=three times a week; USPI = US Package Insert.

Appendix 2 Roxadustat Dose Adjustment Rules

Dose adjustments should occur in two separate study dosing phases: the Correction Phase and the Maintenance Phase (see below). The aim of the Correction Phase is to increase Hb levels from baseline to the target Hb level. This phase is variable in length for each subject. The determination of Hb response and transition from the Correction to the Maintenance Phase of the study is based on the central laboratory Hb value.

All dose adjustments should be based on Hb values using a point-of-care device, such as HemoCue® or CritLine®. In the event that the central lab Hb value of the site visit is significantly different and the dose adjustment decision based on the HemoCue® / CritLine® value is being re-considered, the Medical Monitor should be contacted, if possible.

Dose adjustment reviews will occur on Week 4, and at intervals of every 4 weeks thereafter (Weeks 8, 12, 16, etc.), except in the event of excessive hematopoiesis, in which case doses may be adjusted at any time. In such cases, dose adjustment reviews are resumed at 4-week intervals. For example, if the subject's Hb increases > 2.0 g/dL from Week 1 to Week 3, the subject's dose is reduced by one dose step at Week 3. The next dose adjustment review should occur 4 weeks later at Week 7. If the dose adjustment interval falls on a non-study visit week (starting Week 4), the dose adjustment review should be performed at the next scheduled study visit if a dose adjustment was not required at the previous visit. For example, if a subject's visit is scheduled for Weeks 6 and 8, and the dose adjustment would occur at Week 7, then the dose adjustment should be evaluated at the Week 8 visit.

All subjects will be dosed orally TIW during the Treatment period. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain the target Hb level, the dosing frequency should be reduced in a step-wise fashion eg, 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. The maximum roxadustat dose is 3.0 mg/kg per dose or 400 mg (whichever is lower).

The following scenarios are defined as "excessive hematopoiesis";

1. Hb increases by > 2.0 g/dL at any time within a 4 week period: reduce the dose by one dose step.
2. Hb reaches or exceeds 13 g/dL: hold dosing, check Hb weekly. Resume dosing when Hb < 12.0 g/dL (for US subjects central lab Hb value preferred), at a dose that is reduced by two dose steps.

For subjects on prolonged dose-hold, with stable (not dropping) Hb, PI may use discretion to schedule less frequent visits. Anytime Hb is assessed via HemoCue®/CritLine®/local lab, a central lab Hb should be obtained as well.

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 study 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" (eg,,Hb ≥ 13 g/dL, requiring a dose hold)) or "Overdose" (prescribed >3.0 mg/kg per dose or 400 mg per dose whichever is lower)

<table>
<tr><th colspan="3">CORRECTION PHASE</th><th colspan="4">MAINTENANCE PHASE</th></tr>
<tr><th>Change in Hb from 4 weeks earlier (g/dL)</th><th>Hb < 11 g/dL (central lab)*</th><th>Hb ≥ 13.0 g/dL</th><th>Hb < 10.5 g/dL</th><th>Hb 10.5 to 11.9 g/dL</th><th>Hb 12.0 to 12.9 g/dL</th><th>Hb ≥ 13.0 g/dL</th></tr>
<tr><td>< -1.0</td><td>↑</td><td rowspan="3">Hold, then resume dosing when:
Hb < 12 g/dL, at a dose that is reduced by two dose steps
Subjects are to return weekly to monitor Hb until dosing can be resumed**</td><td>↑</td><td>↑</td><td>No change</td><td rowspan="3">Hold, then resume dosing when:
Hb < 12 g/dL, at a dose that is reduced by two dose steps
Subjects are to return weekly to monitor Hb until dosing can be resumed**</td></tr>
<tr><td>-1.0 to 1.0</td><td>↑</td><td>↑</td><td>No change</td><td>↓</td></tr>
<tr><td>> 1.0</td><td>No change</td><td>No change</td><td>↓</td><td>↓</td></tr>
<tr><td colspan="3">Dose Increases and Reductions:</td><td colspan="4">Dose Adjustment for Excessive Hematopoiesis:</td></tr>
<tr><td colspan="3">Dose increases (↑) and reductions (↓) are preset to dose steps.
The dose steps are as follows:
20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.
Example: A dose increase at a dose of 70 mg results in 100 mg as the new dose. A dose reduction at a dose of 150 mg results in 100 mg as the new dose.
Note: Maximum dose capped at 3.0 mg/kg per dose or 400 mg, whichever is lower.
*Transition from Correction to Maintenance Phase will occur once the central laboratory Hb value is ≥ 11 g/dL and ≥ 1 g/dL from baseline</td><td colspan="4">At any time during the Treatment Period if Hb increases by >2.0 g/dL within 4 weeks, the dose should be reduced by one dose step.
** For subjects on prolonged dose-hold, with stable (not dropping) Hb, PI may use discretion to schedule less frequent visits. Anytime Hb is assessed via HemoCue®/CritLine®/local labs, a central lab Hb should be obtained as well</td></tr>
</table>

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

Appendix 3 Schedule of Assessments

Study Period:	**Screening**		**Treatment**					**Follow-up**
Visit / Week:	**Up to 6 Weeks** [a]		**Day 1 (Wk 0)**	**Weekly (Wks 1 to 4)** ± 2 days	**Every 2 Weeks (Wks 6 to 24)** ± 4 days	**Every 4 Weeks (Wks 28 to EOT)** ± 4 days [b]	**EOT or ET** ± 7 days	**EOS (4 wks post EOT or ET)** ± 7 days
	1	**2**						
Written informed consent	X							
Eligibility criteria	X		X					
Demographics and medical history	X							
Physical examination	X		X		Wks 12 [c], 24 [c]	Wks 36 [c], Q12Wk [c, d]	X	X [c]
Height, weight	X		X [e]			Wk 24 and every 24 weeks [e]		
Blood pressure, heart rate, respiratory rate, temperature [f]	X	X	X	X	X	X	X	X
Hemoglobin		X			X [g]	X [g]		
CBC with WBC differential	X		X	X	Wks 8. 12, 20	Wk 28, Q8Wk	X	X
Serum chemistry	X		X	Wk 2	Wks 8,12, 20	Wk 28, Q8Wk	X	X
LFTs, CPK				Wk 2	Wks 6, 16			
Lipid panel (whenever fasting possible)	X		X	Wk 4	Wks 8, 12, 24	Wks 32, 40, 48, 60, Q24Wk	X	X
Serum iron, ferritin, TIBC, TSAT	X		X	Wk 4	Wks 8, 12, 20	Wk 28, Q8Wk	X	X
CHr	X		X	Wk 4	Wks 8, 12, 20	Wk 28, Q8Wk	X	X
HbA1c	X		X		Wk 12	Wks 28, 44, 60 Q16Wk [d]	X	X
Vitamin B_{12}, folate	X							
HIV ELISA, HBsAg, anti-HCV Ab	X							
Serum hCG pregnancy test	X [h]				Wks 12, 24	Wk 36, then Q12 weeks	X	X
Reticulocyte count			X	Wks 1, 2	Wks 8, 20	Wk 44, Q24Wk	X	X
Special laboratory analytes (hepcidin, hs-CRP)			X	Wk 4	Wks 12, 20	Wk 44, Q24Wk	X	X
Optional archival serum/plasma samples			X	Wk 4	Wks 12, 20	Wk 44, Q24Wk [d]	X	X
HemoCue® assessment			X	X	X	X		
Quality-of-life questionnaires			X		Wk 12	Wks 36, 52 [d]	X	
12-lead ECG			X			Wk 24 and every 24 weeks	X	
Renal ultrasound [i]	X							
Dose adjustment [j]				X	X	X		
Adverse event recording	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X
Procedure and nondrug therapy recording	X	X	X	X	X	X	X	X
Study drug dispensing [k]			X	X [l]	X	X		

Footnotes on following page

Abbreviations: Ab = antibody; BP = blood pressure; CBC = complete blood count; CHr = reticulocyte hemoglobin content; ELISA = enzyme-linked immunosorbent assay; EOT = End of Treatment; EOS = End of Study; ET = early termination; Hb = hemoglobin; HbA1c = glycated hemoglobin A1c; 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; PE = physical examination; RBC = red blood cell; RR = respiratory rate; SmPC = summary of product characteristics; TIBC = total iron binding capacity; TSAT = transferrin saturation; TX = treatment; WBC = white blood cells; Wk(s) = week(s); X = mandatory test/assessment.

a Screening Hb values must be obtained at least 2 days apart.

b Treatment duration is variable for each subject. All subjects will remain in the study treatment until up to 3 years after the last subject randomized.

c Targeted PE only (eg, respiratory and cardiovascular).

d If the indicated assessments fall on a study treatment visit that is within two weeks of the planned EOT visit, then these specified assessments can be postponed until the EOT visit.

e Weight only (HD subjects: use dry weight).

f Perform HR and BP at all week visits. Additional respiratory rate and temperature are measured at Day 1/Week 0 and EOT/ET.

g Dedicated Hb sample for central lab should be collected during the visits where CBC is not collected.

h Collect from female subjects of child bearing potential only (for definition, see Section 3.6.6) .

i A renal ultrasound examination will be performed during screening if no record of a renal imaging modality exists within 12 weeks prior to randomization.

j Roxadustat subjects: Dose adjustments will be permitted from Week 4 onward, and every 4 weeks thereafter (except in extenuating circumstances) to correct and maintain subjects to a target Hb range. Please refer to dose adjustment rules as stated in Appendix 2.

Epoetin alfa subjects: Dose adjustments for HD subjects receiving epoetin alfa will follow the country specific product labeling (eg, PI; SmPC) for dosing and dose adjustments. For HHD and PD subjects, local standard of care may be followed for dosing and dose adjustments.

k All assessments should be done prior to first study drug administration.

l Dispense every other week

m Subjects who prematurely discontinue study treatment will complete the ET and EOS visits, and – unless consent is withdrawn – will continue to be followed for CV events of interest, vital status and hospitalizations until study closure. These subjects will be asked to return for study visits every 3 to 6 months, or be available via telephone.

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. **It is the responsibility of the Investigator to expeditiously review LFTs, follow these guidelines and contact the Medical Monitor if a study subject meets any of the LFT abnormalities specified below.** In addition:

Repeat LFTs within 2 to 3 days if:	**Discontinue Study Drug, if:**
• ALT **or** AST > 3 x ULN, **or** • Tbili > 2 x ULN	• ALT or AST > 8 x ULN, **or** • ALT or AST > 5 x ULN for > 2 weeks, **or** • ALT or AST > 3 x ULN and (Tbili > 2 x ULN or INR > 1.5), **or** • ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; LFT = liver function test; Tbili = total bilirubin; ULN = upper limit of normal.

Repeat LFTs 2 to 3 times weekly, then weekly or less until abnormalities stabilize or return to within normal limits. LFTs should include the usual 4: ALT, AST, Tbili and ALP

If close monitoring for LFTs in a subject is not possible, study drug should be discontinued

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

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 prior to the start of the dialysis procedure that day, preferably using the nondialysis arm. In subjects on HHD/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 HHD/PD and should be measured approximately at the same time of the day at each visit.

Appendix 6 Permitted Intravenous Iron Therapy

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