TITLE PAGE NCT #NCT04484857

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Phase 3b Multicenter, Open-Label Single Arm Study of Roxadustat: Either as Conversion from an Erythropoiesis Stimulating Agent (ESA), or as Initial Anemia Treatment in Hemodialysis (HD) Patients - **ASPEN Study**
PROTOCOL NUMBER:	FGCL-4592-096
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	074454
STUDY DRUG:	Roxadustat (FG-4592)
INDICATION:	Anemia associated with ESRD
FIBROGEN MEDICAL MONITOR:	Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] Fax: [redacted] E-mail: [redacted]
PROTOCOL VERSION & DATE:	
ORIGINAL:	28 February 2020
AMENDMENT 1:	20 August 2020

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Phase 3b Multicenter, Open-Label Single Arm Study of Roxadustat: Either as Conversion from an Erythropoiesis Stimulating Agent (ESA), or as Initial Anemia Treatment in Hemodialysis (HD) Patients – ASPEN Study

FGCL-4592-096

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

CONFIRMATION OF PROTOCOL APPROVAL

Amendment 1 Date: 20 August 2020

This protocol is approved by FibroGen.

DocuSigned by:

[redacted] 09-Sep-20 | 08:22:06 PDT

Date

FibroGen, Inc.

SUMMARY OF CHANGES
Protocol Amendment 1

Description of Change	Rationale for Change	Section(s) Affected
Major Changes:		
Planned study centers and number of subjects have been increased from 20 to approximately 30 centers and from 200 to approximately 300 subjects, respectively.	Number of planned centers and subjects have been increased to evaluate roxadustat dosing (initiation or conversion from ESA) in ESRD patients who are receiving hemodialysis at different dialysis organizations.	Synopsis Figure 2
Exclusion criterion # 13 updated From: Subject has a diagnosis or suspicion (e.g., complex kidney cyst or Bosniak Category II or higher) of renal cell carcinoma as shown on renal imaging performed within 24 weeks prior to enrollment To: Subject has a diagnosis or suspicion (e.g., complex kidney cyst or Bosniak Category II or higher) of renal cell carcinoma (PI's discretion)	To allow the Principal Investigator to make a determination based on clinical judgement in order to minimize additional clinic visit for renal imaging during current pandemic	Synopsis Section 5.2
Minor editorial changes (to correct typographical errors and to improve consistency and clarity)		
Subjects who wish to permanently discontinue roxadustat, after EOT should receive the first ESA dose at least two days after the last roxadustat dose instead of three days.	To correct typographic error	Synopsis Section 4.6 Section 7.4
Word "estimated" added before "Dry weight in HD subjects" for inclusion # 9	For better clarification and consistency	Synopsis Section 5.1
Exclusion criteria #24 and #25 were not numbered separately due to formatting error. This is corrected.	To correct formatting error	Synopsis
Updated the Note to remove the word "post dialysis" for subject's dry weight at enrollment	For better clarification and consistency	Table S2
Body weight categories for patents initiating roxadustat dosing have been corrected as follows (to align with the synopsis): from ≤ 100 kg to < 100 kg and from > 100 kg to ≥ 100 kg	To correct typographic error	Table 2
Temperature collection requirement added with vital signs for applicable visits	To correct an inadvertent error	Section 7
Clarified that central Hemoglobin during weeks 12 to 24 should be a part of CBC	For better clarification	Section 7.3.3

Protocol requirement to perform renal ultrasound removed from screening visit	To align with the revised Exclusion Criterion # 13	Table 4
Sample size determination (width of CI) has been revised	To align with the revised number of subjects in the study	Synopsis Section 9.1

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LIST OF ABBREVIATIONS

~	approximately
Ab	antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration curve
AV	arteriovenous
BIW	twice weekly
BL	baseline
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CHr	reticulocyte hemoglobin content
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum concentration
CM	Concomitant Medication
CS	clinically significant
CYP	cytochrome P450
dBP	diastolic blood pressure
DD-CKD	dialysis-dependent chronic kidney disease
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
eEPO	endogenous erythropoietin
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study
EOT	End of Treatment
EPO	Erythropoietin
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
ET	Early Termination (visit)
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hb	Hemoglobin
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HD	Hemodialysis
HEENT	Head Eye Ear Nose and Throat
HIF	hypoxia-inducible factor
HIF-PH	HIF prolyl hydroxylase
HIF-PHI	HIF prolyl hydroxylase inhibitor
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
ITT	Intent to Treat Population
IV	Intravenous
KDOQI	kidney disease outcomes quality initiative
LFT	liver function test
N (or n)	sample size
NCS	not clinically significant
NDD-CKD	Non-dialysis dependent chronic kidney disease
NYHA	New York Heart Association
PD	peritoneal dialysis
PH	prolyl hydroxylase
PK	Pharmacokinetics
QW	once weekly
RBC	red blood cell
RR	respiratory rate
RRT	renal replacement therapy
SAE	serious adverse event
SAF	safety analysis set
sBP	systolic blood pressure
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIBC	total iron binding capacity
TIW	three times weekly
TSAT	transferrin saturation
UIBC	unsaturated iron binding capacity
ULN	Upper limit of normal
USRDS	United States Renal Data System
VEGF	vascular endothelial growth factor
WBC	white blood cell
Wt	Weight

1. PROTOCOL SYNOPSIS

Study Title:	Phase 3b Multicenter, Open-Label Single Arm Study of Roxadustat: Either as Conversion from an Erythropoiesis Stimulating Agent (ESA), or as Initial Anemia Treatment in Hemodialysis (HD) Patients - **ASPEN Study**
Protocol Number:	FGCL-4592-096
Investigational Product:	Roxadustat (FG-4592)
Target Population:	Subjects with end-stage renal disease (ESRD) on HD, who either are on a stable ESA dose, or are newly initiating anemia treatment
IND Number:	074454
Study Phase:	Phase 3b
Study Centers Planned:	Approximately 30 sites in the USA
Number of Subjects Planned:	Approximately 300 subjects
Primary Objectives:	To confirm safe and effective Roxadustat dosing regimens among in-center HD subjects converted from ESA therapy (>=6 weeks ESA treatment) or who are ESA-naïve (<6 weeks ESA treatment)
Safety / Exploratory Objectives:	• Assessment of treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) • Laboratory parameters, including iron indices • Utilization of intravenous (IV) iron • Dosing compliance • To test operational characteristics of converting a population of ESRD subjects from an injectable to oral anemia therapy
Study Design Overview:	Single-arm study to evaluate roxadustat in correcting or maintaining Hb in ESRD subjects receiving in-center hemodialysis: • Either after conversion from a stable ESA dose: ESA use ≥ 6 weeks prior to conversion to roxadustat dosing • Or as initial anemia treatment, in subjects with < 6 weeks of ESA use or no prior ESA use prior to start of roxadustat dosing The study periods are as follows: ○ **Screening Period:** Up to 6 weeks ○ **Treatment Period:** 24 weeks ○ **Post-Treatment Follow-Up Period**: Subjects permanently discontinuing roxadustat should have one final safety assessment 28 days after the last roxadustat dose. For subjects converted from an ESA, the initial roxadustat dose is based on the average prescribed ESA dose in the last 4 weeks (8 weeks for Mircera) prior to conversion (See Table S1). Roxadustat treatment should start after the following intervals: • Two days after stopping epoetin

	• One week after stopping darbepoetin alfa • Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera®) For subjects initiating anemia treatment (< 6 weeks of prior ESA use), the initial roxadustat dose is based on estimated dry weight at enrollment (See Table S2). Roxadustat dose adjustments should follow the Dose Adjustment Rules, to maintain Hb within the target range specified in Table S3). During the Treatment Period, subjects will attend biweekly study visits from Day 1 to Week 8, followed by every 4-week study visits, from Week 8 – 24. Local Hb values will be drawn, prior to dialysis, in order to determine the need for a dose adjustment, and to assess for excessive rate of Hb rise, in real-time. After completing the Treatment Period (Week 24 /EOT), subjects who wish to permanently discontinue roxadustat, should receive the first ESA dose at least two days after the last roxadustat dose. Subjects permanently discontinuing roxadustat should also have one final safety assessment 28 days after the last roxadustat dose. See Table 4 for the complete Schedule of Assessments. An extension of roxadustat treatment after 24 weeks may be offered to interested subjects within the context of this study protocol upon agreement of the study site, until roxadustat is commercially available, or up to 1 year after completing the 24 weeks, whichever comes first.
Inclusion Criteria:	A subject is eligible for the study if all of the following criteria are met: 1. Subject has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines 2. Subject is ≥ 18 years of age 3. Receiving in-center hemodialysis for end stage renal disease (ESRD) 4. Prior ESA use: • For a subject converting from an ESA: On ESA ≥ 6 weeks and the prescribed ESA dose should remain stable (as determined by PI) during the 4 weeks prior to initiating roxadustat treatment • Subject is initiating anemia treatment: Defined as: < 6 weeks of prior ESA use or no prior ESA use 5. Vascular access must be a functioning native arteriovenous fistula or graft with adequate flow in the opinion of the investigator, or permanent tunneled catheter. 6. Screening Hb (based on central lab value; measured within 10 days prior to initiating roxadustat treatment): • Subjects converting from an ESA: screening Hb is between 9.0 to 12.0 g/dL • Subjects initiating anemia treatment: screening Hb is < 10.0 g/dL

	7. Ferritin ≥ 50 ng/mL, Transferrin saturation (TSAT) ≥ 10% at screening (subject may qualify after receiving iron supplement per local standard of care) 8. Subject's alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are ≤ 3 x upper limit of normal (ULN), and total bilirubin (TBL) is ≤ 1.5 x ULN at screening and prior to initiating roxadustat treatment. (TBL up to 2 x ULN may be allowed if AST and ALT are within normal limit) 9. Subject's body weight (estimated dry weight in HD subjects) is 45.0 to 160.0 kg
Exclusion Criteria:	Subjects will be excluded if any of the following criteria are met: 1. Subject has received a red blood cell (RBC) transfusion within 4 weeks prior to enrollment 2. Subject has a known history of myelodysplastic syndrome or multiple myeloma 3. Subject has a known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia or other known causes for anemia other than chronic kidney disease (CKD) 4. Subject has known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition 5. Subject has a known chronic inflammatory disease that is determined by the investigator to be the primary cause of anemia (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) 6. Subject is anticipated to undergo elective surgery that is expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization. 7. Subject has active or chronic gastrointestinal bleeding 8. Subject has been treated with iron-chelating agents within 4 weeks prior to enrollment 9. Subject has a history of chronic liver disease (eg, chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver) 10. Subject with New York Heart Association (NYHA) Class III or IV congestive heart failure 11. Subject has had an MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (excluding vascular dialysis access stenosis/thrombosis) (eg, DVT or pulmonary embolism) within 12 weeks prior to enrollment 12. Subject has uncontrolled hypertension, in the opinion of the Investigator 13. Subject has a diagnosis or suspicion (e.g., complex kidney cyst or Bosniak Category II or higher) of renal cell carcinoma (PI's discretion) 14. Subject has a history of malignancy, except for the following: cancers determined to be cured or in remission for ≥ 2 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps 15. Subject is positive for any of the following: • Human immunodeficiency virus (HIV)

	• Hepatitis B surface antigen (HBsAg) • Anti-hepatitis C virus antibody (anti-HCV Ab) 16. Subject has an active, clinically significant infection at the time of enrollment as determined by the investigator 17. Subject has any of the following known untreated conditions as determined by the investigator: proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion (subjects who are already blind may qualify to participate) 18. Subjects with prior organ transplant who have one of the following conditions or states a) Experienced rejection of transplanted organ within 6 months of transplantation b) Currently on high doses of immunosuppressive therapy (per discretion of the investigator) c) Are scheduled for organ transplantation (on the waiting list for kidney transplant is not exclusionary) 19. Subject has participated in an interventional clinical study or has been treated with an investigational drug within 4 weeks prior to screening 20. Subject has drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that may lead to reduced absorption of study drug (determined by the investigator) 21. Subject has an anticipated use of dapsone or androgen in any dose amount or anticipated chronic use of acetaminophen or paracetamol > 2.0 g/day during the study 22. Subject has a history of alcohol or drug abuse within 6 months prior to screening as determined by the clinical judgment of the investigator 23. Females of childbearing potential, if not practicing complete sexual abstinence or using contraception as detailed in the protocol; male subjects (if not surgically sterile; i.e., no vasectomy) with sexual partners of childbearing potential, if not practicing complete sexual abstinence or using contraception 24. Pregnant or breastfeeding females 25. Subject has any medical condition that in the opinion of the Investigator may pose a safety risk to the subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation
Study Procedures:	See Schedule of Assessments (Table 4)
Investigational Product	Roxadustat tablets are available in 20, 50, 70, 100 and 150 mg doses for oral administration. All tablets must be administered whole. **Route of Administration:** Oral (all tablets must be administered whole) **Dosing Frequency:** Subjects will be dosed three times weekly (TIW), except if a subject requires < 60 mg/week to maintain Hb levels, in which case dose frequency may be reduced in a stepwise fashion, e.g., to twice weekly (BIW), then once weekly (QW). **Initial Doses:** • **Conversion from ESA to Roxadustat:**

The initial roxadustat dose is determined using a conversion table based on the subject's prescribed ESA dose in the last 4 weeks prior to enrollment (for Mircera®: in the last 8 weeks prior to enrollment) (Table S1).
Roxadustat treatment should start after the following intervals:

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

If the converted initial dose exceeds the maximum dose of 3.0 mg/kg/dose then the next-lower dose step should be chosen as the initial dose.
If a subject is on ESA dose hold for high haemoglobin during screening, enrollment should be delayed until the subject is ready to resume anaemia treatment. Upon enrollment, all subjects must initiate roxadustat at Day 1.

Table S1: Conversion from ESA to Roxadustat

Previous dose of Darbepoetin alfa (mcg/week)	Previous Dose of Epoetin alfa (IU/week)	Previous Dose of Mircera® (mcg/month)	Starting Dose of Roxadustat (mg/dose TIW)
<25	<5000	<80	70
25 to 40	5000 to 8000	80 to 120	100
>40	>8000	>120	150

- **Initiation of Roxadustat in subjects with < 6 weeks of prior ESA use:**

Initial roxadustat dosing is based on broad body weight categories (estimated dry weight at enrollment):

Table S2: Initial Roxadustat Dosing:

Body Weight Category	< 100 kg	≥ 100 kg
Roxadustat Dose (TIW)	70 mg	100 mg

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

Dose Adjustments:

During the Treatment Period, roxadustat dose adjustment will be made starting at Week 4 and at intervals of every 4 weeks thereafter according to the dose adjustment algorithm below, in order to achieve an Hb level of 11 g/dL and maintain an Hb of 11±1 g/ dL:

Table S3: Dose Adjustments:

Change in Hb over previous 4 weeks:	Current Hb level: <10.5 g/dL	10.5 to 11.9 g/dL	12.0 to 12.9 g/dL	≥13.0 g/dL
> 1.0 g/dL	No change	↓	↓	• Hold dosing • Check Hb and resume dosing when Hb <12.0 g/dL, at a dose reduced by 2 steps
-1.0 g/dL to +1.0 g/dL	↑	No change	↓	
< -1.0 g/dL	↑	↑	No change*	

↑: Increase dose by one step; ↓: reduce dose by one step.
*Continue to hold dose

Dose adjustment steps: 20, 40, 50, 70, 100, 150, 200, 250, 300 and 400 mg

If Hb increases by >2.0 g/dL within a 4-week period, reduce dose by one step.
Roxadustat dose adjustment reviews should occur every 4 weeks, except if the following criteria are met:

- Rate of Hb rise > 2 g/dL within 4 weeks: reduce dose by 1 dose step
- Hb level ≥ 13g/dL: hold dose, check Hb weekly or as deemed necessary by investigator until Hb drops to < 12g/dL, resume dosing at 2 dose steps lower

Dose adjustments or temporary dose holds for excessive rate of Hb rise or Hb above 13 g/dL can occur at any time during the Treatment Period. Any dose adjustment will reset the dose-adjustment window to every 4 weeks thereafter (e.g., dose adjustment for a qualified reason at Week 6 leads to next dose adjustment at Week 10).
Prescribed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower. Estimated dry-weight at enrollment should be used for the entire treatment period.

Rescue Therapy and Emergency Procedures:

Rescue Therapy Guidelines:
Rescue therapy guidelines are provided to optimize the standardization of rescue therapy, and to ensure the safety of individual study subjects.
Red Blood Cell Transfusion (for all subjects)
RBC transfusion should be considered if rapid correction of anemia is required to stabilize the subject's condition (e.g., acute hemorrhage) or the Investigator is of the opinion that the blood transfusion is a medical necessity. If the situation permits, the Medical Monitor should be informed prior to any scheduled RBC transfusion. Study treatment may continue during or after the RBC transfusion.
Erythropoiesis Stimulating Agent (ESA) Use
If possible, the use of ESAs as a "Rescue" modality should be carefully considered, and should be restricted to no more than one cycle of use during the Treatment Period; the Investigator may initiate use of an approved erythropoietin (EPO) analogue if all of the following criteria are met:

	• A subject's Hb level has not sufficiently responded to two or more dose increases or the maximum dose of study drug has been reached, and • The subject's Hb is < 8.5 g/dL on two consecutive measurements (central lab) drawn at least five days apart; and • Clinical judgment does not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in Hb, and • Reducing the risk of alloimmunization in transplant eligible subjects and/or reduction of other RBC transfusion-related risks is a goal Such ESA Rescue should be started ≥ 2 days after the last dose of roxadustat. ESA Rescue should be stopped when Hb > 9 g/dL or after 4-weeks, whichever comes first. If a subject requires longer than 4-weeks therapy due to inadequate response, or in other extenuating circumstances, the Medical Monitor should be contacted. Study treatment should be resumed after the following intervals: • Two days after stopping epoetin • One week after stopping darbepoetin alfa • Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera®) If more than one cycle of ESA rescue is required, the Investigator should permanently discontinue study drug. Inadvertent ESA administration, such as ESA administration during a hospitalization, should not be counted as rescue unless above criteria are met; these subjects may be allowed to restart roxadustat dosing if considered safe by the Investigator or Medical Monitor. All ESAs used during the Treatment Period, either planned or inadvertent, should be recorded. ESAs and Roxadustat should not be administered concomitantly. **Emergency Procedure (Therapeutic Phlebotomy)** If there are clinical concerns for a subject's high Hb levels, the Investigator may decide to perform a therapeutic phlebotomy in addition to temporarily withholding the study drug. This should be documented and discussed with the Medical Monitor.
IV Iron Use:	**Intravenous Iron Supplementation** Intravenous iron should be considered for subjects with ferritin <100 ng/mL or TSAT <20%. IV iron should administered in 5 doses of 50 mg/dose. Medical Monitor should be contacted if more IV iron is required. In this study, oral iron may be administered for iron supplementation without restriction. Dose and frequency of administration of oral iron are to be determined by the investigator.
Prohibited Medication:	The following medications/therapies are prohibited during the period identified: • Any investigational drug from 4 weeks prior to screening until EOS • Androgens from screening until EOS

	• Iron-chelating agents (e.g., deferoxamine/desferrioxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to enrollment until EOS • Dapsone (at any dose) from screening until EOS • Chronic doses acetaminophen/paracetamol > 2.0 g/day from enrollment until 1 week after EOT
Efficacy Endpoints and Assessments:	***Efficacy Endpoints:*** • Proportion of subjects with mean Hb ≥ 10g/dL, averaged from Week 16 through Week 24 • Mean Hb change from baseline to average Hb from Week 16-Week 24 ***Exploratory Endpoints/Analyses:*** • Time to first RBC transfusion • Proportion of patients with a mean Hb levels ≥10 g/dL in the first 8 weeks after conversion • Proportion of patients with a mean Hb level ≥10 g/dL based on baseline ESA use status (≥ 6 weeks and < 6 weeks) • Evaluate the utilization of intravenous (IV) iron (IV iron use/4 weeks) • Evaluate the effect on iron indices • Evaluate dosing adherence • Conversion subjects: ○ Comparison of starting dose of roxadustat to roxadustat dose at Week 16-24 • Mean number of dose adjustments during study
Safety Assessments and Endpoints:	**Study-specific safety will be assessed by evaluating the following:** • Incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) • Clinically significant changes in laboratory values from baseline • Vital signs
Statistical Methods:	**Stratification:** Not applicable **Sample size determination:** Approximately 300 subjects with anemia of CKD (either with or without treatment with ESA at enrollment) and on hemodialysis are planned in this study. This number of subjects distributed across the specified number of sites is adequate to evaluate the primary study objective. Assuming the proportion of subjects that maintain Hb levels ≥10g/dL from Weeks 16-24 is at least 80%, with a sample size of 300, the study will be able to produce a two-sided 95% confidence interval (CI) with a width equal of 9.5%. **Analysis Sets:** The FAS set will consist of all subjects who signed informed consent, who were enrolled, and who provided baseline Hb data and data for at least one post baseline Hb time point. The FAS set will be used for all efficacy endpoints and analyses.

	The Safety analysis set will include all enrolled subjects receiving at least 1 dose of study treatment. The safety analysis set will be used for all safety endpoints and exposure to study treatment outcomes. Efficacy analyses: The efficacy endpoint will be evaluated using the proportion (%) of subjects with mean value of Hb measurements of ≥ 10g/dL from Week 16 through Week 24. For the efficacy analysis, a multiple imputation (MI) method will be used. This will be implemented on the raw Hb values, then the endpoint will be derived based on the imputed data (algorithm as used for the previous phase 3 studies). For continuous endpoints, changes from baseline will be presented descriptively. Proportion of responders will be presented descriptively with count and percentages and 95% confidence interval of the responder rate. Time to response will be analyzed using the Kaplan-Meier method with KM curve plotted. **Safety:** The safety analyses will be performed using the Safety Analysis Set (SAF). Safety parameters include TEAEs, TESAEs, laboratory parameters and vital signs. The number and percentage of subjects reporting treatment-emergent AEs (TEAEs) and TESAEs will be tabulated. Descriptive statistics will be presented for laboratories and vital signs.

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

2. BACKGROUND

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

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

2.1. Introduction

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

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

The average prevalence of CKD, regardless of age, ranges between 3%-17% in Europe and the all-cause mortality risk increases exponentially as CKD stages advance (Bruck K, et al). The prevalence of DD-CKD is 887 per million people in China (2011 Shanghai Dialysis Registry Report) and in the US, CKD affected 13% of the US adult population (~ 29 million adults) in 2007, and the prevalence is rapidly growing in both the US (Coresh et al., 2007) and worldwide (Xie Y, et al). In Europe, the average prevalence of CKD regardless of age lies between 5 and 11% (Zoccali et al., 2010).

The number of patients suffering from end-stage renal disease (ESRD) also continues to increase worldwide. The US has one of the highest prevalence rates of ESRD in the world: in 2010, the US had over 1700 patients with ESRD per million population, a 23% increase compared to 10 years before (USRDS, 2011). In 2009 (point prevalence as of December 31st), there were approximately 570,000 patients with ESRD in the US, of whom 370,000 were receiving hemodialysis (HD), 27,000 were receiving peritoneal dialysis (PD), and 173,000 had a functioning kidney transplant (USRDS, 2011). In recent years, those older than 75 years have been observed to have the highest incidence of treated ESRD (1735 per million populations in 2007, US by age and race/ethnicity). The adjusted ESRD incidence rates were 998 per million populations for African Americans, 396 per million population for Asians/Pacific Islanders, and 273 per million populations for whites in 2007 (USRDS, 2009). In Europe, over the period 1992–2005, the overall crude prevalence of RRT for patients with ESRD increased from 480 to 807 patients per million populations (Zoccali et al., 2010). The average expected life expectancy of a dialysis patient is 5.9 years, compared to 16.4 years for a transplant patient, and 25.2 years for someone of comparable age in the general population (USRDS, 2009). The prevalence of ESRD is projected to grow to 774,000 by the year 2020 (USRDS, 2009). Data from selected countries in Europe indicate that the 5-year mortality rates in incident patients on RRT are 52% in all patients, and 21%, 32% and 73% for patients 0 to 14, 15 to 64 and over 65 years of age, respectively (Zoccali et al., 2010).

2.1.2. Anemia Associated with Chronic Kidney Disease

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

Anemia may present in the early stages of CKD and its prevalence increases as CKD progresses. Anemia is present in 17% of patients with late Stage 3 disease; this increases to 25% in patients with Stage 4 disease, and to 49% in patients with Stage 5 disease who have not yet progressed to requiring dialysis (Coresh et al., 2007; Go et al., 2004). Over 90% of patients undergoing dialysis are anemic. Half of all patients new to dialysis (50.1%) have hemoglobin (Hb) levels below 10 g/dL and approximately 28% have Hb levels below 9 g/dL (USRDS, 2003). Some studies from Europe provide data on anemia rates in patients who have been under care of nephrologists. In 1999, Jungers prospectively studied 403 consecutive ambulatory predialysis patients and found that 60% of patients with a creatinine clearance of < 20 ml/min/1.73 m2 were anemic (Hb < 11 g/dL) (Jungers et al., 2002). Between 2003 and 2005, Thilly studied predialysis anemia care in 6271 incident dialysis patients. The average level of predialysis Hb was 10.3 g/dl, and 63.6% of the patients had a Hb value lower than 11 g/dl (Thilly et al., 2008).

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

Anemia is associated with excess morbidity and mortality in patients with CKD and ESRD. In patients with CKD, the severity of anemia correlates directly with the risk of hospitalization, cardiovascular (CV) disease, and death (Collins et al., 1998). Anemia contributes to eccentric left ventricular hypertrophy and maladaptive remodeling of the left ventricle. Patients with the lowest Hb have worse outcomes, as was discussed in the post hoc analysis of mortality by Hb quintiles for the Normal Hematocrit and Correction of Hb and Outcomes in Renal Insufficiency (CHOIR) study in the Food and Drug Administration (FDA) briefing document for the October 2007 Cardiovascular and Renal Advisory Committee (Unger, 2007). Similar observations are found in the United States Renal Data System (USRDS) mortality data stratified by Hb. All-cause mortality stratified by Hb (between the years of 1993 to 1996) indicated significantly higher first-year death rates in patients with Hb levels < 9 g/dL, compared to 11 to 12 g/dL. This trend continued to worsen, as reflected in USRDS data collected between 1998 1999 where the death rate rose by ~75% compared to the 1993 to 1996 period (USRDS, 2000; USRDS, 2002). This increase coincides with the introduction of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in 1997. The relative risk of all-cause mortality for patients with Hb < 9 g/dL is twice that of patients with Hb > 12 g/dL (USRDS, 2002). The relative risk ratio of CV hospitalization increases significantly to 1.26 in patients with Hb levels <9 g/dL compared to those with Hb at 11 to 12 g/dL (USRDS, 2001).

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

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

Today, therapy with erythropoiesis-stimulating agents (ESAs) is a major alternative to transfusion in managing anemia associated with CKD. For those not resistant to ESAs, parenteral administration of exogenous recombinant human EPO (epoetin alfa or beta) or pegylated analogues has been a widely accepted approach for the treatment of anemia in patients with CKD (Winearls et al., 1986; Eschbach et al., 1987; Eschbach et al.,1989a, Eschbach et al. 1989b), despite the documented safety risks. These safety risks include hypertension, thrombosis, and cerebrovascular events which may be

associated with supraphysiologic plasma EPO levels frequently observed with ESA therapy. Anemic patients with CKD or ESRD will require life-long treatment with these agents.

Although the treatment of anemia in CKD and ESRD is thought to contribute positively to a patient's quality of life, several studies in subjects with ESRD and NDD-CKD have shown higher mortality or trends in that direction in the higher-dosed ESA-treated cohorts when the protocol objective was to treat one of the cohorts to high, almost normal target Hb levels (Besarab et al., 1998; Drueke et al., 2006; Singh et al., 2006). An ESA dose relationship to mortality has been reported in a review of the USRDS database (Zhang et al., 2004) of ESRD patients who received higher ESA doses, particularly in those more anemic (i.e., Hb < 11 g/dL). The FDA has recognized these excess morbidity and mortality risks (FDA, 2007). Updated product labeling for the approved ESAs in 2007 include a boxed warning of greater risk of death and CV events when ESAs are administered to target high Hb concentrations (≥ 13.5 g/dL) compared with lower Hb targets. The FDA also acknowledged the potential off-target effect of ESAs contributing to excess mortality due to CV events and thrombosis (Unger, 2010). The currently approved ESA labeling directs prescribers to target Hb levels of 10 to 11 g/dL in the US and 10 to 12 g/dL outside the US. The literature on this topic, including meta-analyses, supports the view that the AEs associated with ESAs are typically observed when high doses are administered (Zhang et al., 2004; Unger, 2007; Szczech, 2008; Fishbane and Beserab, 2007; Besarab et al., 2009). Posthoc analyses of three major RCTs, (Kilpatrick et al., 2008; Szczech, 2008; Solomon et al., 2010) NHCT, CHOIR, and TREAT, indicates that outcomes correlate with "achieved" and not "target" Hb levels.

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

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

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

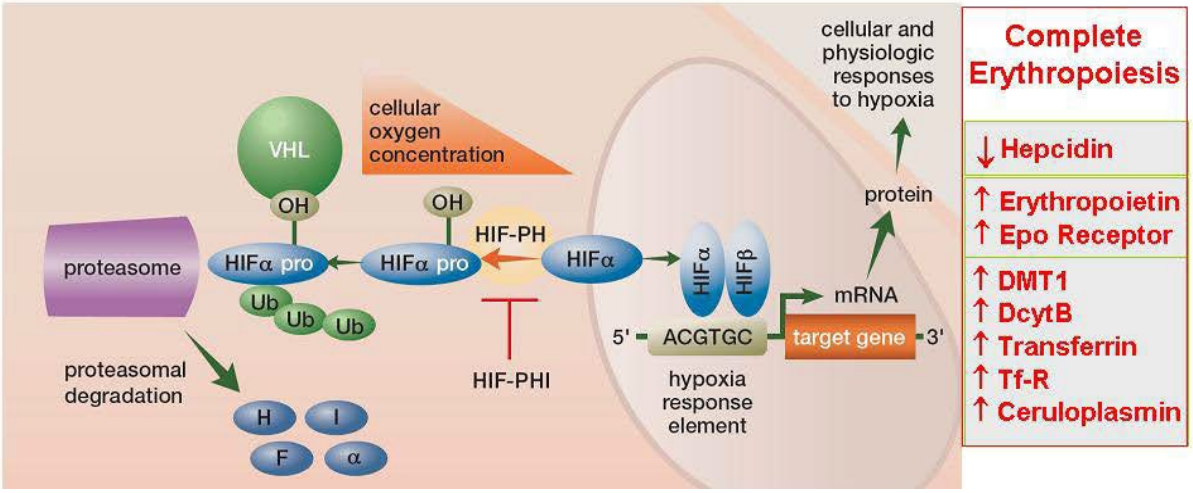
Roxadustat is an oral medication that could potentially deliver effective treatment for CKD-related anemia with less need for IV iron supplementation and without producing supraphysiologic levels of

circulating EPO, which may translate into an improved safety profile. Roxadustat is being evaluated as a potential alternative treatment for anemia in subjects with NDD-CKD and DD-CKD.

2.3. Mechanism of Action of Roxadustat

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

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



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

Source: Epstein, et al, 2001

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

Although HIF-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 HIF-PHs that utilize molecular oxygen as the substrate for hydroxylation. Thus, HIF-PH constitutes the body's main oxygen sensor by regulating the prevalence and activity of nuclear HIF protein. Under hypoxic conditions, HIF PHs are inactive and lead to initiation of the HIF-responsive transcriptional cascade (Wang et al., 1995; Semenza, 1998).
Roxadustat is a potent and reversible hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that transiently induces HIF stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure of humans to intermittent hypoxia. HIF induces expression of not only EPO, but also the EPO receptor and proteins that promote iron absorption and recycling from the macrophage iron storage system (Peyssonnaux et al., 2008). Thus, roxadustat pharmacologically stimulates erythropoiesis via the HIF pathway and in a manner consistent with the body's normal homeostatic response to anemia, but under normoxic conditions. In contrast to the classical paradigm, suggesting that anemia in CKD patients is caused by the inability of these patients to produce EPO, results of a study of roxadustat treatment of CKD subjects not requiring dialysis (Study FGCL-SM4592-017) suggest that the kidneys and other sites of EPO production in this patient population retain the ability to produce sufficient EPO for robust erythropoiesis.
Roxadustat also has the potential to effectively treat anemia caused by inflammation-induced functional iron deficiency, which are typically hyporesponsive to ESAs. In these conditions, iron availability for erythropoiesis is reduced due to a number of inflammatory mediators. Because HIF-PHIs such as roxadustat alter expression not only of the EPO gene but also of genes regulating iron metabolism, it is postulated that roxadustat may be effective in treating these anemias as well (Langsetmo et al., 2005).
Chronic hypoxia and intermittent hypoxia induce different sets of genes associated with HIF transcriptional activity, presumably because intermittent stimulation allows the restoration of HIF degradation, turnover, and inactivation. Transient activation of HIF thereby precludes sustained gene expression and the induction of genes that are expressed late after HIF activation, as well as expression of additional genes that are secondary to activation of HIF-dependent genes. Both nonclinical and clinical studies of roxadustat have successfully used the intermittent dosing paradigm to induce selective erythropoiesis and to optimize the Hb dose response. Furthermore, roxadustat was selected for development over other HIF-PHI candidate molecules based on an optimal biodistribution profile that enhances its selective actions. The specific tissues where roxadustat enters the cytoplasm and triggers gene expression reside in the main target organs for erythropoiesis: the kidney (EPO production), the bone marrow (increase in EPO receptors), the duodenum (transepithelial iron transport), and the liver (EPO production, transferrin production, and down-regulation of hepcidin production); roxadustat distributes preferentially to these organs.
The physiologic mechanisms underlying the effects of roxadustat on erythropoiesis are distinct from that of ESAs, and these differences result in several potential advantages over ESAs beyond the convenience of oral therapy. These potential advantages include:

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

2.4. Clinical Experience with Roxadustat

In the recently completed global Phase 3 program, roxadustat was studied in a broad range of adult CKD patients (including both non-dialysis-dependent [NDD] and dialysis-dependent [DD] CKD populations) with anemia. Roxadustat was compared against placebo in three pivotal NDD CKD studies comprising 4277 patients, and against epoetin alfa (standard of care ESA) in three pivotal DD studies comprising 3880 patients.

The effectiveness of roxadustat was consistently demonstrated across this wide spectrum of adult CKD patients, including NDD patients with baseline eGFR <15 mL/min/1.73 m^2 who were not previously included in prior NDD ESA studies. Roxadustat significantly increased Hb compared to placebo in NDD patients and was non-inferior with respect to ESA comparator in maintaining Hb within intended target range in DD patients. Moreover, roxadustat-treated patients had lower risk of red blood cell transfusions compared to placebo-treated and epoetin alfa-treated patients in the pooled NDD and DD CKD studies, respectively. Roxadustat also effectively treated anemia in patients whose baseline C-reactive protein (CRP), a marker of inflammation, was >ULN (roxadustat dosing was similar regardless if CRP was >ULN or <ULN), and roxadustat improved iron metabolism efficiency by reducing serum hepcidin and ferritin levels.

The safety of roxadustat was evaluated against placebo in NDD CKD studies and against epoetin alfa in DD CKD studies. Incident dialysis (ID) patients (a sub-group of the overall DD population who initiated chronic dialysis with the past four months) who were treated with roxadustat had a lower risk of major adverse CV events (MACE defined as stroke, myocardial infarction, all-cause death) and MACE+ (events that comprised MACE plus hospitalized unstable angina and congestive heart failure), and a trend towards reduction of risk in all-cause mortality, compared with those who were treated with epoetin alfa. The overall safety profile of roxadustat was comparable to placebo for NDD CKD patients and comparable to epoetin alfa for DD and ID CKD patients with respect to most adverse events and serious adverse events. A number of adverse drug reactions (ADRs) were identified, including vascular access thrombosis, deep vein thrombosis, and seizures. Serious infection was considered an important potential risk, but causality was not established. No adverse hepatic risks from liver enzyme monitoring were identified, and there were no clinically important changes in ECG parameters, including no evidence of QT prolongation.

For detailed safety information, please refer to the most current version of the IB.

2.4.1. Pharmacokinetics and Pharmacodynamics

The pharmacokinetics (PK) and pharmacodynamics of roxadustat were characterized in studies in healthy volunteers and in dialysis and nondialysis CKD subjects. Roxadustat showed generally dose proportional PK (except at the lowest dose of 0.3 mg/kg); $t_{1/2}$ was 12 to 14 hours in healthy volunteers, and 15 to 19 hours in dialysis subjects (after a single 1 and 2 mg/kg dose). The exposure was higher in dialysis patients compared to healthy volunteers. Roxadustat can be administered before or after dialysis, since the PK of roxadustat was not significantly altered when administered prior to the start of dialysis compared with after dialysis (Study FGCL-4592-039).
A relative bioavailability study was conducted in 24 healthy volunteers comparing capsule formulation, which was used in Phase 1 and Phase 2 studies, with tablet formulation, which was developed for Phase 3. The study demonstrated bioequivalence to bridge the two formulations. With an intermittent dose regimen (once weekly [QW], twice weekly [BIW[or three times a week [TIW]), no or limited accumulation in mean area under the concentration curve (AUC) or maximum concentration (C_{max}) was observed. Furthermore, no evidence was found for time-dependent PK (no auto-induction or inhibition). Roxadustat is highly protein bound and the PK of roxadustat is not

affected by dialysis. Metabolites found in urine suggested Phase 2 metabolism as the major metabolic pathway. In plasma, parent roxadustat is the main component. The inhibitory potential of roxadustat on cytochrome P450 (CYP) enzymes, based on in-vitro studies is limited, and the lowest inhibition constant (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 EPO (starting from single doses of 0.3 mg/kg), increases in reticulocytes (starting from doses of 2 mg/kg), and Hb responses (starting at 3 mg/kg). The mean peak level of plasma EPO following the Day 26 dose of 2.0 mg/kg TIW (the high therapeutic dose studied) was 326.3 ± 197.0 mIU/mL.

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

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

2.5. Summary

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

2.6. Roxadustat Dose Rationale

The starting roxadustat doses and dose titration algorithm in this study are based on Phase 3 program involving ESRD patients with anemia who converted to roxadustat from stable ESA and patients who never used ESA before. These dosing schedules effectively corrected anemia and or maintained Hb levels close to 11.0 g/dL.

Analysis of the Hb time course after initiation of treatment with roxadustat in patients previously not on ESA treatment stratified by body weight indicated that the starting doses for patients not previously receiving ESA treatment should be 70 mg for patients with a body weight of <100 kg, and

100 mg for patients with a body weight of ≥100kg. The proposed dose adjustment algorithm, applied every 4 weeks, effectively maintained Hb levels close to 11.0 g/dL in these patients.
For patients previously treated with an ESA, the applied starting doses of roxadustat (based on the conversion table) in conjunction with the dose adjustment algorithm resulted in Hb levels that were maintained close to 11.0 g/dL. The full dose range of 20 to 400 mg TIW was utilized in the Phase 3 dialysis studies.
In this study, the initial dose of roxadustat will be determined by the subject's average prescribed ESA dose in the last 4 weeks prior to enrollment if on epoetin or darbepoetin (8 weeks if on Mircera®).
Using the conversion table (Table 1), in this study, subjects will receive starting roxadustat doses of 70 mg, 100 mg, 150 mg, or 200 mg. If the converted initial dose exceeds the maximum dose of 3.0 mg/kg/dose then the lower dose step should be chosen as the initial dose. Roxadustat doses will be administered at a frequency of TIW. If a subject requires < 20 mg TIW (i.e., < 60 mg per week) to maintain a Hb level of 11±1 g/ dL, the dosing frequency should be reduced in a step-wise fashion e.g. TIW to BIW, BIW to QW, QW to Q-2 Week etc.

2.6.1. Maximum Dose for Roxadustat

The maximum allowed roxadustat dose in this study is set at 400 mg or 3.0 mg/kg/dose (based on estimated dry weight at enrollment in subjects on HD), whichever is lower. The highest dose tested in healthy subjects is 5 mg/kg single dose and 3.75 mg/kg TIW. The doses were safe and well tolerated with transient dose-dependent HR increases observed. No maximum tolerated dose (MTD) was reached in the clinical development of roxadustat based on the observed pharmacodynamic response (plasma EPO levels) and the predicted relation between EPO levels and Hb response; therefore exploration of higher doses was not deemed necessary. Plasma EPO levels increased in a supralinear manner with increasing roxadustat doses. In Phase 3 dialysis studies, the full dose range of 20 to 400 mg TIW was utilized.
In this study, prescribed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower.

2.7. Risks/Benefits of Roxadustat Treatment

The primary benefit of roxadustat is the treatment of anemia, including the relief of associated signs and symptoms of anemia and reduced risk of blood transfusion.
Similar to the Phase 3 dialysis studies, dose adjustment algorithm will be used to titrate roxadustat doses based on current Hb levels and the rate of change of Hb levels. Roxadustat doses may be held and/or the use of therapeutic phlebotomy is allowed in the event of Hb excursions above the intended target range. Adverse events (AEs) 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.

In all three pivotal dialysis studies, roxadustat was non-inferior and superior to epoetin alfa in the primary efficacy endpoint of the mean change in Hb from baseline averaged over Weeks 28-52. The efficacy of roxadustat, achieved with less IV iron supplementation, is accompanied by reduction in RBC transfusion, and demonstrated effective erythropoiesis regardless of inflammation with sustained response with stable mean roxadustat doses over time. In these dialysis studies, roxadustat treatment has shown a 14% reduction in MACE+ risk compared to epoetin alfa, and the risk of MACE and ACM in roxadustat treated patients are non-inferior to those treated with epoetin alfa. In

incident dialysis patients, roxadustat treated patients had a 30% reduction in the risk of MACE and a 34% reduction in MACE+, with a trend towards lower ACM risk, in comparison to epoetin alfa.

The safety of treatment with roxadustat will be carefully monitored by the sponsor to detect any potential safety signals that may arise during the study. Based on data so far obtained, treatment with roxadustat is expected to be efficacious in treating anemia in patients with CKD. The safety profile of the compound, together with the safety monitoring implemented would minimize the risk to study participants. The benefit-risk in this study is therefore deemed acceptable.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objectives

To confirm safe and effective Roxadustat dosing regimens among in-center HD subjects converted from ESA therapy (>=6 weeks ESA treatment) or who are ESA-naïve (<6 weeks ESA treatment).

3.1.2. Safety/Exploratory Objectives

- Assessment of treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs)
- Laboratory parameters, including iron indices
- Utilization of intravenous (IV) iron
- To test operational characteristics of converting a population of ESRD subjects from an injectable to oral anemia therapy

3.2. Efficacy Endpoints

3.2.1. Efficacy Endpoints

- Proportion of subjects with mean Hb $\geq$ 10g/dL, averaged from Week 16-through Week 24
- Mean Hb change from baseline to average Hb from Week 16-Week – 24

3.2.2. Exploratory Endpoints/Analyses

The additional exploratory endpoints in this study are:

- Time to first RBC transfusion
- Proportion of patient with a mean Hb levels ≥10 g/dL in the first 8 weeks after conversion
- Proportion of patient with a mean Hb level ≥10 g/dL based on baseline ESA use status (≥ 6 weeks and < 6 weeks)
- Evaluate the utilization of intravenous (IV) iron (IV iron use/4 weeks)
- Evaluate the effect on iron indices
- Evaluate dosing adherence
- Conversion subjects:
    - Comparison of starting dose of roxadustat to roxadustat dose at Week 16-24
- Mean number of dose adjustments during study

3.3. Safety Endpoints

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

- Incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs)
- Clinically significant changes in laboratory values from baseline
- Vital signs

4. STUDY DESIGN

4.1. Description of the Study

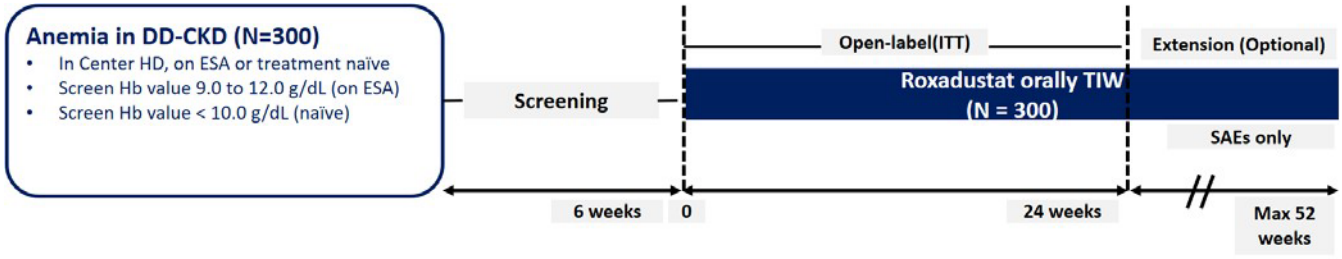
This open-label single arm study is designed to evaluate roxadustat in maintaining Hb in ESRD subjects receiving in-center HD either after conversion from a stable ESA dose: ESA use ≥ 6 weeks prior to conversion to roxadustat dosing or as initial anemia treatment, in subjects with < 6 weeks of total ESA use prior to start of roxadustat dosing.

The study periods are:

- **Screening Period:** Up to 6 weeks
- **Treatment Period:** 24 weeks
- **Post-Treatment Follow-Up Period:** Subjects permanently discontinuing roxadustat, should have one final safety assessment (TEAEs and TESAEs) 28 days after the last roxadustat dose.

An extension of roxadustat treatment after 24 weeks may be offered to interested subjects within the context of this study protocol upon agreement of the study site until roxadustat is commercially available, or up to 1 year after completing the 24 weeks, whichever comes first.

Figure 2: Study Design Overview



Primary Efficacy Endpoint:

- Proportion of subjects with mean Hb ≥ 10.0 g/dL, averaged over weeks 16-24

Secondary Efficacy Endpoints:

- Proportion of subjects with mean Hb between 10-12 g/dL, averaged from week 16 through week 24

Conversion subjects:

- Mean Hb change from baseline to average Hb from week 16-24

4.2. Study Rationale

The parameters of the Phase 3 roxadustat program did not include assessments of center-level, operational characterictics of the drug among subjects with ESRD receiving chronic, in-center hemodialysis. The safe and effective use of roxadustat in commercial dialysis centers requires an understanding of these operational characteristics, which this study will address. For example, drug preparation at the nursing station, distribution to subject, and adherence are all critical safety and efficacy features.

4.3. Screening Period

After signing the informed consent, subjects enter the Screening Period. All screening procedures are to be completed within 6 weeks. Subjects will be evaluated per the protocol inclusion/exclusion criteria to determine eligibility for participation in this trial.

4.4. Treatment Period

At the Day 1, subjects will discontinue prior ESA therapy and initiate roxadustat therapy.

4.5. Starting Dose of Study Drug

4.5.1. Route of Administration: Oral (all tablets must be administered whole)

4.5.2. Dosing Frequency:

Subjects will be dosed three times weekly (TIW), except if a subject requires < 60 mg/week to maintain Hb levels, in which case dose frequency may be reduced in a stepwise fashion, e.g., to twice weekly (BIW), then once weekly (QW).

4.5.3. Initial Doses:

4.5.3.1. Conversion from ESA to Roxadustat:

The initial roxadustat dose is determined using a conversion table based on the subject's previous prescribed ESA dose in the last 4 weeks prior to enrollment (for Mircera®: in the last 8 weeks prior to enrollment) (Table 1).

Roxadustat treatment should start after the following intervals:

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

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

Table 1: Conversion from ESA to Roxadustat

Previous dose of Darbepoetin alfa (mcg/week)	Previous Dose of Epoetin alfa (IU/week)	Previous Dose of Mircera® (mcg/month)	Starting Dose of Roxadustat (mg/dose TIW)
<25	<5000	<80	70
25 to 40	5000 to 8000	80 to 120	100
>40	>8000	>120	150

4.5.3.2. Initiation of Roxadustat Dosing in subjects with < 6 weeks of prior ESA or no prior ESA use:

The initial roxadustat dosing is based on broad body weight categories (estimated dry weight at enrollment) as described in Table 2.

Table 2: Initial Roxadustat Dosing:

Body Weight Category	**< 100 kg**	**≥ 100 kg**
Roxadustat Dose (TIW)	70 mg	100 mg

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

4.5.3.3. Dose Adjustments:

Dose adjustment evaluations will be made every 4 weeks and doses will be titrated based on Hb level and rate of Hb change according to Appendix 1. Any potential dose escalation/dose reduction will be at pre-defined dose step increments.

A dose reduction may be implemented at any time if the following criteria are met:

- Rate of Hb rise > 2 g/dL within 4 weeks: reduce dose by 1 dose step
- Hb level ≥ 13g/dL: hold dose, until Hb drops to < 12g/dL, resume dosing at 2 dose steps lower

Any dose adjustment will reset the dose-adjustment window to every 4 weeks thereafter (e.g., dose adjustment for a qualified reason at Week 6 leads to next dose adjustment at Week 10).

Prescribed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower.

Dose titrations decisions will be based on results from local Hb testing.

4.6. Post-Treatment Follow-Up Period

After completing the Treatment Period (Week 24/EOT) , subjects who wish to permanently discontinue roxadustat and switch to an ESA, the first ESA dose should be administered at least two days after the last roxadustat dose.
Subjects permanently discontinuing roxadustat, should have one final safety assessment 28 days after the last roxadustat dose.

4.7. Concomitant Medications, Procedures and Nondrug Therapies

4.7.1. Concomitant Medications

Concomitant medications (CMs) 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 (e.g., "rash"), documentation of the condition, as specific as possible, should be maintained in the subject's clinical study records as source documentation.
Use of herbal medicine during the study is not prohibited but strongly discouraged. All herbal and natural remedies should be reviewed by the investigator and if considered safe, may be allowed to continue at the same dose.

4.7.1.1. Phosphate Binders

When coadministered with roxadustat, in a clinical pharmacology study, the bioavailability of roxadustat was reduced. Subjects should be advised to discuss with the Investigator when changing the dose or dosing time of their phosphate binder while taking roxadustat. To optimize the absorption of roxadustat, subjects should be advised that roxadustat be taken at least one hour before or one hour after their phosphate binder. This does not apply to Lanthanum.

4.7.1.2. CYP2C8 and UGT1A9 Modifiers

Titrate the dose of roxadustat based on monitoring of Hb levels when initiating or discontinuing concomitant treatment with inducers or inhibitors of CYP2C8, or inhibitors of UGT1A9.

4.7.1.3. Statins

When coadministered with roxadustat, in clinical pharmacolgical studies, hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) exposure was increased 2- to 3-fold. Investigators should consider this interaction and local prescribing information when deciding on the appropriate statin dose for individual subjects, 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 3.

Table 3: Recommended Maximum Daily Dose of Statins

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

4.7.2. Supplemental Iron Use

In the phase 3 dialysis studies, all subjects were encouraged to take oral iron supplements as their first-line iron supplementation. Subjects randomized to roxadustat had a reduced need of IV iron compared to the active ESA comparator.
In this study, oral iron may be administered. Dose and frequency of administration are to be determined by the investigator.

4.7.2.1. Oral Iron Supplementation

In this study, oral iron may be administered for iron supplementation without restriction. Dose and frequency of administration of oral iron are to be determined by the investigator.

4.7.2.2. Intravenous (IV) Iron Supplementation

Intravenous iron should be considered for subjects with ferritin < 100ng/mL or TSAT <20%. IV iron should be administered in 5 doses of 50 mg/dose. Medical Monitor should be contacted if more IV iron is required.

In addition to scheduled assessments (Appendix 2: Table 4), iron indices may be assessed anytime (via central lab) to evaluate iron storage status of the subjects, if considered necessary by the Investigator.

4.7.3. Rescue Therapy Guidelines

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

4.7.3.1. Red Blood Cell Transfusion (all subjects)

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

4.7.3.2. Erythropoiesis Stimulating Agents

If possible, the use of ESAs as a "Rescue" modality should be carefully considered, and should be restricted to no more than one cycle of use during the Treatment Period; the Investigator may initiate use of an approved erythropoietin (EPO) analogue if all of the following criteria are met:

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

Such ESA Rescue should be started ≥ 2 days after the last dose of roxadustat.

ESA Rescue should be stopped when Hb > 9 g/dL or after 4-weeks, whichever comes first. If a subject requires longer than 4-weeks therapy due to inadequate response, or in other extenuating circumstances, the Medical Monitor should be contacted.

Study treatment should be resumed after the following intervals:

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

If more than one cycle of ESA rescue is required, the Investigator should permanently discontinue study drug.

Inadvertent ESA administration, such as ESA administration during a hospitalization, should not be counted as rescue unless above criteria are met; these subjects may be allowed to restart Roxadustat dosing if considered safe by the Investigator or Medical Monitor.
All ESAs used during the Treatment Period, either planned or inadvertent, should be recorded.
ESAs and Roxadustat should not be administered concomitantly.

4.7.3.3. Emergency Procedure (Therapeutic Phlebotomy)

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

4.7.4. Prohibited Medications/Therapies/Substances

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

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

4.7.5. Contraception

Female subjects of childbearing potential, if not practicing complete sexual abstinence, must agree to practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depo progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects (nonsurgically sterile; i.e., no vasectomy) with female partners of childbearing potential who are not on birth control must agree to use a barrier method of contraception (e.g., condom) or the female partner must agree to use contraception as described above unless practicing complete sexual abstinence.
Subjects must agree to practice above contraceptive methods, as applicable, for the entire duration of the study, from enrollment through the EOS visit. It is highly recommended that they continue to practice the contraceptive methods for 1 week following the last dose of study treatment. For subjects discontinuing study medication prematurely, it is recommended that they continue to practice contraceptive methods for 1 week following the last dose of study treatment.
Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy are to be reported on the study pregnancy form provided.

4.8. 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 and physical examination (PE). During the course of the study, vital signs, PE, and laboratory tests will be performed at regular intervals as described in schedule of assessments (Table 4).

Any significant findings prior to administration of study drug will be considered as baseline conditions and if appropriate, will be captured as baseline medical history. Any clinically significant (CS) changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Clinical laboratory tests may be assessed at additional times on unscheduled visits for safety reasons.

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

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

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

1. Subject has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines
2. Subject is ≥ 18 years of age
3. Receiving in-center hemodialysis for end stage renal disease (ESRD)
4. Prior ESA use:
   - For a subject converting from an ESA: On ESA ≥6 weeks and the prescribed ESA dose remain stable (as determined by PI) during the 4 weeks prior to initiating roxadustat treatment
   - Subject is initiating anemia treatment: Defined as: < 6 weeks of prior ESA use or no prior ESA use.
5. Vascular access must be a functioning native arteriovenous fistula or graft with adequate flow in the opinion of the investigator, or permanent tunneled catheter.
6. Screening Hb (based on central lab value; measured within 10 days prior to initiating roxadustat treatment):
   - Subjects converting from an ESA: screening Hb is between 9.0 to 12.0 g/dL
   - Subjects initiating anemia treatment: screening Hb is < 10.0 g/dL
7. Ferritin ≥ 50 ng/mL, Transferrin saturation (TSAT) ≥ 10% at screening (subject may qualify after receiving iron supplement per local standard of care)
8. Subject's alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are ≤ 3 x upper limit of normal (ULN), and total bilirubin (TBL) is ≤ 1.5 x ULN at screening and prior to initiating roxadustat treatment. TBL up to 2 x ULN may be allowed if AST and ALT are within normal limit)
9. Subject's body weight (estimated dry weight in HD subjects) is 45.0 to 160.0 kg

5.2. Exclusion Criteria

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

1. Subject has received a red blood cell (RBC) transfusion within 4 weeks prior to enrollment
2. Subject has a known history of myelodysplastic syndrome or multiple myeloma
3. Subject has a known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia or other known causes for anemia other than chronic kidney disease (CKD)
4. Subject has known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition
5. Subject has a known chronic inflammatory disease that is determined by the investigator to be the primary cause of anemia (e.g., systemic lupus erythematosus, rheumatoid arthritis, celiac disease)
6. Subject is anticipated to undergo elective surgery that is expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization.
7. Subject has active or chronic gastrointestinal bleeding
8. Subject has been treated with iron-chelating agents within 4 weeks prior to enrollment
9. Subject has a history of chronic liver disease (e.g., chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver)
10. Subject with New York Heart Association (NYHA) Class III or IV congestive heart failure

11. Subject has had an MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (excluding vascular dialysis access stenosis/thrombosis) (eg, DVT or pulmonary embolism) within 12 weeks prior to enrollment
12. Subject has uncontrolled hypertension, in the opinion of the Investigator
13. Subject has a diagnosis or suspicion (e.g., complex kidney cyst or Bosniak Category II or higher) of renal cell carcinoma (PI's discretion)
14. Subject has a history of malignancy, except for the following: cancers determined to be cured or in remission for ≥ 2 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps
15. Subject is positive for any of the following:
    - Human immunodeficiency virus (HIV)
    - Hepatitis B surface antigen (HBsAg)
    - Anti-hepatitis C virus antibody (anti-HCV Ab)
16. Subject has an active clinically significant infection at the time of enrollment as determined by the investigator
17. Subject has any of the following known untreated conditions as determined by the investigator: proliferative diabetic retinopathy, diabetic macular edema, macular degeneration or retinal vein occlusion (subjects who are already blind may qualify to participate)
18. Subjects with prior organ transplant who have one of the following conditions or states
    a) Experienced rejection of transplanted organ within 6 months of transplantation
    b) Currently on high doses of immunosuppressive therapy (per discretion of the investigator)
    c) Are scheduled for organ transplantation (on the waiting list for kidney transplant is not exclusionary)
19. Subject has participated in an interventional clinical study or has been treated with an investigational drug within 4 weeks prior to screening
20. Subject has drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that may lead to reduced absorption of study drug (determined by the investigator)
21. Subject has an anticipated use of dapsone or androgen in any dose amount or anticipated chronic use of acetaminophen or paracetamol > 2.0 g/day during the study
22. Subject has a history of alcohol or drug abuse within 6 months prior to screening as determined by the clinical judgment of the investigator
23. Females of childbearing potential, if not practicing complete sexual abstinence or using contraception as detailed in the protocol; male subjects (if not surgically sterile; i.e., no vasectomy) with sexual partners of childbearing potential, if not practicing complete sexual abstinence or using contraception
24. Pregnant or breastfeeding females
25. Subject has any medical condition that in the opinion of the Investigator may pose a safety risk to the subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation

5.3. Subject Discontinuation and Withdrawal

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

Subjects may withdraw consent and discontinue from the study at any time by discontinuing study medication and refusing to return for any form of follow-up without any prejudice.
A subject who decides to discontinue study medication will always be asked about the reason(s) to discontinue study medication and the presence of AEs (if any). These data will be ascertained and documented by the investigator and recorded in the eCRF as appropriate. Any subject discontinuing study medication will be followed up for 28 days after discontinuing study medication whenever feasible for purposes of adverse event reporting.
Reasons for permanent discontinuation of study medication:

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

Upon discontinuation from the study, both female subjects of childbearing potential and male subjects with partners of childbearing potential must continue to use a medically acceptable method of contraception for 1 week following the last study drug administration.

5.4. Replacement of Subjects

Subjects will not be replaced from this study.

6. INVESTIGATIONAL PRODUCT

6.1. Formulation

Roxadustat is supplied by FibroGen, Inc. as red coated, tablets for oral administration, in strengths of 20 mg, 50 mg, 70 mg, 100 mg and 150 mg. The excipients include lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, and colorant Red Opadry II. All ingredients used for manufacture of roxadustat comply with US and European Union compendia or regulatory standards. Strengths are different in size and debossing reflects the strength (i.e., 20, 50, 70, 100 or 150 mg). Due to the light-sensitive nature of roxadustat and to minimize exposure of the active pharmaceutical ingredient to light, tablets should remain in the original packaging for as long as possible and be administered as intact tablets only.

6.2. Storage

Roxadustat tablets should be protected from light, and stored at room temperature between 15°C and 30°C (59ºF to 86ºF).
Study drug should be stored in a securely locked area to which access is limited to appropriately authorized study personnel.

6.3. Study Drug Handling and Disposal

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

6.4. Route of Administration and Dose

Route of Administration: Oral (all tablets must be administered whole)
Dosing Frequency: Subjects will be dosed three times weekly (TIW), except if a subject requires < 60 mg/week to maintain Hb levels, in which case dose frequency may be reduced in a stepwise fashion, e.g., to twice weekly (BIW), then once weekly (QW), then every-2-weekly (Q2W), etc.
The first dose of roxadustat should be administered on Day 1 after completion of all procedures including laboratory draws. Roxadustat doses should be administered at least 2 days apart, and no more than 4 days apart. Dosing should occur at approximately at the same time of day. Roxadustat can be taken with or without food. If phosphate binders are taken with food, roxadustat is advised to be taken at least one hour before or one hour after the phosphate binder.

6.5. Overdose, Emergency Procedures and Management of Overdose

The maximum allowed roxadustat dose is 400 mg or 3.0 mg/kg/dose, whichever is lower. Any dosing exceeding the maximum allowed roxadustat dose should be reported within 24 hours. The Medical Monitor should be contacted as soon as possible. Symptoms associated with overdosing, if any, will be reported as adverse events.

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.

7. STUDY PROCEDURES

7.1. Study Procedures by Visit/ Schedule of Assessments

During study visits, unless otherwise indicated, it is preferred that all assessments including labs and physical examinations should be completed prior to dialysis.

Table 4: Schedule of Assessments

Visit / Week:	**Screening Visit**	**Day 1**	**Wk 2 to 8** (Every 2 weeks ± 4 days)	**Wk 12 to 24** [g] (Every 4 weeks ± 4 days)	**Post-Treatment** [e] **or ET** ± 7 days
Written informed consent	X				
Eligibility criteria	X	X			
Demographics and medical history	X				
Height, weight	X	X [a]			
Blood pressure, heart rate, temperature	X	X	X	X	X
Physical Exam	X			X [c]	
Hemoglobin (central and local)	X [d]		X [f]	X [f]	X [d]
CBC with WBC differential	X	X	Wks 4, 8	Wks 16, 24	X
Serum chemistry	X	X	Wks 4, 8	Wks 16, 24	X
CPK	X	X	Wk 8	Wks 16, 24	
Serum iron, ferritin, TIBC, TSAT, CHr, reticulocytes	X	X	Wk 8	Wks 16, 24	
HIV ELISA, HBsAg, anti-HCV Ab	X				
Serum hCG pregnancy test	X [b]			Q8Wks	X
Dose adjustment			X	X	
AE/CM recording	X	X	X	X	X
Study drug dispensing		X	X	X	

Ab = antibody; CBC = complete blood count; CHr = reticulocyte hemoglobin content; ELISA = enzyme-linked immunosorbent assay; ET = early termination; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LFTs = liver function tests; TIBC = total iron binding capacity; TSAT = transferrin saturation; WBC = white blood cells; Wk(s) = week(s)

a Weight only
b Collect from female subjects of child bearing potential only
c Physical Exam to be performed during W24/End of Treatment (EOT) visit only
d Central labs only
e 28 days post last dose of roxadustat
f Collect a separate central Hb only when CBC is not collected
g Week 24 = EOT

7.2. Screening Period

- Signed written informed consent
- Inclusion/Exclusion criteria verification
- Demographics and medical history
- Height and weight
- Vital signs (BP, HR, temperature)
- Physical Examination: HEENT, respiratory, cardiovascular, abdomen, extremities, and neurological parameters
- Laboratory tests:
    - Hemoglobin (central)
    - Complete blood count (CBC) with WBC differential
    - Serum chemistry
    - CPK
    - Serum iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation (TSAT), Reticulocyte count and hemoglobin in reticulocytes (CHr)
    - Enzyme-linked immunosorbent assay (ELISA) for HIV
    - Hepatitis B surface antigen (HBsAg)
    - Anti-HCV Ab
    - Serum hCG pregnancy test
- Renal ultrasound or other imaging may be performed during screening to rule out renal cell carcinoma or suspicion of renal cell carcinoma if deemed necessary by the PI.
- Review and record concomitant medications
- Review and record procedures and nondrug therapies
- Review and record AEs, if any (capture the event under medical history, if applicable)

7.2.1. Additional Screening Assessments

If a subject's laboratory results do not meet eligibility criteria at Screening, specific laboratory assessments may be repeated within the Screening Period.
If a subject fails screening, he/she may be re-screened (as a new patient) once deemed appropriate by the investigator. Where possible, an approval should be obtained from the Medical Monitor prior to re-screening.

7.3. Treatment Period

The Treatment Period begins on the first day of dosing with study treatment (Day 1).

7.3.1. Day 1

All assessments are to be completed prior to first dose of study drug

- Inclusion/Exclusion criteria verification
- Weight
- Vital signs (BP, HR, temperature)
- Estimated dry weight
- Local Hb assessment
- Laboratory tests:
    - Complete blood count (CBC) with WBC differential

- Serum chemistry
- CPK
- Serum iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation (TSAT), Reticulocyte count and hemoglobin in reticulocytes (CHr)
- Hemoglobin local
- AE/CM recording
- Study drug administration

7.3.2. Weeks 2 to 8 (Every 2 Weeks, ±4 days)

- Vital signs (BP, HR, temperature)
- Laboratory tests:
  - Hemoglobin (central and local lab)
    - Draw a central Hb only on visits CBC is not collected
- Week 4 and Week 8:
  - Complete blood count (CBC) with WBC differential
  - Serum chemistry
- Week 8:
  - CPK
  - Serum iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation (TSAT), Reticulocyte count and hemoglobin in reticulocytes (CHr)
- Dose review at every visit and dose adjustment every 4 weeks
- TEAE/CM recording
- Study drug dispensing

7.3.3. Weeks 12 to 24 (Every 4 weeks, ±4 days)

- Vital signs (BP, HR,temperature)
- Physical Examination: HEENT, respiratory, cardiovascular, abdomen, extremities, and neurological parameters (at Week 24/EOT only)
- Hemoglobin (central as part of CBC and local lab)
- Week 16 and Week 24:
  - Complete blood count (CBC) with WBC differential
  - Serum chemistry
  - CPK
  - Serum iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation (TSAT), Reticulocyte count and hemoglobin in reticulocytes (CHr)
- Every 8 Weeks:
  - Serum hCG pregnancy test (female of child bearing potential only)
- Dose adjustment
- AE/CM recording
- Study drug dispensing

Week 24 visit is considered as End of Treatment (EOT) visit

7.4. Post-Treatment (subjects discontinuing roxadustat treatment) or Early Termination (ET) (±7 days)

Subjects permanently discontinuing roxadustat should have one final safety assessment 28 days after the last roxadustat dose.

- Vital signs (BP, HR, temperature)
- Laboratory tests:
  - Complete blood count (CBC) with WBC differential
  - Serum chemistry
  - Serum hCG pregnancy test (female of child bearing potential only)
  - AE/CM recording

Subjects who wish to permanently discontinue roxadustat, should receive the first ESA dose at least two days after the last roxadustat dose.

An extension of roxadustat treatment after 24 weeks may be offered to interested subjects within the context of this study protocol upon agreement of the study site until roxadustat is commercially available, or up to 1 year after completing the 24 weeks, whichever comes first.

7.5. Missed Visits

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

7.6. Unscheduled Visits

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

7.7. Laboratory Assessments

Details regarding sample collection, preparation and transport can be found in the central laboratory manual. Importantly, dose adjustments per the dosing algorithm will be made on results from local Hb testing.

7.8. Central Laboratory

The following labs will be evaluated by a central laboratory in accordance with the SOA in Table 4.

Table 5: Central Laboratory Tests

CBC:	**Chemistry Panel:**
Basophils	Albumin
Eosinophils	Bicarbonate
Erythrocyte count (RBC)	BUN
Hct	Calcium
Hb	Chloride
Leukocyte count (WBC)	Creatinine
Lymphocytes	Creatine phosphokinase
Mean corpuscular volume	Glucose
Mean corpuscular Hb	Lactic Acid Dehydrogenase
Mean corpuscular Hb concentration	*Liver Function Tests*[1]
Monocytes	ALP
Neutrophils	ALT
Neutrophils, immature (banded)	AST
Platelets	Bilirubin, total and direct
Serum Iron Profile:	GGT
Ferritin	Magnesium
Iron	Phosphorus
TIBC	Potassium
UIBC	Total protein
TSAT	**HIV and viral Hepatitis Panel:**
Additional Laboratory Analytes:	Anti-HCV Ab tests
Reticulocyte count	HBsAg
CHr	HIV ELISA
Serum hCG pregnancy test (for women of childbearing potential only)	

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

[1] In case a patient shows an AST or ALT ≥3xULN and total bilirubin ≥ 2xULN, please refer to Appendix 2 “Liver Function Monitoring”.

8. SAFETY

8.1. Background

Subjects will be asked for the occurrence of potential AEs during each study visit. In addition, all AEs reported spontaneously during the course of the study will be recorded. The Investigator must immediately (within 24 hours of becoming aware) 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.

8.2. Definitions

8.2.1. Definition of an Adverse Event

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

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

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

8.2.2. Definition of a Serious Adverse Event

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

- Death
- A life-threatening AE (i.e., 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
- A medically important event not meeting the above criteria, but which may jeopardize a patient or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization

8.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1. Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 28 days after the last study visit, except for pregnancy reporting (Section 8.3.6). AEs (non-SAE) reported during screening should be reviewed and captured under medical history, if applicable.

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/or 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 "non-treatment 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. If an AE starts on Day 1, the investigator must assess as to whether the AE started prior to or after the administration of study medication and record accordingly.

8.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject/caregiver at each visit to assess for any AEs occurring since the previous visit. All AEs will be collected in response to non-leading, general questions about the subject's well-being and any possible changes from the baseline or previous visit. This does not preclude the site from collecting and recording any AEs reported by the subject/caregiver to site personnel at any other time.

Whenever possible, AE diagnoses should be recorded rather than just the signs and symptoms, 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 conditions will also be recorded as AEs. Abnormal, clinically significant laboratory results, and PE findings will be recorded as AEs if they are deemed by the Investigator to meet the AE 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"

8.3.3. 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 (e.g., 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.

8.3.4. Assessing Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from Investigators are critically important. Moreover, appropriately deciding whether the AE meets the definition of a suspected adverse reaction is usually the most difficult determination, but it is critical to avoid the mis-categorization 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 drug's 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 (e.g., 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 (e.g., 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 reporting suspected adverse reactions and adverse reactions to Health Authorities.

8.3.5. 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 the Sponsor's designated safety management vendor within 24 hours of becoming aware of the serious event. 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

For each SAE observed, the Investigator should obtain all of the information available about the event, including (but not limited to): clinical course of the event, 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).

The medical monitor is available to discuss safety issues if needed.

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

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

8.3.5.2. Deaths

For any death occurring during the subject's study participation, regardless of attribution, the Investigator will report the death within 24 hours to the Sponsor's Medical Monitor and their designated safety management vendor on an SAE form.

The Investigator should notify the 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.

8.3.6. Pregnancies: Reporting and Follow-up

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 the Sponsor (by way of its designated safety management vendor) within 24 hours of the Investigator learning of the pregnancy. 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.

8.3.7. Abnormal Laboratory Findings

Laboratory values will be collected throughout the study to assess for safety. The Investigator must review and assess all laboratory results in a timely manner, and determine whether the abnormal laboratory values, if any, are clinically significant 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 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.

8.3.8. Disease Progression

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

9. STATISTICAL CONSIDERATIONS

Descriptive summaries will be presented for study parameters including baseline characteristics, safety, and efficacy.
Continuous variables will be reported in mean, standard deviation or standard error, median, minimum, and maximum.
Categorical variables will be reported by the frequency and percentage of subjects within each outcome category.
Analyses of the efficacy data will be based on the Full Analysis Set (FAS) Population.
Safety data will be summarized descriptively based on the Safety Population.
Operational characteristics of the drug will be evaluated qualitatively and descriptively.

9.1. Sample Size Determination

Approximately 300 subjects with anemia of CKD (either with or without prior treatment with an ESA before enrolment) and on hemodialysis are planned in this study. This number of subjects distributed across the specified number of sites is adequate to evaluate the primary study objective.
Assuming the proportion of subjects that maintain Hb levels ≥10g/dL from Weeks 16 to 24 is at least 80%, with a sample size of 300, the study will be able to produce a 95% confidence interval (CI) with a width equal of 9.5%.

9.2. Analysis Sets

The FAS set will consist of all subjects who signed informed consent, who were enrolled, and who provided baseline Hb data and data for at least one post baseline Hb time point. The FAS set will be used for all efficacy endpoints.
The Safety analysis set will include all enrolled subjects receiving at least 1 dose of study treatment. The safety analysis set will be used for all safety endpoints and exposure to study treatment outcomes.

9.3. Analysis of the Efficacy Endpoints

The efficacy endpoint will be evaluated using the proportion (%) of subjects with mean value of Hb measurements of Week 16-Week 24 $\geq$ 10g/dL.

The 95% CI of the response rate will be presented based on the exact method of Clopper-Pearson.

For efficacy analysis, a multiple imputation (MI) method will be used. This will be implemented on the raw Hb values, then the Hb-relates endpoint summaries will be derived based on the imputed data (algorithm as used for the previous phase 3 studies).
For continuous endpoints, changes from baseline will be presented descriptively. Missing Hb values will be imputed using a multiple imputation procedure.
Proportion of responders will be presented descriptively with count and percentages and 95% confidence interval of the responder rate.
Time to response will be analyzed using the Kaplan-Meier method with KM curve plotted.

9.4. Safety Analyses

The Safety analyses will be performed using the Safety Analysis Set (SAF). Safety parameters include AEs, SAEs, laboratory parameters and vital signs.

The number and percentage of subjects reporting treatment-emergent AEs (TEAEs) and TESAEs will be tabulated.

Descriptive statistics will be presented for laboratory and vital signs.

10. DIRECT ACCESS TO SOURCE DOCUMENTS

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

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

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

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data Quality Assurance

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by FibroGen and its designee(s), as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, ICH E6 (GCP), and other applicable regulations.

This study will be monitored by FibroGen or designee in accordance with GCP, and may be audited or reviewed by an independent Quality Assurance department, IRB/IEC, and/or regulatory authorities. This implies that monitors and auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to data/source documents, including the subject's file. By participating in this study, Investigators agree to this requirement.

The purpose of trial 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 FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IRT, clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

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.

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 provision of a 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 (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.
The Investigator is responsible for reviewing, verifying, and approving all subject data, i.e., 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, must be maintained at the study site until Sponsor or its designee verifies drug accountability and provides instruction for destruction or the return of the investigational product to Sponsor's drug distribution depot.

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

16.2. Disclosure of Data

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

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

16.3. Retention of Records

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

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

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18. APPENDIX

Appendix 1: Roxadustat Dose Adjustment Rules

		Current Hb level:			
		<10.5 g/dL	**10.5 to 11.9 g/dL**	**12.0 to 12.9 g/dL**	**≥13.0 g/dL**
Change in Hb over previous 4 weeks:	**> 1.0 g/dL**	No change	↓	↓	• Hold dosing • Check Hb and resume dosing when Hb <12.0 g/dL, at a dose reduced by 2 steps
	-1.0 g/dL to +1.0 g/dL	↑	No change	↓	
	< -1.0 g/dL	↑	↑	No change*	

↑: Increase dose by one step; ↓: reduce dose by one step.

*Continue to hold dose

Notes:

Dose Increases and Reductions:

- Dose increases (↑) and reductions (↓) are preset.
- The dose steps are as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.
  If < 20 mg /dose is required, dosing frequency should be reduced in a step-wise fashion e.g., TIW to BIW, BIW to QW.
- The maximum dose is capped at 400 mg or 3.0 mg/kg/dose (whichever is lower). Rounding the mg/kg calculated roxadustat dose up to 10 mg may be allowed, if no safety concerns.

Roxadustat dose adjustment reviews should occur every 4 weeks, except if the following criteria are met:

- Rate of Hb rise > 2 g/dL within 4 weeks: reduce dose by 1 dose step
- Hb level ≥ 13g/dL: hold dose, until Hb drops to < 12g/dL, resume dosing at 2 dose steps lower

Dose adjustments or temporary dose holds for excessive rate of Hb rise or Hb above 13 g/dL can occur at any time during the Treatment Period.
Prescribed dose must not exceed the maximum allowable dose of 3.0 mg/kg/dose or 400 mg per dose, whichever is lower; rounding the mg/kg calculated roxadustat dose up to 10 mg may be allowed, if no safety concerns. For dose adjustment purposes, estimated dry-weight at enrollment should be used for the entire duration of the treatment period.

Appendix 2: Liver Function Monitoring

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

Definition of Liver Abnormalities

Confirmed abnormalities should be characterized as follows:

	ALT or AST		Total Bilirubin
Moderate	> 3× ULN	Or	> 2× ULN
Severe	> 3× ULN	And	> 2× ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
Hy's Law: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant). The two "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 times the upper limit of normal ("2 × ULN elevations are too common in treated and untreated Patients to be discriminating"). 2) Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extrahepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome: Temple, R (2006) Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf **15:** (4):241-243

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

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

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

Follow-up Procedures

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

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

In addition, evaluate the patient 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: e.g., INR, gamma glutamyltransferase (GGT) or direct bilirubin; ultrasound or other imaging to assess biliary tract disease
- Consider gastroenterology or hepatology consultations

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

Discontinuation of treatment should be considered if:

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

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

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