CLINICAL STUDY PROTOCOL

STUDY TITLE:	Open-Label Extension Study to Evaluate the Efficacy and Safety of FG-4592 for the Long-Term Maintenance Treatment of Anemia in Dialysis and Non-Dialysis Patients with Chronic Kidney Disease
PROTOCOL NUMBER:	FGCL-4592-059
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 United States
IND NUMBER:	74,454
STUDY DRUG:	Roxadustat
INDICATION:	Anemia associated with Chronic Kidney Disease or End-Stage Renal Disease
FIBROGEN MEDICAL MONITOR:	Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] E-mail: [redacted]
PROTOCOL VERSION/DATE:	Original Protocol: 06 March 2012 Amendment No. 1: 31 October 2013 Amendment No. 2: 25 July 2018

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

An Open-Label Extension Study to Evaluate the Efficacy and Safety of FG-4592 for the Long-Term Maintenance Treatment of Anemia in Dialysis and Non-Dialysis Patients with Chronic Kidney Disease

FGCL-4592-059

Amendment No. 2

25 July 2018

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/Independent Ethics Committee (IRB/IEC) requirements.

Investigator Name (Printed)	Institution
Signature	Date

SUMMARY OF MAJOR PROTOCOL AMENDMENT CHANGES

Amendment 2

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

Description of Change	Rationale for Change	Section(s) Affected
The treatment period was changed from 260 weeks (5 years) to up to 312 weeks (6 years). Subjects enrolled in the study prior to Amendment 2 may continue treatment for up to an additional 1 year or a maximum of 6 years. New subjects enrolled under Amendment 2 will receive treatment for 52 week.	The increased treatment duration of up to 6 years allows the collection of long-term efficacy and safety data, and gives subjects previously enrolled in other roxadustat Phase 2/3 studies the option of continuing treatment with roxadustat.	Synopsis Section 4.1 Appendix A
Instructions were added for roxadustat starting doses, and initial visit frequency, for subjects who received blinded study treatment in their previous study	To allow subject enrollment without the need to unblind.	Synopsis Sections 4.3.1 4.3.2 10.2 Appendix A Appendix B
Dose adjustment algorithm, and maximum per-kg dose was adjusted.	To align with global phase 3 program.	Synopsis Section 4.3.2 Appendix C
Data Monitoring Committee review will end after last meeting of the global Phase 3 program.	To align with global phase 3 program.	Sections 4.6 10.4
HMP: aligned with text from Phase 3 programs	To align with global phase 3 program.	Section 4.5.1 Table 1
The compound designation of “FG-4592” was replaced with “roxadustat” throughout, except in the title of the study.	The generic name of “roxadustat” is now available. The compound name was not changed in the title of the protocol as that is the name the trial was originally registered.	Entire Document

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve for plasma concentration vs. time
BIW	twice weekly
BP	blood pressure
CBC	complete blood count(s)
CFR	Code of Federal Regulations
CHr	reticulocyte hemoglobin content
CKD	chronic kidney disease
C_{max}	maximum concentration of drug after dosing
CRF	case report form
CRP	C-reactive protein
CYP-450	cytochrome P-450 isoenzymes
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EE	Efficacy Evaluable (population)
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
ET	early termination (visit)
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hb	hemoglobin
hCG	human chorionic gonadotropin
HD	hemodialysis
HDL	high-density lipoprotein
HIF	hypoxia-inducible factor
HIF-PH	HIF prolyl hydroxylase
HIPAA	Health Insurance Portability and Accountability Act
HMP	Hepatic Monitoring Plan
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 Application
INR	international normalized ratio (for anticoagulant monitoring)
IRB	Institutional Review Board
IV	intravenous
K_i	inhibition constant

LDL	low-density lipoprotein
LFT	liver function test
LOCF	last-observation-carried forward
max	maximum
min	minimum
MedDRA	Medical Dictionary for Regulatory Activities
N	number of subjects
NCI	National Cancer Institute
NCI-CTCAE	NCI Common Terminology Criteria for Adverse Events
OSD	Oral Solid Dosage
PD	peritoneal dialysis
PH	prolyl hydroxylase
PK	pharmacokinetic(s)
PT	prothrombin time
QT	time interval between Q and T waves in an ECG
QW	once weekly
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
sTfR	soluble transferrin receptor
$t_{1/2}$	terminal elimination half-life
Tbili	total bilirubin
TIBC	total iron binding capacity
TIW	three times weekly
TSAT	transferrin saturation
ULN	upper limit of normal
US	United States
USRDS	United States Renal Data System
VEGF	vascular endothelial growth factor
WBC	white blood cell

PROTOCOL SYNOPSIS

Study Title:	An Open-Label Extension Study to Evaluate the Efficacy and Safety of FG-4592 for the Long-Term Maintenance Treatment of Anemia in Dialysis and Non-Dialysis Patients with Chronic Kidney Disease
Protocol Number:	FGCL-4592-059
Investigational Product:	Roxadustat
Target Population:	Dialysis and non-dialysis chronic kidney disease (CKD) subjects who have completed the treatment period of an roxadustat study in the U.S.
IND Number:	74,454
Study Phase:	Open-label extension
Study Centers Planned:	Up to 20 study centers in the U.S.
Number of Subjects Planned:	Up to 50 subjects
Primary Objective:	To evaluate the long-term efficacy and safety of roxadustat in the maintenance of hemoglobin (Hb) in dialysis and non-dialysis subjects with CKD
Secondary Objectives:	Evaluate roxadustat doses and dose adjustments
Exploratory Objectives:	Assess the effect of roxadustat on iron utilization parameters Assess the effect of roxadustat on select biomarkers
Study Design:	This is an open-label, long-term maintenance study of roxadustat anemia therapy in dialysis and non-dialysis subjects with CKD who have completed the treatment period of an roxadustat anemia study in the U.S. Subjects enrolled in this study prior to Amendment 1 may continue for an additional 52 weeks (1 year) or a total of 8 years of treatment. Subjects enrolled under Amendment 2 will be treated for up to 52 weeks (1 year). Subjects who received roxadustat in a previous study will return for study visits every 4 weeks until the end of the treatment period. Subjects who received placebo in their previous study will return for study visits weekly, for the first 4 weeks, and every other week, until week 24 (Appendix C), followed by every 4 weeks until the end of the treatment period. Subjects who received placebo in their previous study will receive roxadustat according to their weight as described in Appendix B. If treatment assignment is blinded at the time of enrollment, if the subject has been on a stable dosing regimen for at least 2 months prior to the switch and if the last dose is lower than the starting doses described in Appendix B, the subject may continue on the current dosing regimen. After the end of treatment (defined as last day the subject receives study drug) the subject will return for a follow-up visit 4 weeks later. The baseline Hb value for efficacy analysis is defined as the mean of the central laboratory Hb value from the baseline visit at Day 1 (prior to receiving the first dose of study drug in this study), plus any other central lab Hb values within 15 days prior to Day 1. Safety will be assessed by vital signs, physical examinations, clinical laboratory values (including liver function tests [LFTs] and complete blood counts [CBC]), electrocardiograms (ECGs), and adverse event (AE) and concomitant medication reporting. Clinical laboratory tests, including LFTs and Hb levels, may be assessed at additional, unscheduled visits for safety reasons.

	Rescue Medication: If a subject is not responding adequately to roxadustat, and rescue therapy is considered a medical necessity by the investigator, rescue therapy will be allowed for a subject provided this has been discussed with the study medical monitor, or is deemed to be an immediate medical necessity by the investigator. The three options for rescue therapy are as follows: Blood Transfusion: For subjects requiring a blood transfusion, administration of study medication may continue. Iron Supplementation: Oral iron should be the first-line option for iron supplementation. Intravenous (IV) iron supplementation may be considered if the following criteria are met: The subject has not responded adequately to 2 or more dose increases or reached the maximum dose limit and Ferritin saturation is <50 ng/ml or transferrin saturation (TSAT) is <10% **OR** The subject is intolerant of oral iron therapy and Ferritin saturation is <50 ng/ml or TSAT is <10% roxadustat treatment should continue during IV and oral iron supplementation. The investigator may discontinue IV iron supplementation once he no longer considers the subject to be iron deficient. The investigator should carefully monitor the subject's Hb response after IV iron supplementation. Erythropoiesis-stimulating agents (ESAs): ESAs are not to be concurrently administered with roxadustat . Once a subject is considered a treatment failure due to a lack of efficacy and/or lack of tolerability of roxadustat , and ESA treatment is initiated per the treating physician, roxadustat must be permanently discontinued and the subject is to be discontinued from the study. In the event of an extenuating circumstance during which a subject inadvertently receives an ESA for a short period of time (e.g., recent bleeding, disruption of roxadustat dosing due to hospitalization or vacation, etc.) the study medical monitor should be contacted to evaluate the appropriateness of continuing treatment with roxadustat. Dose Adjustments for Roxadustat Dose adjustments will occur according to Appendix C. All subjects in the roxadustat arm will be dosed orally TIW during the Treatment Period. During the course of the study, the dose and the dosing frequency may be changed to optimize efficacy and tolerability based on the clinical judgment of the investigator and study medical monitor. The maximum roxadustat dose is 3.0 mg/kg per dose or 400 mg, whichever is lower. All dose adjustments as well as assessments of excessive hematopoiesis are based on Hb values using a point-of-care device such as HemoCue® or CritLine®. In the event that the central lab Hb value of the site visit is significantly different and the dose adjustment decision based on the HemoCue® or CritLine® value is being reconsidered, the Medical Monitor should be contacted, if possible. The determination of Hb response is based on the central laboratory Hb value. Dose adjustment reviews will occur on Week 4, and at intervals of every 4 weeks thereafter (Weeks 8, 12, 16, etc.) except in the event of excessive hematopoiesis, in which case doses may be adjusted at any

	time. In such cases, dose adjustment reviews are resumed at 4-week intervals. For example, if the subject's Hb increases >2.0 g/dL from Week 1 to Week 3, the subject's dose is reduced by one dose step at Week 3. The next dose adjustment review should occur 4 weeks later at Week 7 and at 4-week intervals thereafter. If the dose adjustment interval falls on a non-study visit week (starting Week 4), the dose adjustment review should be performed at the next scheduled clinic visit, if a dose adjustment was not required at the previous visit. For example, if a subject's visit is scheduled for Weeks 6 and 8, and the dose adjustment would occur at Week 7, then the dose adjustment should be evaluated at the Week 8 visit. For subjects on prolonged dose-hold, with stable (not dropping) Hb, the Investigator may use discretion to schedule less frequent visits. Anytime Hb is assessed via HemoCue®/CritLine®/local lab, a central lab Hb should be obtained as well. <u>Excessive Hematopoiesis</u> For subjects randomized to Roxadustat, the following scenarios are defined as "excessive hematopoiesis" ; Hb increases by > 2.0 g/dL at any time within a 4 week period: reduce the dose by one dose step. Hb reaches or exceeds 13 g/dL: hold dosing, check Hb weekly. Resume dosing when Hb < 12.0 g/dL, at a dose that is reduced by two dose steps.

Inclusion Criteria	Minimum age 18 years Subjects who have completed the treatment period of an ongoing roxadustat anemia study in the U.S.
Exclusion Criteria:	Subjects assigned to epoetin alfa in a previous roxadustat anemia study in the U.S. Pregnant or breastfeeding females Females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception Subjects who received roxadustat in the previous study that did not demonstrate adequate hemoglobin response in the investigator's clinical judgment Any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study, or which may interfere with study participation
Study Periods:	There will be two study periods: Treatment: Subjects will be dosed up to 416 weeks (6 years). Subjects enrolled under Amendment 2 will be dosed for 52 weeks (1 year) Post-treatment follow-up: 4 weeks.
Study Procedures:	See Schedule of Study Assessments (Appendix A)
Investigational Product, Dose, and Mode of Administration:	Subjects will receive 20, 50, and 100 mg of roxadustat as an oral solid dosage (OSD). All OSDs must be administered whole. **Initial Doses** Subjects who received roxadustat in a previous study will continue to receive roxadustat at the same dose and dosing frequency (three times weekly [TIW], twice weekly [BIW], or once weekly [QW] as they received at the end of their last study, unless a dose adjustment is required. Subjects who received placebo in their previous study will start treatment with roxadustat according to their weight as described in Appendix B. If treatment assignment is blinded at the time of enrollment, the subject has been on a stable dosing regimen for at least 2 months prior to the switch and if the last dose is lower than the starting doses described in Appendix B, the subject may continue on the current dosing regimen. **Dose Adjustment Rules** Guidelines for dose adjustments are provided in Appendix A.
Efficacy Endpoints and Assessments:	Mean monthly Hb values over time Number (%) of subjects maintaining monthly (defined as a 4-week interval) mean Hb at ≥10 g/dL during study participation upon correction (defined as having achieved two consecutive Hb values of ≥10 g/dL) Number (%) of subjects maintaining Hb between 10-13 g/dL for at least 60% of scheduled Hb assessments after the first Hb value is 10 g/dL or higher Composite rate of summarized rescue therapy events (transfusions, IV iron, ESAs) and rate of individual rescue therapy events Number (%) of subjects with phlebotomies Roxadustat weekly total doses over time Dose adjustment frequencies Hb variability Number (%) of subjects withdrawn from the study due to inadequate efficacy
Safety Assessments:	Vital signs, clinical laboratory values, and changes in physical examinations AEs and serious adverse events (SAEs)

Exploratory Laboratory Evaluations:	Collect the following labs only if a baseline value is available for the subject (i.e., test was done prior to start of study drug treatment in previous roxadustat study): Reticulocyte hemoglobin content (CHr); High sensitivity C-reactive protein (hs-CRP); Hepcidin levels in serum; Additional biomarkers.
Statistical Methods:	All subjects who have received any dose of study treatment will be included in the safety analyses. The efficacy population will include all subjects who receive any study treatment and have non-missing Hb measurement at Baseline and at least one non-missing post-baseline Hb measurement. Monthly mean Hb values will be computed based on the average of Hb values within a 4-week period, and Hb data will be summarized accordingly over time. Hb values within 28 days of known gastrointestinal bleeding, substantial surgical blood loss, or receipt of rescue therapy of IV iron, red blood cell (RBC) transfusion, or ESA, will be censored in efficacy analysis. A last-observation-carried-forward (LOCF) method may be used to impute any missing Hb values. Continuous endpoints will be summarized descriptively by number of subjects (N), mean, standard deviation, median, minimum (min), and maximum (max) values. Categorical endpoints will be summarized descriptively by count and percentage. Safety data will be tabulated using descriptive statistics.

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

1. INTRODUCTION

1.1. Epidemiology of Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD)

Chronic kidney disease (CKD) is a growing worldwide public health challenge associated with significant morbidity and mortality that is both underdiagnosed and undertreated. It is characterized by the progressive loss of kidney function, ultimately resulting in end stage renal disease (ESRD) with the need for renal replacement therapy (kidney transplant or dialysis), or premature death. In 2007, CKD affected 13% of the United States (U.S.) adult population, or approximately 29 million adults, and its prevalence is growing rapidly (Coresh, 2007). All-cause mortality risk has been recognized to increase exponentially as CKD stages advance (Tonelli, 2006). The number of people suffering from ESRD continues to increase worldwide, with the US having one of the world's highest prevalence rates with 1,700 cases for every million in the general population (USRDS, 2009). In 2007, there were 527,000 ESRD patients in the US, of whom 341,000 were on hemodialysis (HD), 26,000 were on peritoneal dialysis (PD), and 159,000 had received a kidney transplant; 71,000 were on the transplant waiting list (USRDS, 2009). The expected remaining lifetime of a dialysis patient is 5.9 years, compared with 16.4 years for a transplant patient, and 25.2 years for someone of comparable age in the general population (USRDS, 2009). The prevalence of ESRD is estimated to grow to 774,000 by the year 2020 (USRDS, 2009).

1.2. Anemia Associated with Chronic Kidney Disease

Anemia, or decreased circulating red blood cell (RBC) mass, is a common complication in patients with CKD. Although the pathogenesis of anemia is multifactorial, decreased production of endogenous erythropoietin (EPO), a hormone produced primarily in the kidney, is considered its main etiological agent in patients with CKD. Other factors may include the shortened lifespan of RBCs, the presence of infection and inflammation, and iron and other nutritional deficiencies (Remuzzi, 2000). Anemia may be present in the early stages of CKD, and its prevalence increases with the progressive deterioration of kidney function. In ESRD, anemia is present in over 90% of patients (Kausz, 2002).

It is estimated that there are approximately 1.1 million adult patients in the US with CKD Stages 3b–5 and a hemoglobin (Hb) level <11.0 g/dL. In 2008, at initiation of dialysis, patients had an average Hb level of 9.9 g/dL. Approximately 75% of patients had Hb <11.0 g/dL and many had anemia that was significantly more severe: 48% had Hb <10.0 g/dL, and 25% had Hb <9.0 g/dL (USRDS, 2008).

The main impact of anemia on organ function is the reduction of oxygen delivery to tissues, leading to fatigue and effort intolerance. Other consequences, such as impaired cognitive function, sleep disorder, altered hemostasis, depressed immune function, and impaired cardiac function, are not uncommon. Multiple studies have shown benefits in treating anemia in terms of reduction in RBC transfusion requirements, reductions in morbidity and mortality risks, and possible improvement in health-related quality of life (NKF K/DOQI, 2007).

1.3. Treatment of Anemia

Today, therapy with an erythropoiesis-stimulating agent (ESA) is a major alternative to transfusion in managing anemia associated with CKD. For those not resistant to ESAs, parenteral administration of exogenous recombinant human erythropoietin (epoetin alfa or beta) or pegylated analogues has been a widely accepted approach for treatment of anemia in patients with CKD (Eschbach, 1987; Eschbach, 1989; Winearls, 1986), despite the documented safety risks. These safety risks include hypertension and thrombosis, and may be associated with the supraphysiologic plasma EPO levels frequently observed with ESA therapy. Anemic patients with CKD or ESRD will require life-long treatment with these agents.

There is currently an unmet medical need for a convenient oral treatment that will correct anemia in CKD non-dialysis and dialysis patients to a target Hb level that is safe and well tolerated. An ESA dose relationship to mortality has been reported: higher mortality rates in ESRD patients targeting a higher Hb were reported in the Normal Hematocrit Study (Besarab, 1998) and a review of the USRDS database (Zhang, 2004). Therefore, a treatment option that avoids supraphysiologic levels of circulating plasma EPO levels may be a safer alternative. Furthermore, ESA therapy for anemia in ESRD patients on HD usually requires concomitant intravenous (IV) iron supplementation therapy. Roxadustat is an oral medication that will potentially deliver effective treatment for CKD related anemia with less need for iron supplementation and without producing supraphysiologic levels of circulating EPO.

1.4. Rationale for HIF Prolyl Hydroxylase Inhibitors to Treat Anemia

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. Hypoxia-inducible factor (HIF) is a transcription factor believed to be the key element in the body's oxygen sensing mechanism (Semenza, 2000). HIF regulates expression of genes that modulate both the acute and chronic response to hypoxia, and HIF-responsive genes regulate a wide range of processes, including erythropoiesis, iron metabolism, oxidation, cellular metabolism, glycolysis, vasculogenesis, cell cycle progression, and apoptosis. Chronic hypoxia and intermittent hypoxia induce different sets of genes associated with HIF transcriptional activity (Fan, 2005).

HIF is a heterodimeric transcription factor family comprising three oxygen-sensitive isoforms (HIF 1α, HIF-2α and HIF-3α) and a constitutively expressed HIF-1β subunit. Each heterodimeric isoform is responsible for the induction of specific sets of genes (Greijer, 2005; Hu, 2003). For example, HIF-1α has been shown to regulate vascular endothelial growth factor (VEGF) expression (Buchler, 2003; Gray, 2005), while HIF 2α is critical for the induction of the EPO gene and erythropoiesis (Scortegagna, 2005; Warnecke, 2004). The expression of HIF target genes occurs when the active heterodimer binds to a conserved deoxyribonucleic acid (DNA) motif, termed the hypoxia response element, found within all target genes, and which 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 RBC precursors.

Although HIF-α isoforms are constitutively produced, they fail to accumulate under normoxic conditions, due to recruitment and binding of the Von Hippel-Lindau protein, which targets HIF-

α isoforms for degradation through the ubiquitin proteasome pathway. The molecular mechanism for oxygen-dependent degradation of HIF-α is based on the hydroxylation of specific proline residues, as catalyzed by a family of HIF prolyl hydroxylases (HIF-PH) that utilize molecular oxygen as the substrate for hydroxylation. Thus, HIF-PH constitutes the body's main oxygen sensor by regulating the prevalence and activity of nuclear HIF protein. Under hypoxic conditions, HIF PHs are inactive and lead to initiation of the HIF-responsive transcriptional cascade (Semenza, 1998; Wang, 1995).

The treatment of anemia with HIF-PH inhibitors, by stimulating a broad range of physiological mechanisms of erythropoiesis in vivo, has the potential to address significant unmet medical needs and largely avoid the ESA-related adverse effects, thus significantly improving patient outcomes. Anemia management using a HIF-PH inhibitor is expected to increase Hb levels more physiologically with much lower plasma EPO concentrations than those associated with exogenous parenteral ESA administration in anemia therapy.

1.5. Roxadustat as Therapy for Anemia

Roxadustat is a potent and reversible HIF-PH inhibitor that transiently induces HIF stabilization, and leads to a functional HIF transcriptional response that elevates EPO gene expression and circulating levels of EPO. The reversible inhibition of HIF-PH enzymes and induction of HIF transcription mimics the erythropoietic response associated with exposure of humans to intermittent hypoxia. This response is not limited to increases in endogenous EPO production; rather, it is a coordinated response that also results in transcription of genes for proteins necessary in iron metabolism. In contrast to the classical paradigm suggesting that anemia in CKD patients is caused by the inability of these patients to produce EPO, studies with roxadustat in CKD suggest that the kidneys of subjects with CKD can produce sufficient EPO for robust erythropoiesis. Yet, the median plasma EPO levels resulting from dosing of roxadustat for the treatment of anemia in subjects with CKD and ESRD are within the physiologic range and are lower than the supraphysiologic levels associated with ESA therapy.

Roxadustat also has the potential to effectively treat anemia caused by inflammation-induced functional iron deficiency, which is typically unresponsive to ESA. A number of inflammatory mediators reduce iron availability for erythropoiesis. Because HIF-PH inhibitors such as roxadustat increase expression not only of the EPO gene but also of genes regulating iron metabolism, it is postulated that roxadustat may be effective treatment for anemia.

1.6. Clinical Experience with Roxadustat

Roxadustat is currently being studied in dialysis and non-dialysis subjects with CKD and anemia. Several Phase 1 and 2 clinical studies in the U.S., Europe, and Asia have been completed. Preliminary and final information from these studies is provided below and in the most recent Investigator's Brochure.

As of 7 September 2013, 1197 subjects have been enrolled in roxadustat clinical studies and 969 subjects have been exposed to roxadustat. The 377 healthy subjects and 592 dialysis and non-dialysis subjects with CKD who have been treated with roxadustat in these studies contributed to an estimated total roxadustat exposure of 127 patient-years. Up to 24 weeks of roxadustat dosing, in doses of up to 3.0 mg/kg, have been administered to subjects with CKD, a subset of which have been treated for up to 2 years in this open-label extension study. In completed Phase 1 studies, healthy subjects received single doses of roxadustat up to 4.0 mg/kg and repeat doses up

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

The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in healthy adult subjects, and in dialysis and non-dialysis subjects with anemia and CKD.

1.6.1. Pharmacokinetics and Pharmacodynamics

The pharmacokinetics (PK) and pharmacodynamics of roxadustat were characterized in studies in healthy subjects and in dialysis and non-dialysis subjects with CKD. The PK profile of roxadustat was generally dose proportional (except at the lowest dose of 0.3 mg/kg); terminal elimination half-life (t1/2) was 12 to 14 hours in healthy subjects, and 15 to 19 hours in dialysis subjects (after a single 1 and 2 mg/kg dose).

With an intermittent dose regimen (once weekly [QW], twice weekly (BIW), or three times weekly [TIW]), no or limited accumulation in the mean area under the curve for plasma concentration vs. time (AUC) or maximum concentration of drug after dosing (Cmax) was observed. Furthermore, no evidence was found for time-dependent pharmacokinetics (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. In vitro data suggest that the inhibitory potential of roxadustat on cytochrome P-450 isoenzymes (CYP) is limited, and the most potent 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 subjects (Study FGCL-SM4592-016), roxadustat administered orally as a single dose up to 4.0 mg/kg, and as multiple doses, 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 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. In dialysis subjects (Study FGCL-4592-039), comparable dose-dependent increases in EPO levels were observed, both pre-dialysis and post-dialysis. These increases in endogenous EPO were transient and the effect disappeared within approximately 48 hrs.

In contrast, EPO levels associated with therapeutic ESA dosing range from 1,500 to over 10,000 mIU/mL (Besarab, Frinak, and Yee 131-42). The reported mean administered individual ESA dose in a meta-analysis of subjects undergoing HD in 2005 was 8,000 IU, which would correspond to plasma EPO Cmax levels exceeding 3,000 mIU/mL (Fishbane and Besarab 1274-82). This is approximately 10-fold higher than the physiologic range.

1.6.2. Efficacy

Data from a 4-week dose ranging study in anemic subjects with CKD not on dialysis (Study FGCL-SM4592-017) suggest that roxadustat promotes erythropoiesis at lower doses in subjects

with CKD than in healthy subjects. With 0.7 mg/kg TIW dosing, mean Hb increased by 1.0 g/dL over a 6-week period in anemic subjects with CKD who completed 4 weeks of dosing; greater mean Hb increases of 2.0 to 2.3 g/dL occurred at roxadustat doses of 1.5 and 2.0 mg/kg TIW, respectively. Hemoglobin responder (Hb increase of ≥1.0 g/dL) rates were 62%, 60%, 91%, and 100% in the roxadustat cohorts receiving 0.7, 1.0, 1.5, and 2.0 mg/kg TIW, respectively. The Hb responses were also greater at the higher roxadustat doses (1.5 to 2.0 mg/kg) in the BIW dosing groups. With the additional criterion that Hb achieve a level of ≥11 g/dL as well as increasing by ≥1.0 g/dL, the Hb responder rate at 2.0 mg/kg of roxadustat IW and TIW was 89% and 91%, respectively. The rapid rates of rise in Hb with roxadustat treatment were not accompanied by elevations in blood pressure (BP), as has been reported with ESA treatment (Eschbach et al. 992-1000).

Data from a 16 to 24-week treatment Phase 2b study in subjects with CKD not on dialysis (Study FGCL-4592-041) showed that absolute and weight-based doses of roxadustat, administered TIW and BIW, effectively corrected and maintained Hb levels to a Hb target of 11 g/dL (range of 11-13 g/dL in 96 subjects and 10.5-12.0 g/dL in 48 subjects).

Data from 48 HD and 12 PD subjects enrolled in a 12-week incident-dialysis study (Study FGCL-4592-053), using similar tiered, weight-based initial doses as study FGCL 4592-041, indicate increases in mean Hb of approximately 2 g/dL after six weeks of treatment. Subjects were randomized to receive no iron, oral iron or IV iron. The Hb responses were indistinguishable between the oral and IV iron arms; subjects in the no iron arm had a similar Hb response during the first 8 weeks of treatment which plateaued during the last 4 weeks of treatment, suggesting that with long-term roxadustat treatment, iron supplementation may be necessary. However, data suggest that supplementation with oral iron is as effective as IV iron, and is recommended as the first-line option for iron supplementation in the Phase 3 studies. Starting roxadustat doses between 1.0 and 1.6 mg/kg appeared adequate to correct Hb in these subjects.

Data from a US study in subjects with ESRD on dialysis treated for 6 and 19 weeks suggest that subjects receiving a stable ESA dose can be converted to treatment with roxadustat (Study FGCL-4592-040). During the 6-week dose portion of this study subjects who switched from epoetin alfa to roxadustat had a dose-dependent Hb response. The 1.0 mg/kg roxadustat dose was comparable to the Epoetin alfa control, which had a small decline in Hb level from baseline and a lower percent Hb responder rate compared to the higher doses of roxadustat. The 1.5 and 2.0 mg/kg roxadustat dose arms resulted in a Hb increase of about 1 g/dL from baseline and an 89% response rate, more than double that of the Epoetin alfa arm, despite the absence of IV iron supplementation. Regression slope analyses of Hb values over time showed that the estimated rate of Hb rise was positive and statistically significant for the 1.5 mg/kg and 2.0 mg/kg dose cohorts, with a Hb increase of 0.22 g/dL (p=0.0040) and 0.18 g/dL (p=0.0146) per week, respectively. In the 19-week portion of the study, during which dose-titration was allowed, Hb maintenance was demonstrated to be durable in roxadustat treatment arms (combined) over the treatment period. In contrast, the Hb levels of epoetin alfa controlled subjects appeared to decline gradually over time despite steady levels of epoetin alfa doses, possibly because IV iron was not permitted during the treatment period. Efficacy of roxadustat was confirmed in a similarly designed 6-week study conducted in ESRD subjects in China.

Preliminary data taken at the time of this protocol amendment from an ongoing open label extension study (Study FGCL-4592-059, to which some subjects from Studies FGCL-4592-041

and FGCL-4592-040 rolled over) further suggest the durability of roxadustats effect in maintaining Hb levels in CKD subjects for up to 2 years.

1.6.3. Safety

The overall frequency and type of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) observed in these clinical studies reflect events that would be expected to occur in CKD subjects with multiple co-morbidities and on a number of concomitant medications. There has been no SAE attributable by the sponsor to the use of roxadustat. Safety analyses did not reveal any association between the rates of occurrence of cardiovascular events with roxadustat, or any effect on AE rates related to either increasing Hb levels or on the rate of change of Hb levels.

Adverse event rates of hypertension (1% in Study FGCL-SM4592-017, 7.6% in Study FGCL-4592-041, and 10% FGCL-4592-053) and serious adverse events of arteriovenous-fistula thrombosis (overall incidence in dialysis-dependent CKD subjects: 2%), compare favorably with the rates reported in published ESA studies in similar subject populations (Krapf and Hulter 470-80;Fishbane and Besarab 1274-82). No safety risks were associated with increased rate of rise of Hb levels or with achieving a Hb level above 11 g/dL using roxadustat. Although Study FGCL-4592-041 subjects achieved Hb>11 g/dL in 52% of exposure time during study, no cardiovascular safety events (death, MI, stroke, unstable angina, hospitalization for congestive heart failure, or hospitalization for arrhythmias) were reported while Hb>11 g/dL during treatment with roxadustat.

No increased cancer risk has been noted with roxadustat treatment; however, the study program was not powered to detect absence of cancer risk.

Liver enzymes were monitored closely throughout the roxadustat clinical development program. Increases in liver enzymes were infrequently seen, and were generally mild and transient in nature. No cases of Hy's Law were observed throughout the program. An independent data and safety monitoring committee concluded that there was no concern for hepatotoxicity with roxadustat.

Based on the safety data collected to date, roxadustat has an acceptable safety profile that supports its further development.

1.6.4. Summary

Data from 18 completed and ongoing studies suggest that roxadustat exhibits dose-dependent PK, binds well with protein, and is not filtered out during HD. Intermittent dosing with roxadustat results in transient activation of HIF, intermittent induction of endogenous physiologic-range EPO, and dose-dependent erythropoiesis, suggesting a coordinated mechanism of erythropoiesis that is different from ESA therapy, including beneficial effects on iron handling. The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in dialysis and non-dialysis subjects with CKD and anemia when treated with roxadustat for up to 2 years.

1.7. Rationale for Subject Population

In Phase 1 studies of healthy subjects in Europe, the US, and Japan, roxadustat was generally well tolerated, and resulted in a dose-dependent pharmacodynamic response leading to increased

circulating EPO and reticulocyte levels. Data from a Phase 2a study (FGCL-SM4592-017) in the US in Stage 3 or 4 CKD non-dialysis subjects indicate that roxadustat is well tolerated and results in significant increases in Hb levels in such subjects. A Phase 2b study (FGCL-4592-041) in a similar CKD non-dialysis subject population has been completed, as are a Phase 2 study (FGCL-4592-053) in newly initiated ESA-naïve dialysis subjects, and a Phase 2 study (FGCL-4592-040) in a dialysis subject population that was previously receiving EPO. These studies showed that FG 4592 was effective throughout the continuum of CKD/ESRD: the correction of anemia in CKD non-dialysis subjects, the correction of anemia in newly initiated ESA-naïve ESRD dialysis subjects, and the maintenance of Hb in ESRD dialysis subjects.

Since progression of CKD into ESRD inexorably leads to an increased progression and likelihood of anemia, treatment of anemia in CKD is expected to be chronic, unless the patient successfully receives a renal transplant. It is, therefore, important to evaluate the long-term efficacy, safety, and tolerability of roxadustat in the treatment of anemia in such patients.

Eligible subjects enrolled in an ongoing U.S. roxadustat anemia study, who have completed the treatment period, will be offered participation in this long-term extension study.

1.8. Rationale for Dose Selection

Starting doses of roxadustat were studied in three ways in the Phase 2 program: using a strict weight-based dosing approach that was useful in the proof of concept stage; using a tiered weight-based approach where a subject's starting dose was selected based on categorizing the subject's body weight as low (45 to < 70 kg), medium (70 to 100 kg), or heavy (> 100 kg); and using an absolute starting dose regardless of body weight. The tiered weight-based approach has been chosen for the development of roxadustat in the Phase 3 program to provide a practical starting dose strategy for a controlled Correction to target Hb values, based on the observed relationship between body weight, PK, and Hb response, and the requirements of oral dosing.

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

Based on the Phase 2 data, it is expected that subjects who receive these starting doses to correct anemia will be able to maintain Hb levels with a total weekly dose reduction of the order of 22 to 35%. This dose reduction can be achieved by adjusting the per dose amount towards the protocol-defined Hb target range. The Phase 2 studies evaluated the need for dose adjustments for both Hb Correction and Hb Maintenance. Dose adjustments were allowed at regular 4-week intervals to maintain, increase, or decrease the dose according to prespecified rules. Pre-specified dosing steps were used to correct and maintain Hb levels within treatment thresholds based on absolute Hb levels and change of Hb in the previous 4 weeks. Additional rules for dose adjustment were provided to minimize excessive hematopoiesis. These dose adjustment rules

were successful in Hb Correction and Hb Maintenance and will be adopted in this study with minor modifications.

2. OBJECTIVES

2.1. Primary Objective

Evaluate the long-term efficacy and safety of roxadustat in the maintenance of Hb in dialysis and non-dialysis CKD subjects.

2.2. Secondary Objectives

Evaluate roxadustat doses and dose adjustments.

2.3. Exploratory Objectives

- Assess the effect of roxadustat on iron utilization parameters;
- Assess the effect of roxadustat on select biomarkers.

3. ENDPOINTS AND ASSESSMENTS

3.1. Efficacy

The efficacy endpoints in this study are:

- Mean monthly Hb values over time;
- Number (%) of subjects maintaining monthly (monthly defined as a 4-week interval) mean Hb at ≥10 g/dL during study participation upon correction (correction is defined as having achieved 2 consecutive Hb values of ≥10 g/dL);
- Number (%) of subjects maintaining Hb between 10-13 g/dL for at least 60% of scheduled Hb assessments after the first Hb value is 10 g/dL or higher.
- Composite rate of summarized rescue therapy events (transfusions, IV iron, ESAs) and rate of individual rescue therapy events;
- Number (%) of subjects with phlebotomies;
- Roxadustat weekly total doses over time;
- Dose adjustment frequencies;
- Hb variability;
- Number (%) of subjects withdrawn from the study due to inadequate efficacy.

3.2. Safety

Safety in this study will be assessed by evaluating the following:

- Vital signs, clinical laboratory values, ECG, and changes in physical examinations;
- AEs and SAEs.

3.3. Select biomarkers

Exploratory assessments in this study will evaluate the following parameters:

- Reticulocyte hemoglobin content (CHr);
- Highly sensitive C-reactive protein (hs-CRP);
- Hepcidin levels in serum;
- Additional exploratory biomarkers.

4. STUDY DESIGN

4.1. Description of the Study

This is an open-label, long-term maintenance study of roxadustat anemia therapy in dialysis and non-dialysis subjects with CKD who have completed the treatment period of an roxadustat anemia study in the U.S. Up to 50 non-dialysis, HD, and PD subjects will be enrolled in this study from up to 20 study centers throughout the U.S.

Subjects who received roxadustat in a previous study will continue to receive roxadustat at the same dose and frequency as they received at the end of the treatment period in their previous study, unless a dose adjustment is required.

Subjects who received placebo in their previous study may start treatment with roxadustat at starting doses according to their weight (Appendix B).

Subjects will receive study treatment for up to 312 weeks (6 years). Subjects enrolled in this study prior to Amendment 2 may continue treatment for up to an additional 1 year of treatment.

Subjects who received roxadustat in a previous study will return for study visits every 2 weeks for the first 104 weeks of treatment (including time on previous Phase 2/3 studies of roxadustat), and every 4 weeks thereafter, until the end of the treatment period.

Subjects who received placebo in their previous study will return for study visits weekly until their Hb level has stabilized to a range of 10.0 to 12.0 g/dL (±2.0 g/dL) through 4 consecutive weeks. These subjects will then return for study visits every 2 weeks for the first 24 weeks of treatment, followed by every 4 weeks until the end of the treatment period.

After the end of treatment (defined as the last day a subject receives study drug) the subject will return for a follow-up visit 4 weeks later.

The baseline Hb value for efficacy analysis is defined as the mean of the central laboratory Hb value from the baseline visit at Day 1 (prior to receiving the first dose of study drug in this study), plus any other central lab Hb values within 15 days prior to Day 1.

Safety will be assessed by vital signs, physical examinations, clinical laboratory values (including liver function tests [LFTs] and complete blood counts [CBC]), electrocardiograms (ECGs), AEs and concomitant medication reporting. Clinical laboratory tests, including LFTs and Hb levels, may be assessed at additional times on unscheduled visits for safety reasons.

4.1.1. Control Groups

No control group will be included in this study.

4.2. Randomization and Treatment Assignment

4.2.1. Randomization Procedures

No randomization will be performed for this study.

4.2.2. Treatment Assignment

Subjects who received roxadustat in a previous study will continue to receive roxadustat.

Subjects who received placebo in their previous study may start treatment with roxadustat.

The roxadustat oral solid dosage (OSD) will be supplied in an open-label manner to all subjects.

4.3. Study Treatment

4.3.1. Dose and Schedule

Subjects who received roxadustat in a previous study will continue to receive roxadustat at the same dose and dosing frequency (TIW, BIW, or QW) as they received at the end of their last study, unless a dose adjustment is required.

Subjects who received placebo in their previous study will receive roxadustat by weight category as described in Appendix B.

If treatment assignment is blinded at the time of enrollment, the subject has been on a stable dosing regimen for at least 2 months and if the last dose is lower than the starting doses described in Appendix B, the subject may continue on the current dosing regimen.

4.3.2. Dose Adjustments

Guidelines for dose adjustments are provided in C. In general:

- The Hb thresholds for dose adjustments are < 10 g/dL for dose increases and $\geq$ 12 g/dL for dose reductions
- Dose adjustment rules are based on changes in Hb values over 4 weeks and whether the Hb target has been reached or exceeded.
- Dose increases and decreases are pre-set at the dose steps described in Appendix A.
- The maximum dose is 3.0 mg/kg.
- The time interval between dose adjustment reviews should be 4 weeks, except in the event of excessive hematopoiesis (when the subject's dose should be reduced), or rapidly declining Hb (when the subject's dose should be increased). For example, even if a subject's dose is not increased or decreased following a dose adjustment review visit, the next dose adjustment review will be 4 weeks after the last dose adjustment review.
- For subjects who received placebo in their previous study, no dose adjustment will occur from Weeks 1 through 4 except in the event of excessive hematopoiesis or rapidly declining Hb.
- For subjects who received roxadustat, or blinded study drug, and on a stable dose for the past 2 months, in a previous study, dose adjustment review will occur 4 weeks from the last dose adjustment review in the previous study.
- During the course of the study, the dose and the dosing frequency may be changed to optimize efficacy and tolerability based on the clinical judgment of the investigator and study medical monitor.

In the event of an extenuating clinical circumstance (e.g., recent bleeding, disruption of dosing due to hospitalization or vacation, etc.), the investigator may dose a subject outside of the dose adjustment parameters provided this has been discussed with the study medical monitor.

Dose Frequency Adjustments should be done according to Appendix C.

Dose Adjustment for Excessive Hematopoiesis

At any time during the treatment period, if Hb increases by > 2.0 g/dL in 2 weeks that is not due to an RBC transfusion the dose should be reduced by one dose step (Appendix A).

If there are clinical concerns for a subject's excessively high Hb value outside the dose adjustment intervals (as described in Appendix A), the investigator may adjust the dose immediately; the investigator may also decide to perform a therapeutic phlebotomy in addition to the dose adjustments—these situations should be documented and discussed with the study medical monitor whenever possible.

4.4. Concomitant Medications, Procedures and Nondrug Therapies

4.4.1. Concomitant Medications

Concomitant medications are any prescription or over-the-counter preparations (including herbal products and "natural remedies") used by a subject while participating in this clinical trial.

For all concomitant medication use, the study site must provide an indication for its use. If the stated indication is a nonspecific condition, e.g., "rash," documentation of the condition, as specific as possible, must be provided by the subject's primary care physician and maintained in the subject's clinical study records as source documentation.

4.4.2. Contraception

Female subjects of childbearing potential must agree to use a medically acceptable form of birth control (e.g., oral contraceptive pills, depot progesterone, or intrauterine device). The above list is not comprehensive. Abstinence alone suffices as adequate contraception. Male subjects with sexual partners of childbearing potential who are not using birth control (as described above) must use contraception (e.g., condom) if not surgically sterile (i.e., vasectomy). Contraceptive methods must be practiced from the time informed consent is signed and through at least 1 month after the last dose of study drug.

4.4.3. Rescue Medication

If a subject is not responding adequately to roxadustat, and rescue therapy is considered a medical necessity by the investigator, rescue therapy will be allowed for a subject provided this has been discussed with the study medical monitor, or is deemed to be an immediate medical necessity by the investigator.

The three options for rescue therapy are as follows:

1. Blood transfusion: For subjects undergoing rescue therapy with transfusion, administration of study medication may continue.
2. Iron supplementation: Oral iron should be the first-line option for iron supplementation. IV iron supplementation may be considered if the following criteria are met:

- The subject has not responded adequately to 2 or more dose increases or reached the maximum dose limit and
- Ferritin saturation is <50 ng/ml **or** transferrin saturation (TSAT) is <10%

OR

- The subject is intolerant of oral iron therapy and
- Ferritin saturation is <50 ng/ml **or** TSAT is <10%

Roxadustat treatment should continue during oral and IV iron supplementation. The investigator may discontinue IV iron supplementation once he no longer considers the subject to be iron deficient. The investigator should carefully monitor the subject's Hb response after the IV iron supplementation.

3. ESAs: ESAs are not to be concurrently administered with. Once a subject is considered a treatment failure due to a lack of efficacy and/or lack of tolerability, and ESA treatment is initiated per the treating physician, roxadustat must be permanently discontinued and the subject also is to be discontinued from the study. In the event of an extenuating circumstance during which a subject inadvertently receives an ESA for a short period of time (e.g., recent bleeding, disruption of dosing due to hospitalization or vacation, etc.), the study medical monitor should be contacted to evaluate the appropriateness of continuing treatment with roxadustat.

4.4.4. Excluded (Prohibited) Medications/Therapies/Substances

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

Concomitant therapy with any of the following is prohibited:

- Androgen, deferoxamine, deferiprone, or deferasirox therapy until completion of the study
- Red blood cell transfusion until completion of the study, unless used as rescue therapy
- Intravenous iron supplementation, unless used as rescue therapy
- Any ESA therapy until completion of the study, unless used as rescue therapy
- Dapsone, or chronic acetaminophen use > 2.0 g/day or > 500 mg per dose repeated every 6 hours, from the week 1 visit until completion of the study
- Use of herbal medicine is strongly discouraged during the course of the study. If a subject insists on starting use of an herbal medicine during the study, this should be discussed with the study medical monitor on a case-by-case basis

4.5. Safety Plan

Safety will be assessed throughout the study. A baseline profile of each subject will be established through clinical laboratory values (serum chemistry and LFTs, CBCs, iron studies, and pregnancy status), physical assessments, and ECGs. During the course of the study, vital signs, complete and targeted physical assessments, laboratory tests (CBC with differential, serum

chemistry, serum iron studies, and special laboratory tests), and ECGs will be performed at specific intervals. Any medically significant changes from baseline will be monitored throughout the study and appropriate interventions will be made accordingly. Clinical laboratory tests, including LFTs and Hb levels, may be assessed at additional times on unscheduled visits for safety reasons.

Adverse events, SAEs, and ongoing concomitant medication usage will be monitored and recorded throughout the study. Serious adverse event reports will be evaluated individually to assess the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. All SAEs and AEs will be followed until resolved, stable, or until the subject's final visit. See Section 11 for details on AE and SAE reporting.

Subjects will be closely monitored for inadequate or excessive hematopoiesis, which will be managed according to guidelines stipulated in the protocol and based on protocol-defined dose adjustment rules (Section 4.3.2) and reasons for study drug discontinuation. Liver function will also be closely monitored and investigators will follow the Hepatic Monitoring Plan (HMP; described in Section 4.5.1) to determine when heightened surveillance is required and what actions, if any, are needed with study drug administration.

4.5.1. Hepatic Safety Monitoring

The guidelines described in this section are intended to enable early detection and action following abnormal liver function test (LFT) results. **It is the responsibility of the Investigator to expeditiously review LFTs, follow these guidelines and contact the Medical Monitor if a study subject meets any of the LFT abnormalities specified below.** In addition, repeat LFTs 2 to 3 times weekly, then weekly or less until abnormalities stabilize or return to within normal limits. LFTs should include the usual 4: ALT, AST, Tbili and ALP

Table 1: Summary of investigator actions with respect to Hepatic Monitoring

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

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

If close monitoring for LFTs in a subject is not possible, study drug should be discontinued Evaluate the subject for potential causes, which may include the following:

- Detailed history of symptoms and prior or concurrent diseases
- Concomitant drug use, including nonprescription medications, herbal and dietary supplements, alcohol or recreational drug use, or special diets
- Exposure to environmental chemical agents

- Rule out acute viral hepatitis Types A, B, C, D, E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; biliary tract disease
- Obtain additional tests as appropriate: eg, INR, GGT or direct bilirubin; ultrasound or other imaging to assess biliary tract disease
- Consider gastroenterology or hepatology consultations

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

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

4.6. Data Monitoring Committee

A Data Monitoring Committee (DMC) will review pre-specified safety data (including AE and laboratory data) periodically in collaboration with the sponsor to ensure subject safety. A separate DMC charter will establish meeting frequency and scope of responsibilities. DMC review will continue until the last meeting for the Phase 3 program is completed.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

1. Minimum age 18 years
2. Subjects who have completed the treatment period of an ongoing roxadustat anemia study in the U.S.

5.2. Exclusion Criteria

1. Subjects assigned to epoetin alfa in a previous ongoing roxadustat anemia study
2. Pregnant or breastfeeding females
3. Females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception
4. Subjects who received roxadustat in a previous study that did not demonstrate adequate hemoglobin response per the investigator's clinical judgment
5. Any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study, or which may interfere with study participation

6. STUDY DRUG/TREATMENT SUPPLY

6.1. FibroGen Investigational Product

6.1.1. Formulation of roxadustat

Roxadustat is supplied by FibroGen, Inc. as an OSD of 20, 50, or 100 mg strength, made from active pharmaceutical ingredient and common USP/NF excipients and components. Complete traceability of the OSD will be documented in the CRF.

6.1.2. Storage of Study Drug

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

All study-drug should also be stored in a securely locked area to which access is limited to appropriately qualified and authorized study personnel.

6.1.3. Administration of Study Drug

The study treatment OSD's are to be swallowed whole with room-temperature drinking water. Study treatment (roxadustat) will be dispensed to subjects at each study visit with instructions for self-administration of the OSD on each dosing day, according to the dosing schedule.

Study drug doses scheduled for a dosing frequency of TIW must be administered at least 2 days apart, and no more than 4 days apart. Study drug doses scheduled for a dosing frequency of BIW must be administered at least 3 days apart, and no more than 5 days apart. Study drug doses scheduled for a dosing frequency of QW must be administered at least 5 days apart, and no more than 9 days apart.

See Section 4.3.2 for guidelines for dose adjustment to help maintain subjects' Hb levels within a predefined target range.

See Section 4.5.1 for guidelines on withholding and discontinuing dosing in response to changes in LFT values outside of acceptable limits, and other hepatic abnormalities.

7. STUDY PROCEDURES

7.1. Study Procedures by Visit

An outline of the specific procedures and evaluations for each study visit is provided below. Refer to Appendix A for the Schedule of Assessments and the Study Reference Manual for details.

Although it would be ideal for study assessments to be performed precisely at specified dates, assessments will be allowed practical windows for completion.

7.1.1. Treatment Period

7.1.1.1. Baseline (Week 1)

The following assessments will be performed prior to study drug administration. Assessments performed at the end-of-study visit in the previous roxadustat study may be used for those assessments noted below that need to be completed within 4 weeks prior to study drug administration.

- Signed written informed consent within 4 weeks prior to study drug administration;
- Inclusion criteria verification;
- Exclusion criteria verification;
- Vital signs: BP, heart rate (HR) and respiratory rate;
- Complete physical examination within 4 weeks prior to study drug administration;
- Weight (use dry weight in HD subjects) within 4 weeks prior to study drug administration;
- 12-lead ECG within 4 weeks prior to study drug administration;
- Quality of Life questionnaire (FACT-An) within 4 weeks prior to study drug administration.
- Laboratory tests:
  - CBC with white blood cell (WBC) differential and reticulocyte count;
  - Fasting serum chemistry (with LFTs, lipid profile, and glucose);
  - Human chorionic gonadotropin (hCG) test within 4 weeks prior to study drug administration (for women of childbearing potential only);
  - Serum iron studies: iron, ferritin, transferrin (or total iron binding capacity [TIBC]), and TSAT;
  - Special laboratory tests (CHr, hepcidin, hs-CRP, plus select biomarkers) within 4 weeks prior to study drug administration (only for subjects who had a baseline collected during prior roxadustat study);
- Adverse events;

- Concomitant medications;
- Dispense roxadustat (2-week supply for subject previously assigned to roxadustat and 1 week supply for newly initiated to roxadustat with unstable Hb).

7.1.1.1.1. Weekly Visits (±3 days) up to week 4

- Weekly visits are only for the optional group of subjects newly initiated to roxadustat and only need to be performed until Hb stabilizes.
- Dispense weekly roxadustat
- Vital signs: BP, HR, and respiratory rate
- Laboratory tests:
  - CBC with WBC differential and reticulocyte count
- Adverse events
- Concomitant medications

7.1.1.1.2. Every 2 Week Visits (±3 days) up to week 24

- Dose Adjustments as needed
- Dispense roxadustat
- Vital signs: BP, HR, and respiratory rate
- Laboratory tests:
  - CBC with WBC differential and reticulocyte count
- Adverse events
- Concomitant medications

7.1.1.1.3. Every-4-Week Visit (±3 days)

- Dose adjustment as needed
- Dispense roxadustat
- Vital signs: BP, HR, and respiratory rate
- Laboratory tests:
  - CBC with WBC differential and reticulocyte count
  - Fasting serum chemistry (with LFTs, lipid profile, and glucose)
  - Serum iron studies: iron, ferritin, transferrin (or TIBC), and TSAT
- Adverse events
- Concomitant medications

7.1.1.1.4. Every-12-Week Visits (±7 days)

- Dose adjustment as needed
- Dispense roxadustat
- Vital signs: BP, HR, and respiratory rate
- Physical examination
- Weight (use dry weight in HD subjects)
- Laboratory tests:
  - CBC with WBC differential and reticulocyte count
  - Fasting serum chemistry (with LFTs, lipid profile, and glucose)
  - Serum iron studies: iron, ferritin, transferrin (or TIBC), and TSAT
- Adverse events
- Concomitant medications

7.1.1.1.5. Every 24 Week Visits (±7 days)

- Dose adjustment as needed
- Dispense roxadustat
- Vital signs: BP, HR, and respiratory rate
- 12-lead ECG
- Physical examination
- Weight (use dry weight in HD subjects)
- Laboratory tests:
  - CBC with WBC differential and reticulocyte count
  - Fasting serum chemistry (with LFTs lipid profile, and glucose)
  - Serum iron studies: iron, ferritin, transferrin (or TIBC), and TSAT
  - Special labs (CHr, hepcidin, hs-CRP, plus select biomarkers) (only for subjects who had a baseline collected during prior roxadustat study)
- Quality of Life questionnaire (FACT-An)
- Adverse events
- Concomitant medications

7.1.1.1.6. Termination / Early Termination (ET) Visit

This visit is to occur 4 weeks after final dose. If a subject discontinues from the study during the treatment period, perform the ET assessments at the time of withdrawal from dosing:

- Physical examination
- Weight (use dry weight in HD subjects)
- Vital signs: BP, HR, and respiratory rate
- 12-lead ECG
- Laboratory tests:
  - CBC with WBC differential and reticulocyte count
  - Fasting serum chemistry (with LFTs, lipid profile, and glucose)
  - hCG test for women of childbearing potential only
  - Serum iron studies: iron, ferritin, transferrin (or TIBC), and TSAT
  - Special labs (CHr, hepcidin, hs-CRP, plus select biomarkers) (only for subjects who had a baseline collected during prior roxadustat study)
- Quality of Life questionnaire (FACT-An)
- Adverse events
- Concomitant medications

7.2. Post-Treatment Follow-Up Period

The Follow-up Period begins on the week after the last dose of study treatment, and continues for 4 weeks.

7.3. Missed Visits

Every attempt should be made to complete all study visits as outlined in the Schedule of Study Assessments (Appendix A). All missed study visits will be considered protocol deviations.

7.4. Unscheduled Visits

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

7.5. Assessments

Central laboratory data should be reviewed as soon as they are received. Subject management is dependent upon close review of the laboratory data. Vital signs should be recorded in a quiet room.

7.5.1. Central Laboratory

All laboratory tests of blood specimens will be performed by a central laboratory. A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Serum chemistry, iron studies, serum pregnancy tests, and CBC with white cell differential and reticulocyte counts will be performed and analyzed by a central laboratory during the treatment and post-treatment Follow-up Periods. Fasting is preferred for serum chemistry, if possible.

The central laboratory will also be able to perform unscheduled testing (e.g., to confirm abnormal LFTs or to obtain an additional Hb value). Acute clinical management may dictate the need for the services of a local laboratory.

Required scheduled laboratory tests are to be performed by a central laboratory unless otherwise specified. Laboratory parameters to be measured in this study are as follows:

- (Fasting) Serum Chemistry

  Fasting is preferred for serum chemistry, if possible. Serum chemistry in this study will consist of the following laboratory analytes:

• Sodium • Potassium • Chloride • Calcium • Magnesium • Bicarbonate • Phosphorus • Creatinine • Glucose • Uric Acid • Albumin • Total protein • Lactate dehydrogenase	• Lipid Profile – Total Cholesterol – LDL – HDL – Triglyceride • LFTs: – ALT – AST – Bilirubin (total and direct) – GGT – ALP

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; LDL = low density lipoprotein; LFT = liver function test;

The LFTs and Lipid Profile are subsets of the serum chemistry panel.

- Complete Blood Count

  Complete blood count will consist of the following laboratory analytes:

• Hb • Hematocrit • RBC • Mean corpuscular volume • Mean corpuscular Hb • Mean corpuscular Hb concentration • WBC	• Neutrophils • Banded neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils • Platelet count • Reticulocyte count

Abbreviations: Hb = hemoglobin; RBC = red blood cell; WBC = white blood cell.

- Coagulation Parameters

  The central laboratory may be requested to draw PT and calculate an INR in subjects whose LFT results trigger the HMP (see Section 1.1).

- Serum Iron Studies: iron, ferritin, transferrin (or TIBC), and TSAT.
- Serum Pregnancy Test.
- Special Laboratory Analytes: CHr, hepcidin, and hs-CRP.
- Select Biomarkers: A set of serum samples will be drawn and stored for the future analysis of relevant select biomarkers.

7.5.2. Local Laboratory

No local laboratories will be used for regular, standard-laboratory testing during the study.

7.5.3. Vital Signs

Subjects should take their study medication after the vital sign measures and not immediately before. For subjects on HD, BP should be taken prior to and after the dialysis procedure. For subjects on PD, BP should be taken during study visit.

7.5.4. Electrocardiogram

Twelve-lead ECGs will be performed on all subjects for safety assessments at Baseline (may use end of study visit of previous roxadustat study if it is within 4 weeks prior to study drug administration), Termination/ ET visit. Triplicate ECGs are not required.

7.5.5. Quality of Life Questionnaire

All study subjects will be asked to complete Quality of Life questionnaire (FACT-An) at Baseline (may use end of study visit of previous roxadustat study if it is within 4 weeks prior to study drug administration), and Termination/ ET Visit.

8. SUBJECT DISCONTINUATION

Subjects may withdraw from the study at any time. Withdrawn subjects should be strongly advised to complete the 4-week Follow-up Period procedures as outlined in the Schedule of Study Assessments in Appendix A. The appropriate documentation must be entered on the Study Termination CRF. Subjects should be discontinued from the study for any of the following reasons:

- Significant noncompliance with study procedures, as determined by principal investigator and study medical monitor;
- Subject no longer consents to participate in the study;
- Physician decision that it is in the best interest of the subject to be withdrawn from the study;
- Need for ESA rescue therapy due to lack of efficacy and/or lack of tolerability to roxadustat;
- Study medical monitor and principal investigator agree that a subject's intercurrent illness is significantly interfering with study assessments;
- The study is terminated by FibroGen for any reason or by the DMC due to safety concerns;
- Subject is lost to follow-up for the duration of the study;
- At FibroGen's discretion;
- Subject is found to be pregnant;
- Death.

Subjects who withdraw from the study will be followed for AEs as described in Section 11 of this protocol. The reason for withdrawal from the study will be documented in the CRFs.

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

9. STUDY TERMINATION BY FIBROGEN

FibroGen has the right to terminate this study at any time.

10. STATISTICS

10.1. Sample Size Determination

This is an open-label, long-term maintenance study of roxadustat anemia therapy in dialysis and non-dialysis CKD subjects who have completed the treatment period of an roxadustat anemia study in the U.S.

Power analysis not used to determine the sample size.

10.2. Treatment Assignment

Subjects assigned to roxadustat in the previous study will receive the same study treatment assignment.

An optional treatment group allows subjects who received placebo or blinded study drug to start treatment with roxadustat.

Data will be summarized using the following subject populations as deemed appropriate

- Dialysis Group: Subjects on dialysis previously treated with roxadustat at the time of entry to study
- Non-Dialysis Group: CKD subjects previously treated with roxadustat not on dialysis at the time of entry to study
- Newly Initiated Group: Subjects who were not previously treated with roxadustat at study entry that have to be corrected

The roxadustat (OSD) will be supplied in an open-label manner to all subjects.

10.3. Analysis Population

The Safety population, defined as all subjects who have received any dose of study treatment, will be included in the safety analyses.

The Efficacy Evaluable (EE) population is defined as all subjects who receive any dose of study treatment and have non-missing Hb measurement at Baseline and at least one non-missing post-baseline Hb measurement.

10.4. Interim Analysis

The study will have no formal interim analysis with statistical inference. Safety and efficacy will be monitored on an ongoing basis.

A DMC will review pre-specified safety data (including AE and laboratory data) periodically in collaboration with the sponsor to ensure subject safety. A separate DMC charter will establish meeting frequency and scope of responsibilities. DMC review will continue until the last meeting for the Phase 3 program is completed.

10.4.1. Subject Enrollment and Disposition

A table will provide the number of enrolled subjects, Safety subjects, EE subjects, and subjects who terminated the treatment period/study early along with the reason for ET.

10.5. Replacement of Subjects

No replacement is planned for subjects who drop out prematurely.

10.6. Statistical Analysis

Summary statistics will consist of number of subjects (N), means, standard deviations, medians, and minimum (min) and maximum (max) values for continuous variables, and counts and percentages for categorical variables. A last-observation-carried-forward (LOCF) method may be used to impute any missing Hb values. For efficacy endpoints, the standard error and 95% confidence intervals will be added as part of the descriptive summaries. Tables will summarize all efficacy and safety measures by Dialysis, Non Dialysis, and Newly Initiated group and time point, as appropriate.

10.6.1. Demographics and Baseline Characteristics

Demographics (age, race, sex), baseline characteristics (e.g., height, weight), and subject disease characteristics will be summarized for all enrolled subjects.

Descriptive statistics will be calculated for continuous variables (age and weight) and frequency counts and percentages will be tabulated for categorical variables (e.g., gender, race, and body mass index).

10.6.2. Efficacy Analyses

Hemoglobin results obtained from the central laboratory will be used for all efficacy analyses.

Baseline Hb value for efficacy analysis is defined as the mean of the central laboratory Hb value from the Baseline Visit Day 1 (prior to receiving the first dose of study drug in this study), plus any other central laboratory Hb values obtained within 15 days prior to Day 1. Baseline eGFR, ferritin, TSAT, and other efficacy endpoints are defined as the last value prior to the first dose of study treatment.

All efficacy analyses will be based on the EE population.

- Monthly mean Hb values and changes from baseline will be summarized descriptively for the Dialysis, Non-Dialysis , and Newly Initiated populations at each scheduled time point as well as monthly
- The number (%) of subjects maintaining Hb ≥10 g/dL during study participation, the composite rate of summarized rescue therapy events (transfusions, IV iron, ESAs) and rate of individual rescue therapy events, and the number (%) of subjects receiving phlebotomies will be summarized for the Dialysis, Non Dialysis and Newly Initiated populations
- The dose level at the time of Hb response will be summarized descriptively
- The frequency of dose increases and decreases and use of rescue therapy will also be tabulated. Median time to Hb response will be estimated for each subject previously receiving placebo (Newly Initiated group) using the Kaplan-Meier method. Hemoglobin response is defined as a Hb increase from baseline of at least 1.0 g/dL. In addition, median initial responsive time and dose will be tabulated to evaluate when an initial Hb change from baseline reaches at least 1.0 g/dL. Number (%) of

subjects, scheduled Hb values, and consecutive Hb values achieved for a variety of Hb ranges between 11.0 and 13.0 g/dL, as well as above or below these ranges, during 4-week study intervals throughout the treatment period will be tabulated.

10.6.3. Exploratory Analyses

Quality of life composite scores, as well as selected subscale scores will be compared to baseline values and between treatment assignments.

Descriptive statistics will be generated for exploratory endpoints and biomarkers. Correlations between parameters will be explored.

10.6.4. Safety Analyses

All subjects who received any dose of roxadustat will be included in the safety analyses.

All safety assessment data, including laboratory assessments, vital signs, physical examinations, ECGs, AEs, and concomitant medications and therapies, will be summarized by time point of collection as appropriate for the Dialysis, Non-Dialysis, and Newly Initiated populations.

An AE data listing by subject, including verbatim term, preferred term, study treatment, severity, and relationship to study treatment, will be presented.

The number (%) of subjects experiencing treatment-emergent AEs will be summarized using frequency counts for the Dialysis, Non-Dialysis, and newly initiated populations.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Laboratory data will be summarized for each time point that specimens are collected. Change-from-baseline values may be calculated for selected laboratory parameters (baseline refers to blood drawn prior to the first study treatment). Laboratory values outside of normal limits will be identified in the subject data listings with flags for high and low values. Laboratory results obtained from the central laboratory will be used for all safety analyses.

ECG results will be classified using frequency counts for normal, clinically insignificant abnormalities, and clinically significant abnormalities by time point of collection. Descriptive statistics will be calculated for QT intervals.

Blood pressure, HR, and respiratory rate data will be summarized descriptively by various time intervals both as absolute values and as changes from baseline.

A summary table and/or listing will present all abnormal physical examination results throughout the study.

10.7. Statistical Analysis Plan

A detailed Statistical Analysis Plan (SAP) will be finalized prior to data analysis. Any significant changes to the analyses described in this protocol will be highlighted in the SAP. Deviations in analyses from the SAP will be detailed in the clinical study report.

11. SAFETY

11.1. Background

Adverse event reports from investigators are the critical building blocks to the developing safety profile of the study drug. Therefore, with the exception of study endpoints, the investigator must immediately report to the sponsor all SAEs, regardless of whether the investigator believes they are drug related. Additionally, the investigator must record nonserious AEs at regular intervals during the course of the study.

The definitions of an AE, suspected adverse reaction, adverse reaction, and SAE are described below in accordance with the Food and Drug Administration (FDA) Final Rule Vol 75, No 188, September 29, 2010 and the International Conference on Harmonization (ICH) E2A guidance.

11.2. Definitions

11.2.1. 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 laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. 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.

Out-of-range Hb values need not be reported as AEs as these Hb values will be captured and analyzed in the efficacy analyses.

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 (see Section 11.3.1).

11.2.2. Definition of an Adverse Reaction

An adverse reaction means any AE caused by a drug.

11.2.3. Definition of a Suspected Adverse Reaction

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

11.2.4. Definition of a Serious Adverse Event

An SAE is an AE 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 include an event that, had it occurred in a more severe form, might have caused death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly or birth defect; or
- Is an important medical event (based on appropriate medical judgment, the event jeopardizes the subject and may require medical or surgical intervention to prevent one of the above-listed outcomes).

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

11.3.1. 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 treatment.

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

Adverse events collected prior to dosing of study drug will be considered "treatment non-emergent" while those reported after the first dose of study drug will be considered "treatment emergent" and be assessed for relationship to study drug.

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

11.3.2. Assessing Adverse Event Severity

The investigator should use the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0), which may be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

This will serve as guidance for specific severity assessment criteria.

The NCI CTCAE provides a descriptive terminology used for AE reporting and severity grading. It is a comprehensive dictionary of medical terms that facilitates accurate and consistent medical coding. It does not contain every event that may occur in a given study. Adverse events that are not covered by the NCI-specific criteria will be assessed for severity using the following criteria:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

11.3.3. Assessing Relationship of Adverse Event to Study Drug

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

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

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

Related (Adverse Reaction):

- Any event for which there is evidence to conclude that the study drug caused the event.

Possibly Related (Suspected Adverse Reaction):

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure, such as angioedema, anaphylaxis during infusion, rhabdomyolysis, Stevens-Johnson syndrome, etc.
- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug, such as tendon rupture.

Not Related:

- The event represents the underlying disease (e.g., disease-related symptoms, disease progression)

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

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

In order to support this practice, FibroGen will perform periodic aggregate data reviews to assess for: 1) one or more occurrences of rare/uncommon AEs, and; 2) increases in the observed frequencies of AEs that would be expected for the underlying disease and study population.

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

11.3.4. Reporting Serious Adverse Events on the SAE Report Form

All SAEs must be reported to FibroGen immediately.

To report an SAE, the investigator must e-mail or fax an SAE Report Form to FibroGen within 24 hours of becoming aware of the event. Follow-up reports must be submitted in a timely fashion as additional information becomes available.

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

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

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of SAEs in accordance with local regulations. FibroGen, 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.

11.3.4.2. Deaths

For any death occurring during the subject's study participation, regardless of attribution, the investigator will report the death immediately to the study medical monitor.

The investigator should notify FibroGen 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. This includes death attributed to progression of anemia or CKD.

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.

11.3.5. Pregnancies: Reporting and Follow-up of Subjects

A pregnancy in a female subject or a male subject's female partner must be confirmed by a positive serum beta-hCG test. If a female subject or the female partner of a male subject becomes pregnant while the subject is receiving study treatment or within 3 months after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to FibroGen 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. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, recorded on an SAE Report Form, and reported to FibroGen within 24 hours of the investigator learning of the event. Similarly, any medically significant congenital anomaly/birth defect in a child born to a female subject or the female partner of a male subject exposed to the investigational product should be recorded and reported as an SAE.

The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to FibroGen within 24 hours of the investigator learning of the outcome.

11.3.6. 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 must report abnormal laboratory findings if they are clinically significant or if there are associated signs and symptoms.

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE/SAE. If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE/SAE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

Clinically significant laboratory abnormalities that reflect a change from the initial screening value and that require active management may be considered AEs (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.). However, out-of-range Hb values should not be reported as AEs as these Hb values will be captured and analyzed in the efficacy analyses.

12. STUDY MONITORING

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

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

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

12.1. Data Quality Assurance

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

- Investigator meeting and/or investigator site initiation;
- Routine study site monitoring;
- Documented study and system training;
- CRF and query review against source documents;
- Collection of local laboratory normal ranges, if applicable.

12.2. Compliance with Laws and Regulations

This study will be conducted in accordance with the US FDA regulations, the ICH E6 Guideline for GCP, the Declaration of Helsinki, and applicable local, state, and federal laws, as well as other applicable country laws.

12.3. Data Collection and Handling

Source Documents

Source records are original documents, data, and records that are relevant to the clinical trial. 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 trial. Source records must be adequate to reconstruct all data transcribed onto the CRFs and resolved queries.

Data Collection, Handling, and Verification

Authorized site personnel will enter all required data onto paper or electronic CRFs. Data may be entered into a validated, clinical database compliant with 21 Code of Federal Regulations (CFR) Part 11 regulations. The database will be a secured, password-protected system with full audit trail.

FibroGen and/or its designee will review all subject data. Data that appear inconsistent, incomplete, or inaccurate will be queried for site clarification.

Adverse events and concomitant medications will be coded using industry standard dictionaries (e.g., Medical Dictionary for Regulatory Activities [MedDRA] and World Health Organization drug dictionaries).

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion.

Quality Compliance

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

13. HUMAN SUBJECTS

13.1. Ethical Considerations

The study will be conducted in accordance with US FDA regulations, the ICH E6 Guideline for GCP, the Declaration of Helsinki, any other applicable regulatory requirements, and IRB or IEC requirements.

13.2. Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the informed consent form (ICF), 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; these have to be 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 presented to the subject.

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 IB, and other safety-related communications from FibroGen. Written documentation of IRB/IEC 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.

13.3. Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written ICF from the subject or the subject's legally authorized representative. IRB/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 ICF during the subject's participation in the study, the revised ICF must receive the written approval of the IRB/IEC before use; current subjects must be re-consented to the revised version of the ICF.

13.4. 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 Health Insurance Portability and Accountability Act (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.

14. INVESTIGATOR REQUIREMENTS

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

14.1. Study Medication Accountability

All study drug required for completion of this study will be provided by FibroGen. 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 roxadustat investigational product, including partial and empty bottles, must be maintained at the study site until FibroGen or its designee verifies drug accountability and provides instruction for the return of the investigational product to FibroGen's drug distribution depot.

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

14.2. 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, FibroGen monitors/representatives and collaborators, auditors, and the IRB/IEC for each study site.

The Principal Investigator or sub-investigator should promptly notify FibroGen of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

14.3. 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 if a back-up exists and a hard copy is obtainable if required. No records will be destroyed without the prior written consent of FibroGen.

15. PUBLICATION POLICY

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

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APPENDIX A. SCHEDULE OF STUDY ASSESSMENTS

	Treatment Period [a]						**Follow-Up Period** [b]
	Baseline (Week 1)	**Weekly Visits (Weeks 1-4) (± 3 days)**[c]	**Every 2 weeks (Weeks 6-24) (± 3 days)**	**Every 4 weeks (± 3 days)**	**Every 12 weeks (± 7 days)**	**Every 24 weeks (± 7 days)**	**Termination Visit or ET (± 3 days)**
Written informed consent	X						
Eligibility criteria	X						
Dispense study drug	X	X	X	X	X	X	
Physical examination	X				X	X	X
Weight [d]	X [e]				X	X	X
BP, HR, respiratory rate	X	X	X	X	X	X	X
12-lead ECG	X [e]					X	X
hCG test for female subjects of child bearing potential only	X [e]						X
CBC with WBC differential and reticulocyte count	X	X	X	X	X	X	X
Fasting [f] serum chemistry (including LFTs, lipid panel, glucose)	X			X	X	X	X
Serum iron, ferritin, transferrin (or TIBC), TSAT	X			X	X	X	X
Special labs (CHr, hepcidin, hs-CRP, plus exploratory biomarkers)[g]	X [e]					X	X
Dose adjustment review			X	X	X	X	
Quality-of-life questionnaire (FACT-An)	X [e]					X	X
AE reporting	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood count; CHr = reticulocyte hemoglobin content; CRP = C-reactive protein; ECG = electrocardiogram; ET = Early Termination; FACT-An = . Functional Assessment of Cancer Therapy-Anemia; hCG = human chorionic gonadotropin; HR = heart rate; LFT = liver function test; TIBC = total iron binding capacity; TSAT = transferrin saturation; WBC = white blood cell.

[a] Subjects are to be dosed for up to 260 weeks (5 years) or 52 weeks if newly enrolled in Amendment 2

[b] Follow up Visit is 4 weeks after last dose of study treatment

[c] Weekly visits are only for subjects newly initiated to roxadustat until Hb stabilizes

[d] Use dry weight in HD subjects

[e] To be performed prior to study drug administration. The End-of-Study assessments in the previous roxadustat study may be used for assessments if they were completed within 4 weeks prior to study drug administration.

[f] Fasting is preferred, if possible

[g] Only collect for subjects who have a baseline special lab collected during prior roxadustat study.

APPENDIX B. DOSING FOR SUBJECTS PREVIOUSLY TREATED WITH PLACEBO

Subjects who received placebo in their previous study will receive roxadustat according to their weight as described in the table below.

If treatment assignment is blinded at the time of enrollment, the subject has been on a stable dosing regimen for at least 2 months and if the last dose is lower than the starting doses described in Appendix B, the subject may continue on the current dosing regimen

Weight-Based Doses for Subjects Previously Treated with Placebo

Low Weight (< 60 kg)	Medium Weight (>60 to 90 kg)	Heavy Weight (>90 kg)
70 mg	100 mg	150 mg

APPENDIX C. DOSE ADJUSTMENT GUIDELINES FOR ROXADUSTAT

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

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

All subjects will be dosed orally TIW during the Treatment period. During the course of the study, the dose and the dosing frequency may be changed to optimize efficacy and tolerability based on the clinical judgment of the investigator and study medical monitor. If a subject requires < 20 mg TIW (ie, < 60 mg per week) to maintain the target Hb level, the dosing frequency should be reduced in a step-wise fashion eg, TIW to BIW, BIW to QW, QW to Q-2 Week etc. The Medical Monitor should be notified as soon as possible of such dose change. The maximum roxadustat dose is 3.0 mg/kg per dose or 400 mg (whichever is lower).

The following scenarios are defined as "excessive hematopoiesis";

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

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

Given the complexity in roxadustat dose adjustments, and the need to take into account the various clinical parameters in roxadustat dose titration, one would not consider it a protocol deviation when study subjects are dosed based on their clinical circumstances, whether or not it is concordant with the roxadustat dose adjustment guidelines unless it was related to "excessive hematopoiesis" (eg,,Hb ≥ 13 g/dL, requiring a dose hold)) or "Overdose" (prescribed >3.0 mg/kg per dose or 400 mg per dose whichever is lower)

<table>
<tr><th colspan="5">Roxadustat Dose Adjustment Rules</th></tr>
<tr><th>Change in Hb from 4 weeks earlier (g/dL)</th><th>Hb < 10.5 g/dL</th><th>Hb 10.5 to 11.9 g/dL</th><th>Hb 12.0 to 12.9 g/dL</th><th>Hb ≥ 13.0 g/dL</th></tr>
<tr><td>< -1.0</td><td>↑</td><td>↑</td><td>No change</td><td rowspan="3">Hold, then resume dosing when: Hb < 12 g/dL, at a dose that is reduced by two dose steps

Subjects are to return weekly to monitor Hb until dosing can be resumed**</td></tr>
<tr><td>-1.0 to 1.0</td><td>↑</td><td>No change</td><td>↓</td></tr>
<tr><td>> 1.0</td><td>No change</td><td>↓</td><td>↓</td></tr>
<tr><td colspan="5">Dose Adjustment for Excessive Hematopoiesis:
At any time during the Treatment Period if Hb increases by >2.0 g/dL within 4 weeks, the dose should be reduced by one dose step.
** For subjects on prolonged dose-hold, with stable (not dropping) Hb, PI may use discretion to schedule less frequent visits. Anytime Hb is assessed via HemoCue®/CritLine®/local labs, a central lab Hb should be obtained as well

Dose Increases and Reductions:
Dose increases (↑) and reductions (↓) are preset to dose steps. The dose steps are as follows:
20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.
Example: A dose increase at a dose of 70 mg results in 100 mg as the new dose. A dose reduction at a dose of 150 mg results in 100 mg as the new dose.
Note: Maximum dose capped at 3.0 mg/kg per dose or 400 mg, whichever is lower.

*Transition from Correction to Maintenance Phase will occur once the central laboratory Hb value is ≥ 11 g/dL and ≥ 1 g/dL from baseline</td></tr>
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